Hot Topics in Acute Care Surgery and Trauma

Massimo Sartelli
Matteo Bassetti
Ignacio Martin-Loeches *Editors*

Abdominal Sepsis

A Multidisciplinary Approach

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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.

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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].

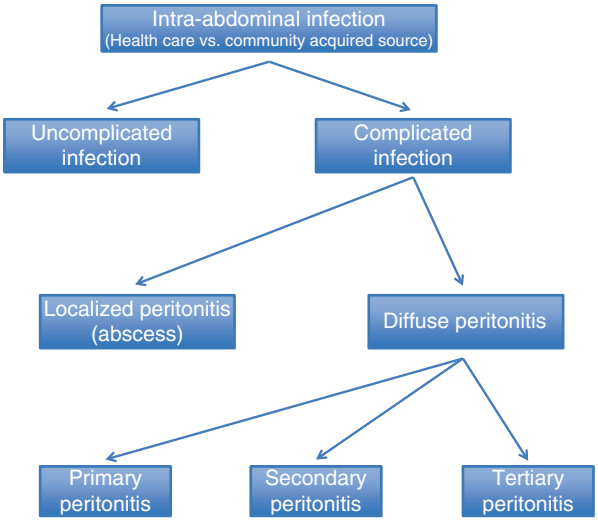

Fig. 1.1 Classification of intra-abdominal infections

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^3, 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^3 [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].

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].

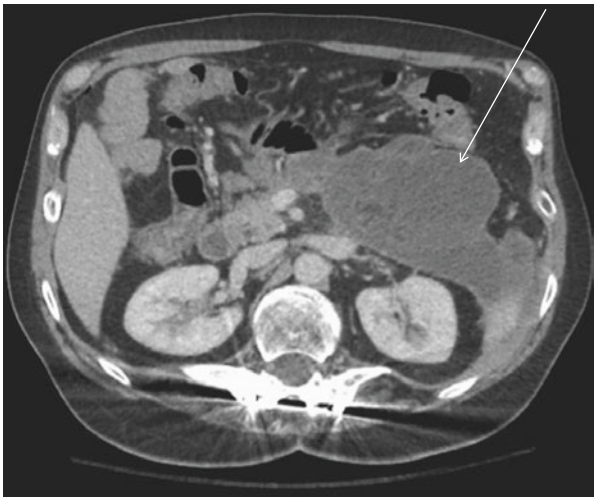

Fig. 1.2 A CT image of an intra-abdominal abscess (*arrow*) amenable to percutaneous drainage

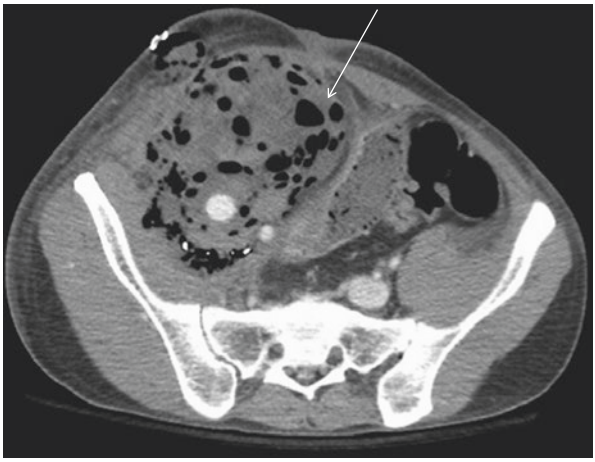

Fig. 1.3 A CT image of a complex intra-abdominal fluid collection with free air (*arrow*) and fecal contamination requiring surgical exploration

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_2). 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_2 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_2 is dependent on cardiac output, oxygen demand, and hemoglobin and arterial oxygen saturation. A septic patient may have normal or elevated SVO_2 but not have adequate tissue oxygenation due to misdistribution of blood flow. Despite this, a low SVO_2 is an indicator of inadequate tissue oxygenation and requires quick intervention to increase oxygen delivery [61]. Using a resuscitation goal of $SVO_2 > 65\%$ 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].

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

Andrew W. Kirkpatrick, Jimmy Xiao, Craig N. Jenne, and Derek J. Roberts

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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burns. A major host response to these noninfectious insults is to release many endogenous mediators or damage-associated molecular patterns (DAMPs) that, like the microbial pathogen-associated molecular patterns (PAMPs), activate the immune system and initiate the inflammatory response that is responsible for the major lethality of sepsis as a result of multisystem organ failure (MSOF). For clinical operationalization, organ dysfunction can be represented by an increase in the Sequential [Sepsis-Related] Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with in-hospital mortality greater than 10%. Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone [4].

DAMPs and PAMPs share a number of conserved families of pattern recognition receptors (PRRs), including the prototypical PRR family, the toll-like receptors (TLRs). Activation of TLRs on immune cells and endothelial cells leads to the release of pro- and anti-inflammatory mediators, which are the

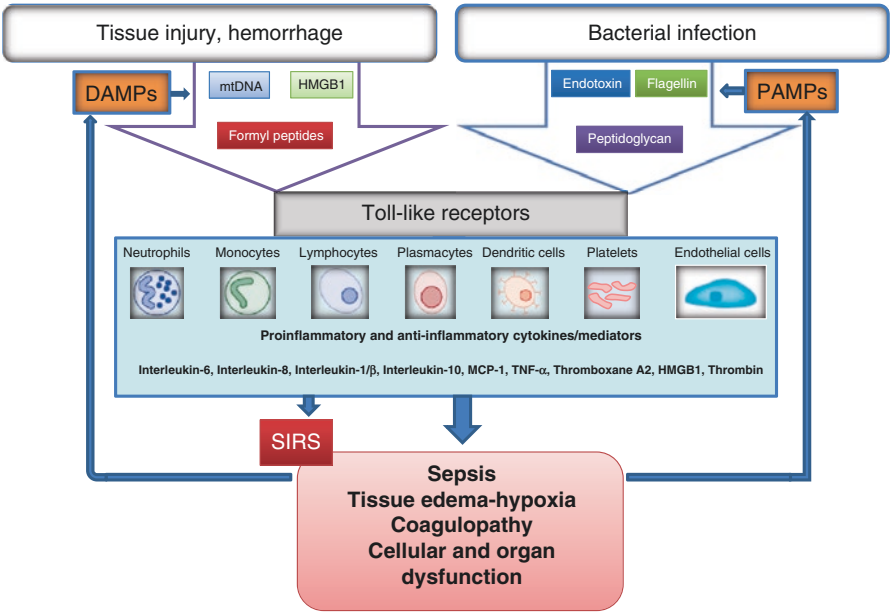

Fig. 2.1 Schematic pathways of injury and infection leading to systemic inflammatory response syndrome (SIRS) and sepsis. Tissue damage leads to the extracellular release of damage-associated molecular patterns (DAMPs). Infection is associated with exposure of the immune system to pathogen-associated molecular patterns (PAMPs). DAMPs and PAMPs stimulate cells of the innate immune system, which lead to release of pro- and anti-inflammatory mediators and endothelial damage, resulting in further tissue hypoxia, organ dysfunction, and immunoparesis causing persistent inflammation, immunosuppression, and catabolism syndrome (PICS), which lead to the release of further DAMPs and PAMPs. *HMGB1* high mobility group box 1 protein, *mtDNA* mitochondrial DNA, *TNF-α* tumor necrosis factor alpha, and *MCP-1* monocyte chemoattractant protein 1

effectors triggering excessive inflammation and multiple organ failure (Fig. 2.1) [5–7, 8]. Additionally, activation of platelets results in the release of additional pro-inflammatory molecules, modulates vascular tone, and can result in sepsis-associated coagulopathy [9, 10]. Activated platelets modify the effector functions of other immune cells including the induction of neutrophil extracellular trap (NET) release from neutrophils [11]. NETs are extracellular DNA structures comprised of decondensed chromatin decorated with both nuclear and granular proteins [12] and DAMPs. These "webs" are designed to catch and kill pathogens but are very cytotoxic, causing damage to surrounding tissues and further potentiating coagulation. Multichannel molecular mediators will likely to better characterize specific subsets of sepsis. They may be used as biomarkers to differentiate sepsis from noninfectious insults and provide new therapeutic approaches.

2.2 Abdominal Sepsis

Intra-abdominal sepsis (IAS) is a continuing challenge as it remains frequent, being the second most common cause of sepsis with high mortality rates, and in particular it can be difficult to distinguish sepsis from "sterile" SIRS, and delays in recognizing "failed source control" can often be fatal although it is often a very difficult task [13, 14]. Despite advances in diagnosis, surgery, and antimicrobial therapy, mortality rates associated with complicated intra-abdominal infections and intra-abdominal sepsis remain exceedingly high [15]. As recommended by the World Society of Emergency Surgery (WSES), patients with sepsis or septic shock of abdominal origin require early hemodynamic support, source control, and antimicrobial therapy [16]. Despite many practical recommendation regarding interventions and support, the WSES also noted that the progression to septic shock is characterized by excessive inflammation.

2.3 Inflammatory Mediators and Potential Compartmentalization

Emr and colleagues have suggested that multi-organ dysfunction syndrome (MODS) occurs because of cascading system failure, wherein the positive feedback loop of inflammation drives tissue damage, which propagates inflammation that exceeds compartment-specific thresholds [17]. In terms of abdominal infections, the relevant compartments are the local ascites and the distant systemic endothelia, particularly that in the lungs. The pathways between these compartments *include* mesenteric lymph and the systemic circulation (Fig. 2.2). This conceptualization of interrelated compartments and sepsis is congruous with the WSES clinical concept in which an uncomplicated case of abdominal infection only involves a single organ and does not extend to the peritoneum [15, 16].

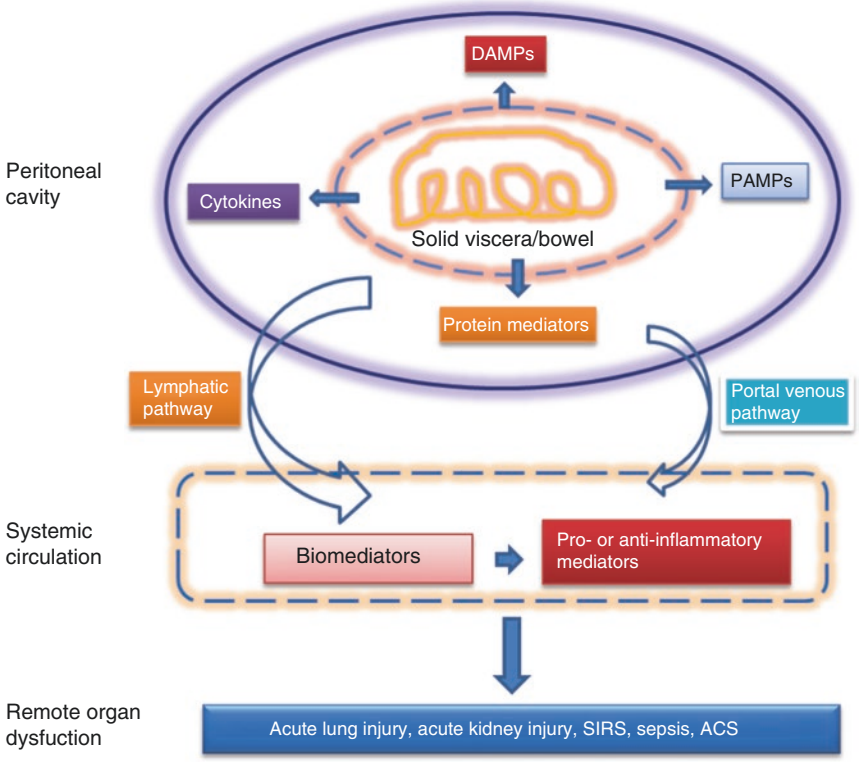

Fig. 2.2 Schematic important pathways of biomediators entering systemic circulation from inflammatory peritoneal fluid, leading to remote organ dysfunctions. *ACS* abdominal compartment syndrome

2.4 Serum Biomediators in Abdominal Sepsis

The reasons to study inflammatory mediators (IMs) include (1) to better understand the basic pathogenesis of sepsis and injury-related organ dysfunction; (2) to provide earlier diagnoses of sepsis syndromes and predict complications or outcomes, especially "failed source control"; and (3) to determine therapeutic targets for randomized controlled trials (RCTs) of sepsis modulating agents [8]. Despite this, the identification of therapeutic targets and development of sepsis modulating drugs have been an expensive and frustrating process thus far. There have been literally hundreds of failed anti-mediator trials, and thus the developmental pipeline for novel therapeutics for treating sepsis has diminished to a trickle with the one potential drug activated protein C (APC) being taken off the market [18]. It has become readily apparent from these failed anti-mediator trials that the attempt to neutralize, block, or promote a single biomediator after they have been generated is not helpful [19].

Xiao and colleagues recently extensively reviewed inflammatory mediators (IMs) in intra-abdominal sepsis and/or injury [8]. The overriding message of this review was one that De Waele independently concluded in his contemporary summary of abdominal sepsis [14]:

> …while preclinical data suggest that inflammatory mediators play an important role in intra-abdominal sepsis and injury, ultimately there is **NO** consensus on the clinical use of inflammatory mediators in diagnosing or managing intra-abdominal sepsis, their exact role remains incompletely understood.

To derive this message, 182 studies were retained that assessed or discussed IMs in relation to intra-abdominal sepsis or injury out of 2412 potential studies screened [8]. Another high-level summary of the overall conclusions was that before 1992 C-reactive protein remained the most studied IM. After 1992, the interleukins and tumor necrosis factor (TNF) were primary foci of interest. After 2000, procalcitonin was investigated, and until most recently, DAMPs and endothelial dysfunction molecules have been focused upon in the reported English language literature.

2.4.1 C-Reactive Protein

At the time of writing, at least 33 studies have evaluated CRP in relation to IAS. In general, CRP levels elevate on postoperative day (POD) 1, peak from POD2 to POD3, and decline by POD5 provided there is no complication or infection. While four reports suggest that a persistent threshold of greater than 100 mg/l might indicate abscess/septic complications [20–23], other studies have refuted this conclusion, leaving uncertainty for clinical practice [24–28].

2.4.2 Procalcitonin

Twelve trials, including two RCTs, have evaluated procalcitonin. In general, levels increase immediately after surgical injury, peak on POD 1, and decline to half its peak level from POD2 to POD3 after uncomplicated abdominal surgery. Again, in some reports persistently high levels have been associated with infection and/or increased septic mortality in patients with sepsis [21, 26, 29, 30], but not consistently enough to be adopted for use in clinical practice [31, 32].

2.4.3 IL-6

Like in most areas of sepsis, IL-6 is one of the most commonly studied markers. The plasma levels are rapidly dynamic. They peak from wound closure to POD1 and then return to baseline by POD3. The role of IL-6 as a marker to diagnose sepsis or

predict outcomes remains uncertain, with wide range of cutoff values suggested (from 12 to 2760 pg/ml). One of the most recent published studies (retrospective review of prospectively captured samples), which compared CRP, IL-6, and TNF levels after major abdominal surgery, noted that IL-6 as a single test had early prognostic information by day 1 with an area under the curve of 0.67, although CRP started to discriminate from day 3 onward with an improved area under the curve of 0.73 [33].

2.4.4 Damage-Associated Molecular Patterns

DAMPs are early pro-inflammatory mediators released from damaged host cells upon lysis or injury, such as high mobility group box protein 1 (HMGB1), which is elevated in plasma early in shock. DAMPs signal for necrotic cell clearance by phagocytic cells of the immune system. Freely circulating DAMPs may trigger an inflammatory reaction, much in the same fashion as pathogen-associated molecular patterns found on many bacterial pathogens, by binding to host cell receptors on a variety of immune cells. Some DAMPs, such as HMGB-1, have been shown to be both markers of damage and mediators of inflammation in sterile and non-sterile injury [34–36]. These have promise in IAS, but much more needs to be learned about them.

2.4.5 Interventional Trials

Despite the marked resources expended on attempting to find a pharmacologic solution for sepsis, there have only been nine such clinical interventions for abdominal sepsis, of which four were randomized controlled trials. One was our own RCT of peritoneal vacuum therapy [37, 38], which will be later discussed. Three concerned open versus minimally invasive techniques for treating seemingly less complex cases of sepsis related to appendicitis, cholecystitis, and perforated peptic ulcer [39–41]. Overall, there is unfortunately no clear message for clinicians to measure and especially to try to manipulate IMs to influence the outcome of abdominal sepsis at the current time.

2.4.6 Inflammatory Ascites

In contemporary critical care medicine, low-density peritoneal fluid (PF) is typically assumed to be benign. However, upon careful scientific scrutiny, the free intraperitoneal fluid found in critical illness actually more resembles a hostile sea of inflammatory mediators and toxins that may be a primary driving force for systemic sepsis and resultant multi-organ failure [17]. It has been found that increased levels of both systemic and peritoneal cytokines are associated with postoperative complications, which may discriminate survivors from those dying [42–45]. Although data

from research with animal models [44], inflammatory bowel disease [46, 47], and surrogate outcomes [48] are suggestive, direct evidence does not yet exist to prove that more efficiently draining this fluid will make a difference to complications or survival. Therefore, as a tantalizing area of current research, this topic should be further reviewed.

2.4.7 The Implications of Inflammatory Ascites

Severe intra-abdominal hypertension (IAH) has been shown to directly lead to multisystem organ failure in animal models [49, 50]. Grade III [defined as an intra-abdominal pressure (IAP) of 21–25 mmHg] and IV (IAP >25 mmHg) IAH has been shown to significantly reduce perfusion to the intestinal mucosa, which ultimately increases intestinal permeability and results in systemic endotoxemia and irreversible damage to the mitochondria and necrosis of the gut mucosa [50]. This disruption of the intestinal mucosal barrier may be one of the important initial factors responsible for the onset of abdominal compartment syndrome (ACS) and the impetus for the development of multi-organ dysfunction syndrome [49, 50]. For years it has been postulated that the damaged gut is a continual source of inflammation and MODS, referred to as the "Motor of MSOF" [51–56], by inducing the production of cytokines and other biomediators and propagating acute respiratory distress syndrome (ARDS). The release of endotoxin induces production of cytokines, including IL-6, IL-1β, IL-8, TNF-α, and other mediators. Movement of these mediators into the systemic circulation may possibly be largely facilitated through the mesenteric lymphatic channels [57]. This movement initiates pulmonary damage and development of acute respiratory distress syndrome (ARDS) [17, 51, 52, 54–56, 58]. Further, circulation of these mediators results in systemic inflammation.

With critical abdominal illness and surgery, there is a remarkably active biomediator response in the local peritoneal environment. One study comparing intraperitoneal cytokine levels in patients who required abdominal surgery for active inflammatory bowel disease (n = 50), colorectal cancer (n = 25), and appendicitis (n = 25) found that intraperitoneal cytokines were significantly elevated in the patients with inflammatory bowel disease [46]. Very notably, commonly used systemic inflammatory markers (e.g., the white blood cell count) showed no correlation with the measured cytokine levels. Intraperitoneal cytokines were also significantly higher in patients with postoperative septic complications than in those without such complications, suggesting that their measurement might potentially predict earlier which patients would be at the highest risk for such complications. The authors therefore suggested that levels of intraperitoneal cytokines might better stratify the degree of intraperitoneal inflammation and guide local therapy for the prevention of postoperative septic complications [46], a capability certainly not yet possible with serum IMs. A further prospective study measuring intraperitoneal cytokines on the first 3 postoperative days in patients who had elective colorectal surgery (n = 100) found that key cytokines (IL-1β, IL-6, and TNF) were significantly increased in patients with postoperative sepsis (n = 8) and significantly

decreased in patients without sepsis ($n = 92$), implicating these mediators as potential early markers of peritonitis [47].

A laboratory study assessed the biological activity of peritoneal fluid from swine with intra-abdominal sepsis using peritoneal fluid collected 12 h after induction of ischemia/fecal sepsis [48]. The study used peritoneal fluid from either septic or control animals to prime naïve human neutrophils and then measured neutrophil superoxide production and surface antigen expression. Levels of IL-6 and TNF-α in peritoneal fluid were also measured and found to be significantly increased in the sepsis group compared with the control group. The study demonstrated that in the face of sepsis, peritoneal fluid may greatly increase the pro-inflammatory characteristics of abdominal cavity-derived lymph flow [48]. The authors suggested that such sepsis-primed neutrophils may make patients more susceptible to any second insult, such as pneumonia or bleeding [48]. They also recommended that future research should investigate whether early removal of inflammatory ascites downregulates local and/or systemic inflammation or alters pro-inflammatory characteristics of mesenteric lymph [48].

Further laboratory work has associated increased intraperitoneal cytokines with adverse outcomes. Such associations in secondary peritonitis were investigated in a rat model of induced peritonitis [44]. Measurement of intraperitoneal mediators at 24 and 72 h found that intraperitoneal cytokine levels (IL-6, TNF-α, and IL-10) significantly predicted survival [44]. The gross predictive value of such measurements also seems consistent at the bedside. A human study of 29 burn patients with severe IAH/ACS measured cytokine levels in the peritoneum and in plasma and found that mortality was associated with increased interferon-γ, IL-10, IL-6, IL-4, and IL-2 in peritoneal fluid [59]. A study in 34 elective colorectal surgery patients compared cytokine levels in patients with anastomotic leakage ($n = 4$) with those who had no leakage ($n = 30$) [60]. Peritoneal cytokine levels progressively decreased in those without anastomotic leakage and progressively increased in those with leakage or peritonitis [60].

Thus, there appears to be circumstantial evidence that intraperitoneal cytokines are likely involved in the production of poor outcomes in critical illness/injury and even if not causal are at least markers of harmful processes. Mechanistically, there does also appear to be compartmentalization of these processes, meaning that local environments of mediators may be different from other compartments and their influence on the systemic outcomes dependent on tipping points such as transport factors [61]. Thus, hemoadsorption in a rat model of gram-negative sepsis appears to re-compartmentalize inflammation and reduce organ dysfunction [62].

2.5 Preventing Systemic Dissemination of Intraperitoneal Inflammatory Mediators

In regard to IAS, the internal flow of mesenteric lymph may serve a crucial previously underappreciated role. A canine study of the effect of mesenteric lymph duct ligation in an inflammatory injury model of portal vein occlusion and reperfusion

compared with portal vein occlusion and laparotomy only found significantly decreased lung injury and decreased TNF-α, IL-1β, and endotoxin in thoracic duct lymph in dogs with lymphatic duct ligation, but not in those with portal vein occlusion, indicating that cytokines reached the systemic circulation through the lymph [63]. In addition, a rat study of mesenteric lymph diversion in an ischemia-reperfusion model found significantly increased lung injury in animals with an intact lymphatic duct compared to those whose lymphatic duct was ligated [57]. Finally, a canine model assessing the effect of primary (originating because of diseases in the abdominopelvic cavity) and secondary (originating because of diseases or conditions outside of the abdominopelvic cavity) IAH on hemodynamics, intestinal fluid balance, and mesenteric lymph flow found that secondary IAH increased lymph flow and contributed to the development of gut edema, supporting the importance of abdominal decompression to prevent mediator release and entry into the lymphatic circulation [64].

Given the potentially profound consequences emanating from the generation, accumulation, and eventual dissemination of biomediators from the peritoneal space, investigators have sought to remove or block them at the source. An elegant laboratory study utilized barrier prevention methods *within* the peritoneal cavity. Narita studied an ischemia-reperfusion model of intestinal ischemia, involving three groups consisting of controls (no ischemia) compared to 90 min of ischemia followed by 180 of reperfusion versus the same ischemia-reperfusion model except with bowel isolation in a condom [65]. Remarkably, it was noted that the bowel isolation group had lower plasma cytokine levels (IL-β, TNF, IL-8) and reduced lung injury compared to the non-isolated ischemic group [65].

2.6 Practical Bedside Approaches to Inflammatory Ascites Drainage

Based on biological plausibility, it appears reasonable and possibly desirable to remove ascites from the severely ill and injured with sepsis or SIRS when it can be safely performed. Realistically, placement of barrier precautions around ischemic/leaking viscera or lymphatic ligation is not clinically practical. In clinical practice, the accumulation of intraperitoneal mediators can be removed by either percutaneous drainage or negative pressure therapy with an open abdomen. Percutaneous drainage is recommended to treat intra-abdominal hypertension if it is possible to safely perform, as it may obviate the need for decompressive laparotomy [49, 66, 67]. We are not aware of data confirming that percutaneous drainage removes inflammatory ascites and improves outcomes in patients with sepsis or SIRS, and such work should be conducted. If percutaneous drainage is not safely possible, negative pressure peritoneal therapy (NPPT) may be another appropriate option if the patient already has an open abdomen. NPPT involves the application of a continuous suction action to the peritoneal cavity through specially designed temporary abdominal closure systems with visceral-protective covers containing multiple suction channels.

There exists animal data suggesting that NPPT may profoundly ameliorate the overall system effects of inflammatory ascites and its causal conditions. A comparison of NPPT therapy with passive drainage in a porcine sepsis model found that NPPT removed inflammatory ascites and cytokines better than passive drainage, thereby reducing circulating cytokines and greatly improving organ function [17, 68]. While the study of inflammatory ascites and its constituents is in its infancy, there is a clinical signal that NPPT may benefit the critically ill. Cheatham et al. [69] compared the more efficient commercial NPPT system with one that is potentially less efficient, the Barker's vacuum pack. This non-randomized study included 280 patients, of whom 168 had 48 h of TAC therapy. The 30-day all-cause mortality was 14% for the commercial system and 30% for Barker's ($p = 0.01$). While the non-randomized design cannot confirm causality, reasons postulated for the improved result may be improved peritoneal drainage with a more uniform suction effect with the commercial system [69]. A recent systematic review of negative pressure therapy for critically ill adults with open abdominal wounds found two randomized controlled trials and nine cohort studies (three prospective and six retrospective) that met inclusion criteria [70]. The review concluded that limited prospective comparative data suggested that negative pressure therapy may be linked with improved outcomes compared with alternative temporary abdominal closure (TAC) techniques. Clinical heterogeneity and the quality of the studies precluded definitive conclusions. It was concluded that further randomized controlled trials are urgently required [38].

Subsequently an RCT was conducted in critically ill and injured patients with an average APACHE score of over 22 in patients with sepsis and an average ISS of over 23 in the injured. This study compared the same more efficient commercial NPPT system to the Barker's vacuum pack [71]. Although this study did not find a difference in actual peritoneal fluid drainage or in the behavior of the high-level mediators examined (IL-1β, IL-8, IL-10, or IL-12 p70 or tumor necrosis factor α), there was a survival difference in favor of the commercial system which is currently unexplained. It is possible that patient heterogeneity in the complex setting of mixed critical care populations solely explains the findings, and thus further studies are required.

Conclusions

Sepsis is a syndrome with an incompletely understood process. At present, there are no unambiguous clinical criteria or laboratory markers to uniquely distinguish sepsis from noninfectious insults. Overall the current state of science still has a limited understanding of the complete complexity of the effects, counter-effects, and interactions and effects of IMs in abdominal sepsis. Their serum measurement cannot yet be routinely recommended on clinical grounds. Conversely the measurement of intraperitoneal mediators appears to be a promising area of both scientific study and potentially a target for clinical guidance and potential intervention. However, the evidence is as yet mostly circumstantial, and further studies likely with more homogeneous populations will be required.

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Intra-abdominal Sepsis and Imaging Considerations

3

Asanthi M. Ratnasekera and Paula Ferrada

3.1 Anatomy and Physiology

The abdominal cavity extends from the undersurface of the diaphragm to the floor of the pelvis. It is divided to intraperitoneal and retroperitoneal spaces. In men the peritoneum is a closed space, where as in women it communicates to the outer surface via the free ends of the fallopian tubes. The peritoneal space has multiple recesses that fluid may be loculated. The pelvic recess is the most dependent portion in the supine position. In men the pouch of the peritoneal cavity is between the rectum and the bladder, and in women the pouch of Douglas is between the rectum and the uterus. The pelvic recess is continuous with the right and left paracolic gutters. Morrison's pouch is the posterior extension of the right paracolic gutter and right perihepatic space and lies posterior to the transverse colon. This is the most dependent portion to the right of the vertebra. The largest recess is the lesser sac which is bounded anteriorly by the posterior stomach wall, posteriorly by the pancreas and kidneys, and laterally by the liver and spleen and has a lateral opening through the foramen of Winslow. The subphrenic spaces are divided by the falciform ligament to left and right subphrenic spaces.

The peritoneal cavity is lined by mesothelial cells and responds to bacterial contamination. Normally about 50–100 cc of peritoneal fluid circulates to maintain moisture of the viscera and fluid movement. The peritoneum is permeable and is used as a site for dialysis for movement of fluid, electrolytes, and blood. Major host defense system includes phagocytosis of bacteria and clearance of bacteria by lymphatics and by abscess formation. The peritoneum in the event of intra-abdominal infection may be inflamed and cause musculoskeletal response via guarding and

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rigidity over the organ involved in inflammation. It can sequester up to 1.7 L of fluid in the intraperitoneal space and can hinder phagocytosis and lymphatic function to eradicate infection. This also requires large-volume transfusion to maintain euvolemia. The absorption of fluid is also enhanced by the diaphragmatic lymphatics and is enhanced by the diaphragmatic motion.

3.2 Peptic Ulcer Perforation

The stomach flora may contain up to 10^3 colony-forming units per milliliter. Common organisms in the stomach are acid-resistant species, yeast, and oropharyngeal flora and gram-positive organisms. Organisms that are found in the stomach are *Bacteroides*, *Lactobacilli*, *Candida*, and streptococci. Risk factors for complicated peptic ulcer disease leading to perforation are smoking, excessive alcohol use, *Helicobacter pylori* infection, and NSAID use. Patients with perforation of ulcer disease present with sudden-onset epigastric abdominal pain. The gastric content spillage caused by perforation can be diffuse and constant and may radiate to the shoulders if gastric contents are in the subphrenic spaces. On exam patient will demonstrate peritoneal signs with abdominal rigidity, signs of shock, fever, and tachycardia. Laboratory studies may demonstrate leukocytosis with a left shift. On upright abdominal radiography, free air can be demonstrated. Other diagnostic modalities include upper gastrointestinal study with water-soluble contrast such as gastrografin that may demonstrate contrast extravasation. Computed tomography of the abdomen and pelvis will demonstrate free air, air around the perforation, and extravasation of contrast (Fig. 3.1).

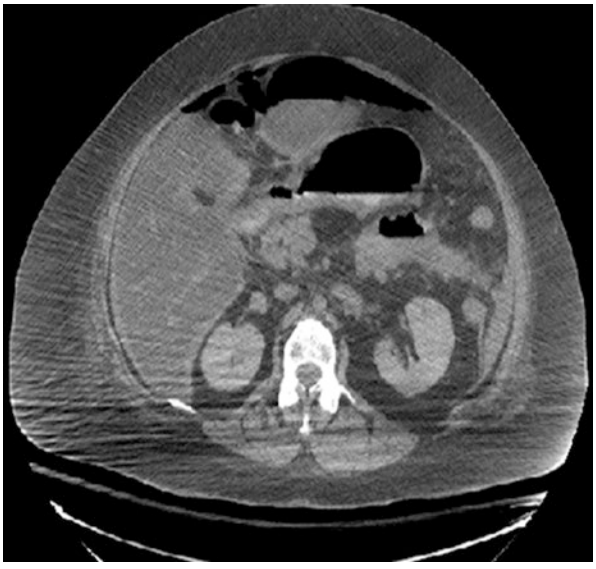

Fig. 3.1 Patient presented with acute abdominal pain. CT demonstrated free air with duodenal and prepyloric area thickening concerning for perforated duodenal ulcer

3.3 Acute Cholecystitis

Acute cholecystitis can range from mild inflammatory process to gangrene of the gallbladder [2]. Acute calculous cholecystitis is seen in patients with gallstones. Patients may present with "biliary colic" and constant right upper quadrant and epigastric abdominal pain 1 h or more after heavy meal with associated nausea and vomiting. The pain is caused by the contraction of the gallbladder induced by CCK; however, the gallbladder is unable to empty due to gallstones blocking the cystic duct. This thereby creates stasis and bacterial inoculation causing cholecystitis. The patient may present with elevated leukocytosis. Elevated bilirubin may also be present if the patient is presenting with choledocholithiasis or cholangitis. In this case Charcot's triad can be seen with fever, right upper quadrant pain, and jaundice. When hypotension and altered mental status are present indicating sepsis and shock, Reynolds pentad is observed. Elevated bilirubin levels >2.5 mg/dL may present as scleral icterus and jaundice in the sublingual regions. Diagnostic imaging used to evaluate for biliary disease should start with a limited abdominal ultrasound. Ultrasounds to evaluate biliary pathology are sensitive and inexpensive. On ultrasound, gallstones, gallbladder wall thickening, and pericholecystic fluid are all indicative of acute cholecystitis. The proximal common bile duct can also be measured, and if dilated may indicate choledocholithiasis and in the presence of Charcot's triad or Reynolds pentad may indicate cholangitis. When acute cholecystitis is diagnosed, the standard of care has been to perform a laparoscopic cholecystectomy with or without intraoperative cholangiogram. The intraoperative cholangiogram is also a diagnostic tool for biliary pathology and obstruction caused by stones or masses. In the event cholangitis is diagnosed, biliary decompression with percutaneous transhepatic cholangiography or endoscopic retrograde cholangiopancreatography is used. Broad-spectrum IV antibiotics are also started to target the most common biliary organisms such as *E. coli*, *Enterococcus* species, and *Klebsiella pneumoniae*. When choledocholithiasis is present, patient may require ERCP with stone extraction and sphincterotomy.

In contrast to acute calculous cholecystitis that is due to gallstones, acute acalculous cholecystitis is due to secondary infection of the gallbladder, ischemia, and stasis. Patients with acute acalculous cholecystitis have hypoperfusion following burns, trauma, cardiopulmonary bypass surgery, and prolonged critical illness in the ICU setting. Diagnosis of acute acalculous cholecystitis can be challenging. Patients with prolonged critical illness with new-onset septic shock, fever, right upper quadrant abdominal pain, and hyperbilirubinemia should warrant a workup of the biliary tract. Acalculous cholecystitis has a rate of perforation in 20% of patients. Bedside right upper quadrant ultrasound may demonstrate gallbladder wall thickening of >3.5 mm and pericholecystic fluid with the absence of gallstones. CT of the abdomen and pelvis may also be beneficial in this setting. Hepatobiliary scintigraphy is an option for diagnosis; however, it has 40% false-positive rate due to lack of dietary stimulus of the gallbladder. Critically ill patients with acalculous cholecystitis may not be able to undergo cholecystectomy; therefore, the treatment of choice is ultrasound or CT-guided percutaneous cholecystostomy tube placement. With this method, approximately 90% of the patients will improve. The drainage catheter can eventually be removed once the patient's clinical condition has improved and interval cholecystectomy can be considered (Fig. 3.2).

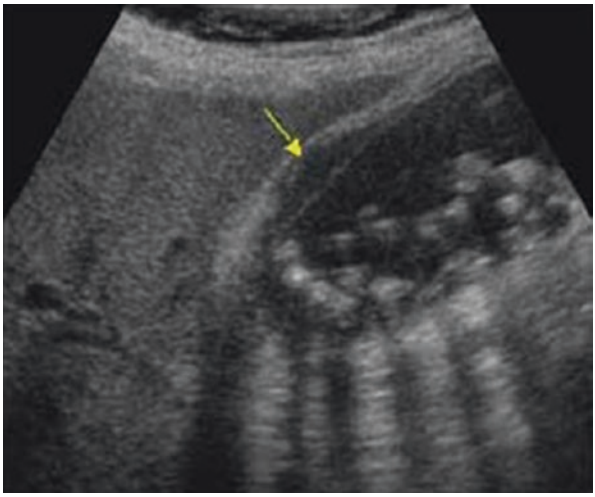

Fig. 3.2 Ultrasound of gallbladder demonstrating multiple stones with acoustic shadowing, thickened gallbladder wall, and *arrow* pointing to pericholecystic fluid indicative of acute cholecystitis

3.4 Pancreatitis

Acute pancreatitis is a relatively common disease found in approximately 240,000 patients per year. The most common causes in the United States are gallstones and alcohol. Majority of the patients with acute pancreatitis have a self-limiting disease process and improve with bowel rest, intravenous fluid resuscitation, and supportive care. However, 20% of the patients can present with necrotizing pancreatitis with metabolic and physiologic derangements with multiple organ dysfunction. The inciting etiology causes activation of proteolytic enzymes within pancreatic acinar cells. Activation of proteolytic enzymes further activates other enzymes such as trypsin which can cause a cascade of activation of complement coagulation and fibrinolysis within the pancreatic cells causing further destruction. As injury progresses, vasoconstriction and thrombosis cause pancreatic ischemia and necrosis. The inflammatory mediators resulting from this necrosis can cause systemic inflammatory response syndrome (SIRS) and multiorgan failure.

Patients with acute pancreatitis usually present with acute epigastric abdominal pain with radiation of pain to the back. Patients also experience nausea and vomiting. Jaundice may be present if choledocholithiasis and cholangitis are the inciting etiologies of pancreatitis. Other signs such as Grey Turner's, Cullen's, and Fox's may be present as hemorrhagic pancreatitis causes ecchymosis in the flanks, around the umbilicus, and in the inguinal region.

Serum amylase and lipase are useful in diagnosis of acute pancreatitis. Lipase is more sensitive than amylase; however, lipase has a longer serum half-life than amylase and may be elevated longer when amylase has already normalized later in the course of the disease.

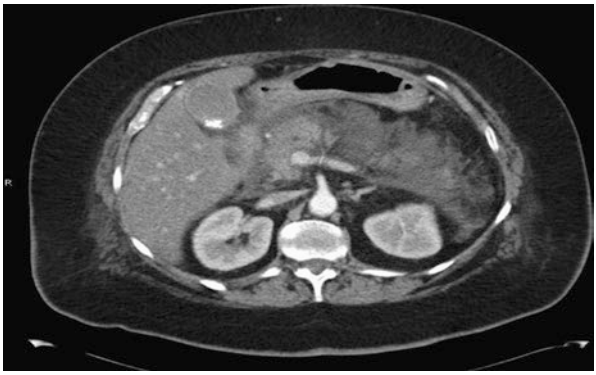

Fig. 3.3 Pancreatic inflammation with peripancreatic fluid. Areas of necrosis can be appreciated with hypoattenuation of pancreas

Computed tomography of the abdomen and pelvis and intravenous contrast are most useful in the diagnosis of pancreatitis and other pancreatic complications such as necrosis, abscess, and pseudocyst formation. Abdominal ultrasound may be helpful to evaluate for gallstones and can demonstrate the presence of dilated common bile duct in the event of choledocholithiasis and cholangitis. It will also demonstrate peripancreatic fluid and pancreatic duct abnormalities. Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) are useful modalities to assess biliary and pancreatic anomalies; however, they are more expensive and have a longer duration of study.

If pancreatic necrosis is suspected by patient clinical status or CT evidence of air within the pancreas, a fine-needle aspiration of the suspected area will be useful. If the fine-needle aspirate demonstrates pancreatic necrosis, pancreatic drainage procedures are recommended [9].

If pancreatic abscess or infected pseudocyst is seen, percutaneous drainage can be sufficient along with aforementioned antibiotics (Fig. 3.3).

3.5 Mesenteric Ischemia

Mesenteric ischemia and bowel ischemia can be brought on by multiple causes. The most common cause is an arterial embolus from a cardiac source. Atrial fibrillation and cardiac thrombus are the most common causes of a cardiac source. Other causes are arterial thrombus from a diseased SMA and low-flow nonocclusive mesenteric ischemia from vasoconstriction of the mesenteric vessels. Common causes for low-flow nonocclusive mesenteric ischemia are from disease states causing shock, hypovolemia from gastrointestinal losses, or vasoactive agents causing splanchnic vasoconstriction. Mesenteric venous thrombosis can also cause ischemia of the intestines due to hypercoagulability state, trauma, or portal hypertension states.

Patient presentation usually consists of severe epigastric or mid-abdominal pain, emesis, and diarrhea. Blood in stool and peritoneal signs are late presentations of the disease process. Patients presenting early usually demonstrate pain out of

proportion to the exam with no physical findings. There are no pathognomonic laboratory values for evaluating mesenteric ischemia. However, leukocytosis, elevated lactic acidosis from ongoing ischemia, and transaminitis may be evident. Diagnostic modality that is most sensitive will be a selective mesenteric angiogram; however, computed tomography angiography is useful to visualize arterial and venous anatomy. CT can also demonstrate viability of the bowel, bowel wall thickening, ascites, and pneumatosis from ischemia.

3.6 Acute Diverticulitis

Colonic diverticular disease is acquired from lack of dietary fiber. Diverticular disease is most abundant in the sigmoid colon and is rare below the peritoneal reflection where the tenia splays out into the rectum. The intrinsic pressures required to propel hard stool forward cause herniation of the bowel wall at the vascular insertion sites and colon wall muscular hypertrophy. Up to 25% of patients with diverticular disease will have diverticulitis. Diverticulitis occurs with diverticular perforation and fecal content extravasation either micro- or macroscopically. Diverticulitis can be categorized into complicated and uncomplicated disease states. Complicated disease occurs with occurrence of abscess, peritonitis, obstruction and fistulas [3]. Uncomplicated diverticulitis occurs with micro perforation with no complicating states.

Diverticular disease can also cause lower gastrointestinal hemorrhage when the arterioles that perforate the diverticula can undergo pathologic changes and bleed into the diverticula and colon. This arterial bleed may cause massive GI hemorrhage at times.

Presentation of diverticulitis is commonly seen with left lower quadrant and suprapubic dull abdominal pain, fever, and malaise. Symptoms may worsen with defecation and urination. If the patient has a redundant sigmoid colon, right-sided abdominal pain can also be seen. On exam, patient may have tenderness, a palpable mass, and/or peritoneal signs in case of complicated diverticulitis with peritonitis. Patient may also present with hemodynamic instability with complicated diverticulitis with peritonitis. Laboratory values may demonstrate leukocytosis. Computed tomography of the abdomen and pelvis with oral and intravenous contrast will confirm suspected diagnosis of diverticulitis. Sigmoid wall thickening, associated pelvic or pericolonic abscess, phlegmonous pericolonic tissue, and inflammatory changes or free air can be evident on CT. Radiological findings can be subtle with colonic standing, or obvious with fecal peritonitis. The Hinchey classification of diverticulitis classifies a colonic perforation due to diverticular disease according to the severity: I pericolic abscess, II pelvic abscess, III purulent peritonitis, IV fecal peritonitis.

3.7 *Clostridium difficile* Colitis

Clostridium difficile is found in soil and water and in health-care environments. It is an obligate anaerobic spore-forming bacterium that can survive in the environment by forming spores. The spores are difficult to eradicate, and patients

may be exposed to the spores and may ingest spores in the health-care setting. The spores are viable in the hospital environment and homes of patient's up to 20 weeks. Alteration of normal gut microbiota can cause pathogenesis of *Clostridium difficile* infection (CDI). Antibiotic use can alter normal gut microbiota and replace with pathogenic microbiota. Community-acquired CDI is also a significant health-care concern. There are two toxins, A and B, which are produced. The toxins are taken up by the mucosal epithelium and generate an inflammatory response with formation of pseudomembranes. The pseudomembranes are made out of inflammatory cells, epithelial cells, and fibrinous exudate. CDI is the most common nosocomial gastrointestinal infection in the United States. Patients with recent antibiotic use are at increased risk for developing CDI depending on the duration of use and class of antibiotics. Stomach acid-inhibiting agents such as proton pump inhibitors and histamine-2 antagonists are also implicated. Other risk factors include advanced age, severity of illness, and hospitalization duration. Complications of CDI include recurrence, toxic megacolon, and perforation [4–8].

Certain population of patients with CDI may be asymptomatic. Majority of patients who had initiation of antibiotic therapy may have symptoms concurrently or weeks after discontinuation of therapy. Symptomatic patients present with diarrhea, fever, crampy abdominal pain, and tenesmus. Laboratory findings are significant leukocytosis and leukemoid reaction, with peripheral WBC counts greater than 15000. Diagnosis is made from stool sample collected for *C. difficile* toxin enzyme immunoassay or cell cytotoxin assay or toxin genes. Colonoscopy or sigmoidoscopy can be used to visualize colonic pseudomembranes but is used sparsely. Computed tomography of the abdomen and pelvis can also demonstrate pancolitis, with pericolonic inflammation and severe colonic wall thickening. Perforation of the colon can be seen with the presence of free air or ascites (Fig. 3.4).

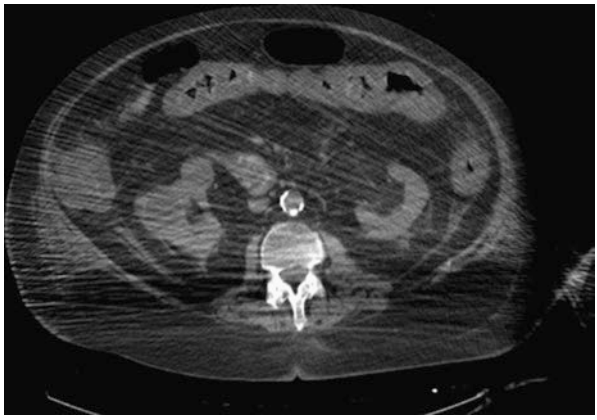

Fig. 3.4 Pancolitis is demonstrated on this CT in a patient with fulminant CDI. The visualized ascending, transverse, and descending colon demonstrates severe wall thickening with pericolonic stranding. Some patients can present without diarrhea especially with advanced disease. Prompt initiation of the appropriate therapy and surgical consultation are necessary to improve patient outcome [4].

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High-Risk Patients and Prognostic Factors for Abdominal Sepsis

4

Bruno M. Pereira and Gustavo P. Fraga

4.1 Introduction

As a basic review, prior to defining high-risk patients and prognostic factors for abdominal sepsis, it is mandatory to stress some important introductory concepts. Intra-abdominal sepsis is an inflammation of the peritoneum caused by pathogenic microorganisms and their waste products. The infectious process may be localized with the clinical presentation of an abscess or diffuse with a commonly severe condition represented by peritonitis. Intra-abdominal infections (IAI) are classified as primary (hematogenous dissemination); secondary (related to a pathologic process in a visceral organ, such as perforation or trauma-related missed injury); or tertiary (recurrent infection after adequate initial therapy). Secondary peritonitis is by far the most common form of peritonitis encountered in clinical practice and results from direct spillage of luminal contents into the peritoneum [1]. With the spillage of the contents, gram-negative and anaerobic bacteria, including common gut flora, such as *Escherichia coli* and *Klebsiella pneumoniae*, contaminate the peritoneal cavity. Endotoxins produced by gram-negative bacteria lead to the release of cytokines that induce cellular and humoral cascades, resulting in cellular damage, septic shock, and multiple organ dysfunction syndrome (MODS). It is important to highlight at this point that secondary intra-abdominal sepsis (IAS) could also happen when microscopic endoluminal injury is present, allowing direct transmural migration of bacteria from an intestinal or hollow organ lumen, a phenomenon called bacterial translocation [1, 2].

The physiologic response to IAS though is variable from patient to patient and is determined by several factors, including the virulence of the contaminant, size of the inoculum, current immune status and overall health of the host (indicated by the

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acute physiology and chronic health evaluation score II (APACHE II) or sequential organ failure assessment score (SOFA), and elements of the local environment, such as necrotic tissue or other sources of contamination [3–6]. Alterations in fibrinolysis (through increased plasminogen activator inhibitor activity) and the production of fibrin exudates have an important role in IAI and IAS. The production of fibrin exudates is an important part of the host defense, but large numbers of bacteria may be sequestered within the fibrin matrix. This may retard systemic dissemination of intraperitoneal infection and may decrease early mortality rates from sepsis, but it also is integral to the development of residual infection and abscess formation. As the fibrin matrix matures, the bacteria within are protected from host clearance mechanisms. Whether the fibrin ultimately results in containment or persistent infection may depend on the degree of peritoneal bacterial contamination. The role of cytokines in the mediation of the body's immune response and their role in the development of the systemic inflammatory response syndrome (SIRS) and multiple organ failure (MOF) have been a major focus of research over the past decade. Comparatively few data exist about the magnitude of the intraperitoneal/abscess cytokine response and implications for the host. Existing data suggest that bacterial peritonitis is associated with an immense intraperitoneal compartmentalized cytokine response. Higher levels of certain cytokines (TNF-alpha, IL-6) have been associated with worse outcomes, as well as secondary (uncontrolled) activation of the systemic inflammatory cascade. Bacterial load and the nature of the pathogen also play important roles. Some studies suggest that the number of bacteria present at the onset of abdominal infections is much higher than originally believed (approximately 2×10^8 CFU/mL, much higher than the 5×10^5 CFU/mL inocula routinely used for in vitro susceptibility testing) [7]. This bacterial load may also overwhelm the local host defense. Common etiologic entities of secondary peritonitis (SP) are demonstrated on Table 4.1 [8]. The pathogens involved in SP differ according to GI tract anatomic segment. Gram-positive organisms predominate in the upper GI tract, with a shift toward gram-negative organisms in the upper GI tract in patients on long-term gastric acid suppressive therapy. Contamination from a distal small bowel or colon source initially may result in the release of several hundred bacterial species (and fungi); host defenses quickly eliminate most of these organisms. The

Table 4.1 Common causes of SP, according to anatomic topography

GI anatomic location	SP common cause
Esophagus	Trauma, malignancy, Boerhaave syndrome, iatrogenic
Stomach	Trauma, malignancy, peptic ulcer perforation, iatrogenic
Duodenum	Trauma, peptic ulcer perforation, iatrogenic
Biliary tract	Trauma, cholecystitis, gallbladder perforation, malignancy, iatrogenic
Pancreas	Trauma, pancreatitis, iatrogenic
Small bowel	Trauma, obstruction, ischemia, Crohn, Meckel, malignancy
Large bowel and appendix	Trauma, obstruction, ischemia, inflammatory, malignancy, volvulus, iatrogenic
Uterus, salpinx, ovaries	Trauma, pelvic inflammatory disease, malignancy

resulting peritonitis is almost always polymicrobial, containing a mixture of aerobic and anaerobic bacteria with a predominance of gram-negative organisms. Bacterial virulence factor that interferes with phagocytosis and with neutrophil-mediated bacterial killing mediates the persistence of infections and abscess formation [3]. Among these virulence factors are capsule formation, facultative anaerobic growth, adhesion capabilities, and succinic acid production. Synergy between certain bacterial and fungal organisms may also play an important role in impairing the host's defense. One such synergy may exist between *Bacteroides fragilis* and gram-negative bacteria, particularly *E. coli,* where co-inoculation significantly increases bacterial proliferation and abscess formation. Enterococci may be important in enhancing the severity and persistence of peritoneal infections. In animal models of peritonitis with *E. coli* and *B. fragilis*, the systemic manifestations of the peritoneal infection and bacteremia rates were increased, as were bacterial concentrations in the peritoneal fluid and rate of abscess formation. Nevertheless, the role of *Enterococcus* organisms in uncomplicated intra-abdominal infections remains unclear. Antibiotics that lack specific activity against *Enterococcus* are often used successfully in the therapy of peritonitis, and the organism is not often recovered as a blood-borne pathogen in IAS [9]. The role of fungi in the formation of intra-abdominal abscesses is not fully understood. Some authors suggest that bacteria and fungi exist as nonsynergistic parallel infections with incomplete competition, allowing the survival of all organisms. In this setting, treatment of the bacterial infection alone may lead to an overgrowth of fungi, which may contribute to increased morbidity [10–12].

The current approach to IAI and sepsis targets early correction of the underlying process, administration of systemic antibiotics, and supportive therapy to prevent or limit secondary complications due to organ system failure. Early control of the septic source is mandatory and can be achieved operatively and nonoperatively. Nonoperative interventions include percutaneous abscess drainage, as well as percutaneous and endoscopic stent placements. Operative management addresses the need to control the infectious source and to purge bacteria and toxins. The type and extent of surgery depends on the underlying disease process and the severity of intra-abdominal infection. Some rare, nonsurgical causes of intra-abdominal sepsis include the following:

- *Chlamydia* peritonitis
- Tuberculosis peritonitis
- Acquired immunodeficiency syndrome (AIDS)-associated peritonitis

Common organisms cultured in secondary peritonitis are presented in Table 4.2 [8, 13].

The most common cause of postoperative IAI is anastomotic leak, with symptoms generally appearing around postoperative days 5–7 [12]. After elective abdominal operations for noninfectious etiologies, the incidence of SP (caused by anastomotic disruption, breakdown of enterotomy closures, or inadvertent bowel injury) should be less than 2%. Operations for inflammatory disease (i.e.,

Table 4.2 Microbial flora of SP

Type	Organism
Aerobic	
Gram-negative	*E. coli* (60%), *Enterobacter*/*Klebsiella* (20%), *Proteus* (22%), *Pseudomonas* (8%)
Gram-positive	Streptococci (28%), enterococci (17%), staphylococci (7%)
Anaerobic	*Bacteroides* (72%), *Eubacteria* (24%), *Clostridia* (17%), peptococci (11%)
Fungi	*Candida* (2%)

appendicitis, diverticulitis, cholecystitis) without perforation carry a risk of less than 10% for the development of SP and peritoneal abscess. This risk may rise to greater than 50% in gangrenous bowel disease and visceral perforation [12].

After operations for penetrating abdominal trauma, SP and abscess formation are observed in a small number of patients. Duodenal and pancreatic involvements, as well as colon perforation, gross peritoneal contamination, perioperative shock, and massive transfusion, are factors that increase the risk of infection in these cases.

4.2 High-Risk Factors for IAS

In general, patients in high risk are those who have elevated chances of acquiring and failing IAS treatment. Many factors are associated with these conditions and need to be identified quickly as the effective management of this specific sick population requires the early use of broad-spectrum empirical antimicrobial therapy. The increased mortality associated with inappropriate empiric antibiotic therapy cannot be reversed by subsequent modifications. Therefore knowledge of the patient's risk is essential to begin treatment as soon as possible with the most appropriate regimen. Table 4.3 shows some examples of patients on high risk of developing IAS and treatment failure. Among intra-abdominal infections, postoperative peritonitis is a life-threatening infection and carries a high risk of complications and mortality.

High-risk patients can also be stratified through using NICE risk stratification tool for adult patients over with suspected sepsis as demonstrated in Table 4.4. Although it is primarily described for sepsis in general, it can also be used for IAS [14]. According to NICE guideline:

1. Use the person's history and physical examination results to grade the risk of severe illness or death from sepsis.
2. Recognize that adults with suspected sepsis and any of the symptoms or signs below are at high risk of severe illness or death from sepsis:
   - Objective evidence of new altered mental state
   - Respiratory rate of 25 breaths/min or above or new need for 40% oxygen or more to maintain oxygen saturation more than 92% (or more than 88% in known chronic obstructive pulmonary disease)
   - Heart rate of 130 beats/min or above

Table 4.3 High-risk patients on developing IAS and treatment failure

High-risk factors for IAS
Delay in the diagnosis and initial intervention
Extremes of age (under 1 year and older 75 years) or people who are very frail
Impaired immune system due to illness or drugs, chemotherapy, immunosuppressant use
Recent surgical procedure (past 6 weeks)
Any degree of organ dysfunction or presence of malignancy
Poor nutrition status and low albumin level
High severity of illness (APACHE II ≥ 15)
Degree of peritoneal involvement or diffuse peritonitis
Inability to achieve adequate debridement or control sepsis source
Pregnant women, have given birth, or had termination of pregnancy or miscarriage (past 6 weeks)

Table 4.4 NICE risk stratification tool for adult patients over with suspected sepsis

Category	High-risk criteria
History	Acute deterioration of functional ability, objective evidence of altered mental state
Respiratory	≥25 rpm, need of oxygen support to keep saturation over 92%
Systolic blood pressure	≤90 mmHg
Circulation	>130 bpm, oligoanuria, peripheral hypoperfusion
Temperature	High (>40 °C) or low (<36 °C)
Skin	Mottled, cyanosis, non-blanching rash of the skin, abdominal signs of infection or necrosis

- Systolic blood pressure of 90 mmHg or less or systolic blood pressure more than 40 mmHg below normal
- Not passed urine in previous 18 h (for catheterized patients, passed less than 0.5 mL/kg/h)
- Mottled or ashen appearance
- Cyanosis of the skin, lips, or tongue and non-blanching rash of the skin

3. Recognize that adults with suspected sepsis and any of the symptoms or signs below are at moderate to high risk of severe illness or death from sepsis:
   - History of new-onset changed behavior or change in mental state, as reported by the person, a friend, or relative
   - History of acute deterioration of functional ability
   - Impaired immune system (illness or drugs, including oral steroids)
   - Trauma, surgery, or invasive procedure in the past 6 weeks
   - Respiratory rate of ≥25 breaths/min, heart rate ≥130 beats/min, or new-onset arrhythmia
   - Systolic blood pressure of ≤90 mmHg
   - Not passed urine in the past 18 h (for catheterized patients, passed 0.5 mL/kg/h)
   - Temperature less than 36 °C or higher than 40 °C
   - Signs of potential infection, including increased redness, swelling or discharge at a surgical site, or breakdown of a wound [14]

Table 4.5 Antibiotic regimens that can be used for initial empiric treatment in IAS high-risk patients

Regimen	Community-acquired infection	Healthcare-associated infection
Single agent	Imipenem, meropenem, piperacillin-tazobactam	Goal-directed (based on culture) complex multidrug regimens are recommended
Combination	Cefepime, ceftazidime, ciprofloxacin, or levofloxacin, each in combination with metronidazole	

In high-risk patients, the normal flora may be modified, and intra-abdominal infections may be caused by several unexpected pathogens and by more resistant flora, which may include methicillin-resistant *Staphylococcus aureus*, enterococci, *Pseudomonas aeruginosa*, extended-spectrum β-lactamase (ESBLs)-producing *Enterobacteriaceae*, and *Candida* spp. In these infections antimicrobial regimens with broader spectrum of activity are recommended, because adequate empirical therapy appears to be important in reducing mortality [15, 16].

Healthcare-associated infections are commonly caused by more resistant flora, and for these infections, complex multidrug regimens are always recommended. Although the transmission of multidrug resistant organisms is most frequently documented in acute care facilities, all healthcare settings are affected by the emergence and transmission of antimicrobial-resistant microbes. Table 4.5 suggests antibiotic regimens that can be used for initial empiric treatment in high-risk patients [15–17].

4.3 Prognostic Factors for Patients with IAS Diagnosis

Over the past decade, the combination of better antibiotic therapy, more aggressive intensive care, and earlier diagnosis and therapy with a combination of operative and percutaneous techniques have led to a significant reduction in morbidity and mortality related to intra-abdominal sepsis.

Uncomplicated SP and simple abscesses carry a mortality rate of less than 5%, but this rate may increase to greater than 30–50% in severe infections. The overall mortality rate related to intra-abdominal abscess formation is less than 10–20%. Factors that independently predict worse outcomes include advanced age, poor nutrition status, presence of malignancy, a high APACHE II score on presentation, preoperative organ dysfunction, the presence of complex abscesses, and failure to improve in less than 24–72 h after adequate therapy. The concurrent development of sepsis, SIRS, and MOF can increase the mortality rate to greater than 70%, and, in these patients, more than 80% of deaths occur with an active infection present [5, 6].

Soriano et al. found that cirrhotic patients with SP who underwent surgical treatment tended to have a lower mortality rate than did those who received medical therapy only (53.8% vs 81.8%, respectively) [18]. Among the surgically treated

patients with SP, the survival rate was greater in those with the shortest time between diagnostic paracentesis and surgery. These researchers concluded that the prognosis of cirrhotic patients with SP could be improved via a low threshold of suspicion.

4.3.1 Other Factors Affecting Prognosis

Several scoring systems (e.g., APACHE II, SIRS, multiple organ dysfunction syndrome [MODS], Mannheim peritonitis index) have been developed to assess the clinical prognosis of patients with peritonitis. Most of these scores rely on certain host criteria, systemic signs of sepsis, and complications related to organ failure. Although valuable for comparing patient cohorts and institutions, these scores have limited value in the specific day-to-day clinical decision-making process for any given patient. In general, the mortality rate is less than 5% with an APACHE II of less than 15 and rises to greater than 40% with scores above 15. Rising APACHE II scores on days 3 and 7 are associated with an increase of mortality rates to greater than 90%, whereas falling scores predict mortality rates of less than 20% [5, 6, 13].

The mortality rate without organ failure generally is less than 5% but may rise to greater than 90% with quadruple organ failure. A delay of more than 2–4 days in instituting either medical therapy or surgical therapy has been clearly associated with increased complication rates, the development of tertiary peritonitis, the need for reoperation, multiple organ system dysfunction, and death. Outcomes are worse in patients requiring emergent reoperations for persistent or recurrent infections (30–50% increase in the mortality rate); however, patients undergoing early planned second-look operations do not demonstrate this trend.

Persistent infection, recovery of enterococci, and multidrug-resistant gram-negative organisms, as well as fungal infection, are related to worse outcomes and recurrent complications. Patients older than 65 years have a threefold increased risk of developing generalized peritonitis and sepsis from gangrenous or perforated appendicitis and perforated diverticulitis than younger patients and are three times more likely to die from these disease processes [19]. Older patients with perforated diverticulitis are three times more likely than younger patients to have generalized rather than localized (i.e., pericolic, pelvic) peritonitis. These findings are consistent with the hypothesis that the biologic features of peritonitis differ in elderly persons, who are more likely to present with an advanced or more severe process than younger patients with peritonitis.

Overall, studies suggest that host-related factors are more significant than the type and source of infection with regard to the prognosis in intra-abdominal infections [1, 3, 6, 8].

Conclusion

Early recognition of high-risk factors in patients with IAS is essential for improved management, better prognosis, and therefore lower mortality in this critical scenario. Factors that independently predict worse outcomes include advanced age, poor nutrition status, presence of malignancy, a high APACHE II

score on presentation, preoperative organ dysfunction, the presence of complex abscesses, and failure to improve in less than 24–72 h after adequate therapy. The concurrent development of sepsis, SIRS, and MOF can increase the mortality rate to greater than 70%, and, in these patients, more than 80% of deaths occur with an active infection present.

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5 Acute Appendicitis: What Is the Best Strategy to Treat Acute Appendicitis (Both Complicated and Uncomplicated)?

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5.1 Introduction

Acute appendicitis is the most frequent surgical emergency in western countries [1], more frequently affecting young people with the greatest incidence in the 10–19 age range [1]. Nonetheless, acute appendicitis is not uncommon in elder patients up to even more than 90 years of age. Because of longer life spans and better diagnostic testing with improved technology including the increased use of CT scans over the last few decades [1], early and easier detection has increased effective treatment and improved successful outcomes. Complicated acute appendicitis is defined as gangrenous or perforated appendix and/or when a purulent collection, abscess, or diffuse peritonitis is present. This definition is in accordance with a score ≥2 on the laparoscopic grading system of acute appendicitis described by Gomes and colleagues [2].

The best strategy for the treatment of acute appendicitis begins with an accurate diagnosis which is of utmost importance when acute appendicitis is suspected. In fact, despite its high frequency as a surgical emergency, a correct diagnosis may be challenging especially in females of childbearing age, in which negative intraoperative findings are still as high as 34% [3]. In such cases, gynecological diseases, like hemorrhagic corpus luteum as well as pelvic inflammatory disease, are the main different causes of right iliac fossa pain. In elderly as well, two more common pathologies must be excluded: the adenocarcinoma of the right colon and the

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diverticular disease of the sigmoid colon. In this interest, laparoscopy offers superior visualization of the peritoneal cavity compared to the McBurney laparotomy in the diagnosis of alternative diseases in cases of normal appendices.

Laparoscopic appendectomy (LA) was first described back in 1983 by Semm [4] and today represents state-of-the-art care in cases of acute appendicitis worldwide [5, 6]. Although trials show LA to be superior to open appendectomy (OA) due to shortened hospital stays, lower complication rates, and earlier returns to work/normal activity [7–12], the higher costs of LA still limit its widespread use thus far. Most of the increased costs involve the employment of staplers and disposable devices [13, 14], even if various accepted and safe options have been described to secure the stump, such as metal and nonabsorbable polymeric clips as well as endoloops or intracorporeal knots [15, 16]. The cost issue is not of secondary importance when considering a surgical approach. In this instance, a recent paper emphasized the need to improve quality while reducing the costs of emergency general surgery [17]. Nonetheless, costs may vary largely, and outcomes can be influenced by both technique and surgical ability. Therefore, standardizing a low-cost, safe, and effective technique for laparoscopic appendectomy may improve the outcomes while reducing costs [18].

5.2 Surgical Perspectives

With the intent to greatly improve the impact of surgery, further progress in laparoscopy has been made by single-incision laparoscopic surgery (SILS). SILS appendectomy was first described in 1992 by Pelosi [19]. Through a single incision, usually transumbilical, a multichannel port is applied, and the operation is then performed with curved instruments to permit work within very small operative spaces. Since surgical evidence is hidden within the umbilicus, transumbilical SILS has the great advantage of leaving no visible exterior abdominal scars. Despite the undisputed cosmetic results related to the reduced number of incisions and trocars, there is no unanimous consensus regarding postoperative pain and recovery times [20–23]. In fact, although there is a smaller skin incision in SILS, the instance of postoperative pain may correlate more closely with the inflammatory process around the appendix rather than with the surgical approach [24]. The use of bent instruments and the coaxiality between them associated with the decreased space in which the instruments operate are all factors that raise the difficulty level of the operation, correlate with longer surgical times, and may also increase the risk of postoperative complications [22]. Another important drawback of SILS is the possibility to use a drain. The decision to put a drain at the end of an SILS procedure requires an additional trocar through which the drain is inserted because the placement of a drain via the umbilicus should be avoided due to the increased risk of wound infection [25, 26]. Similar to LA, the increased cost is the major disadvantage that limits this practice [22, 27]. Therefore, a novel SILS technique modified by the introduction of a single port made of a surgical glove has lately been described by several authors [21, 28] with the intent to make SILS equally or less expensive than classic LA [22, 27]. Also, surgical glove port SILS has advantages with respect to conventional SILS: a larger operating space allowed by the surgical glove port and a reduced coaxiality between instruments [29].

Conclusions

Today LA represents, where resources and skills are available, the standard of care for the treatment of either acute complicated or uncomplicated appendicitis with reported conversion rates even as low as 0–1.3% [30–32]. By contrast, SILS appendectomies should be considered for the minimally invasive treatment of acute appendicitis in selected cases at centers capable of this technique.

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Acute Cholecystitis

6

Paola Fugazzola, Federico Coccolini, Giulia Montori, Cecilia Merli, Michele Pisano, and Luca Ansaloni

6.1 Introduction

According to the third National Health and Nutrition Examination Survey, 6.3 million men and 14.2 million women aged 20–74 years old in the United States had gallbladder disease [1–5].

Despite the presence of several studies, meta-analysis, and guidelines, definition, diagnosis, and treatment of acute cholecystitis (AC) are still debated issues. The 2007 and 2013 Tokyo guidelines (TG) attempted to resolve these problems and to establish objective parameters for the diagnosis of AC [6, 7]. However, controversies are still present in the diagnostic value of single ultrasound (US) signs, in the timing of surgery, in the need to diagnose potential associated biliary tree stones during AC, in treatment options, in the type of surgery, in definition and management of high surgical risk patients, and in the role of cholecystostomy. In order to resolve these controversies, the World Society of Emergency Surgery (WSES) developed the 2016 WSES guidelines for acute calculous cholecystitis (ACC) [8].

6.2 Definition

Before 2007, year of the first publication of the TG for AC, there were no definite and clear diagnostic criteria for AC. The TG defined AC as:

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Table 6.1 Diagnostic criteria for acute cholecystitis according to TG

(A)	Local signs of inflammation
	1. Murphy's sign
	2. RUQ mass, pain, or tenderness
(B)	Systemic signs of inflammation
	1. Fever
	2. Elevated CRP
	3. Elevated WBC count
(C)	Imaging findings
	Imaging findings characteristic of acute cholecystitis
Definitive diagnosis	
	One item in A + one item in B + C

RUQ right upper quadrant, *CRP* C-reactive protein, *WBC* white blood cells; modified from Ref. 7

an acute inflammatory disease of the gallbladder, often attributable to gallstones, but many factors, such as ischemia, motility disorders, direct chemical injury, infections by microorganism, protozoon and parasites, collagen disease, and allergic reaction are also involved [9].

AC is caused by the presence of gallstones in almost the totality of cases. According to the TG, a diagnosis of AC can be made when all these three proposed criteria are satisfied [7, 10] (see Table 6.1):

1. The presence of local inflammation, represented by the presence of right upper quadrant pain and Murphy's sign; this sign has a high specificity (79–96%) but a poor sensitivity (50–65%): although it is the most famous and considered pathognomonic sign for gallbladder diseases, it cannot be used as a single item in making diagnosis [7].
2. The presence of systemic inflammation, represented by fever or elevated white blood cell count or C-reactive protein level [7].
3. Imaging findings characteristic of AC [7].

According to WSES guidelines, there is no single clinical or laboratory finding with sufficient diagnostic accuracy to establish or exclude AC, and only a combination of detailed history, complete clinical examination, laboratory tests, and imaging investigation may strongly support the diagnosis of AC, although the best combination is not yet known [8].

6.3 Imaging

US is the gold standard imaging technique for AC because of its lower cost, better availability, and lack of invasiveness [8, 11]. The TG recommended it as the first step in diagnosis too, and the diagnostic signs were identified as an enlarged gallbladder, a thickened wall greater than 5 mm, the presence of stones, the debris echo, and the US Murphy's sign. In the study by Hwang et al. [12], a sensitivity of 54% and a specificity of 81% were reported by using the combination of sonographic

Murphy's sign, gallbladder wall thickening greater than 3 mm, pericholecystic fluid collection as major criteria, and hepatic biliary dilation and gallbladder hydrop as minor criteria. In the study by Borzellino et al. [13], distension of the gallbladder, wall edema, and pericholecystic fluid collection were adopted as the criteria for the diagnosis of AC. The presence of at least one of these three criteria from US resulted in a sensitivity of 83.7% and a specificity of 47.7%. Therefore US alone seems to be of limited utility to diagnose or exclude the diagnosis of AC.

Diagnostic accuracy of computed tomography (CT) is poor, while diagnostic accuracy of magnetic resonance imaging (MRI) is comparable to US, but it is poorly applicable in urgency contest. Hepatobiliary iminodiacetic acid scan (HIDA scan) has the highest sensitivity and specificity for AC, although its scarce availability, long time required to perform the test, and exposure to ionizing radiation limit its use [8].

6.4 Acute Calculous Cholecystitis (ACC)

In high- and intermediate-income countries, 10–15% of the adult population are affected by gallstones, and AC occurs in 10–20% of untreated patients [8].

6.4.1 Classification

The TG suggested a classification for AC, structured in three different levels of severity, based on the characteristic of the acute inflammatory process [7]:

1. Grade III, *severe AC*: an AC associated with organ dysfunction.
   (a) Cardiovascular dysfunction: Hypotension with dopamine >5 μg/kg per min or norepinephrine, any dose
   (b) Neurological dysfunction: Decreased level of consciousness
   (c) Respiratory dysfunction: PaO_2/FiO_2 ratio < 300
   (d) Renal dysfunction: Oliguria, creatinine > 2.0 mg/dL
   (e) Hepatic dysfunction: PT-INR > 1.5
   (f) Hematological dysfunction: Platelet count < 100,000/mm^3
2. Grade II, *moderate AC*, associated with any one of the following conditions:
   (a) Elevated white blood cell count (>18,000/mm^3)
   (b) Palpable tender mass in the right upper abdominal quadrant
   (c) Duration of complaints >72 h
   (d) Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis)
3. Grade I, *mild AC*, does not meet the criteria of "Grade III" or "Grade II" AC: Grade I can also be defined as AC in a healthy patient with no organ dysfunction and mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure.

This clinical classification was the first attempt to create an international grading system in order to standardize data and patients characteristics and to choose the best treatment option. However these criteria are based mainly on the characteristics of the local acute inflammatory process taking little account of the patient's clinical characteristics and risk factors [14].

6.4.2 Common Bile Duct Stones Associated to Acute Calculous Cholecystitis

In patients with ACC, the presence of a concomitant lithiasis of the common bile duct (CBD) is reported in literature ranging from 8.7% to 25% [15–17]. Liver biochemical tests, including ALT, AST, bilirubin, ALP, and gamma-glutamyl transferase (GGT), should be performed in all patients with AC to assess the risk for CBD lithiasis [8]. The treatment of CBD stones can be performed before, during, or after the cholecystectomy: if performed before, the suspected choledocholithiasis is one of the major factors implicated in the delaying of surgery. The TG didn't analyze this problem, while the ASGE (American Society for Gastrointestinal Endoscopy) guidelines for the choledocholithiasis are a very useful tool, even if not specific for ACC [18]. These guidelines created a stratification for the risk of choledocholithiasis (high, >50%; intermediate, 10–50%; low, <10%) based on moderate, strong, and very strong predictive factors (see Table 6.2). As a consequence, the choledocholithiasis management suggested was based on the predicted risk: in case of low risk, no further investigations were recommended; in case of high risk, ERCP before surgery was suggested; and in case of intermediate risk, preoperative endoscopic US or MRCP or intraoperative cholangiography or a laparoscopic US of the CBD was suggested depending on the local expertise and availability; if positive, ERCP was recommended (see Fig. 6.1).

Table 6.2 ASGE predictive factors and risk classes for choledocholithiasis

Predictive factor for choledocholithiasis	
Very strong	Evidence of CBD stone at abdominal ultrasound
Strong	Common bile duct diameter > 6 mm (with gallbladder in situ)
	Total serum bilirubin > 4 mg/dL
	Bilirubin level 1.8–4 mg/dL
Moderate	Abnormal liver biochemical test other than bilirubin
	Age older than 55 years
	Clinical gallstone pancreatitis
Risk class for choledocholithiasis	
High	Presence of any very strong
Low	No predictors present
Intermediate	All other patients

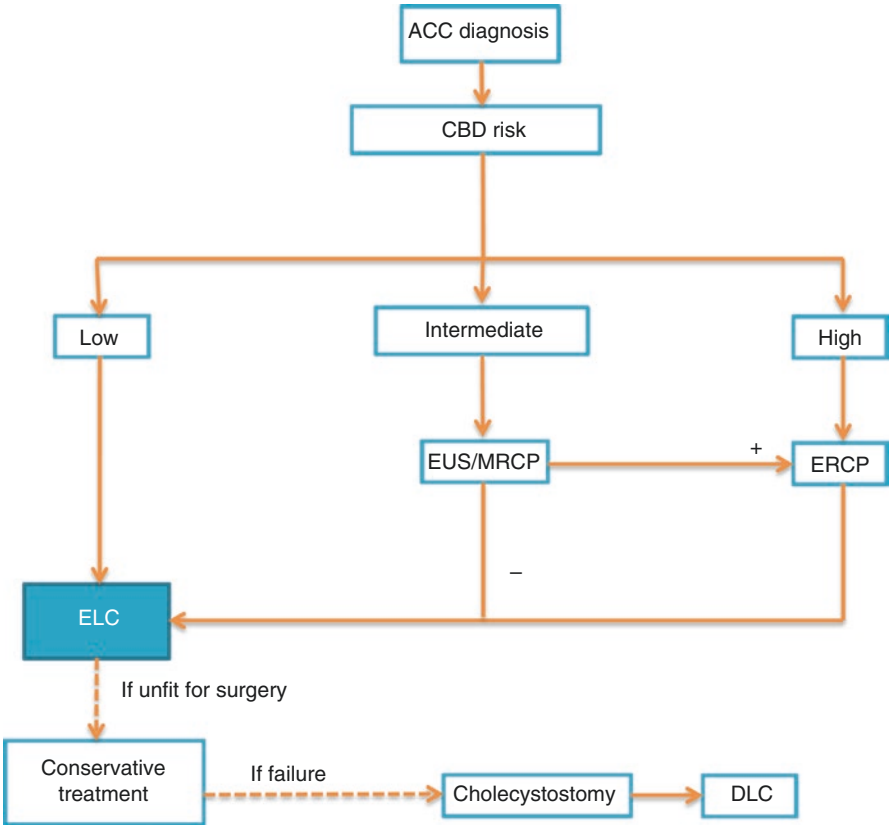

Fig. 6.1 Comprehensive WSES algorithm for the treatment of acute calculous cholecystitis. *ACC* acute calculous cholecystitis, *CBD* common bile duct calculus, *ELC* early laparoscopic cholecystectomy, *ERCP* endoscopic retrograde cholangiopancreatography, *EUS* endoscopic ultrasound, *MRCP* magnetic resonance cholangiopancreatography, *DLC* delayed laparoscopic cholecystectomy

6.4.3 Treatment

6.4.3.1 Surgical Therapy

In the second half of the 18th century, AC started to be treated by Petit with a cholecystostomy with a permanent biliary fistula; at the end of the 19th century, precisely in 1882, the first open cholecystectomy was performed by Langenbuch, and the removal of gallbladder during the initial hospitalization became the gold standard for symptomatic cholelithiasis [19]. During the prelaparoscopic era, several studies found that the better treatment was early open cholecystectomy within 7 days from the onset of symptoms, also in order to reduce rehospitalization for the high rate of recurrence [20, 21]. With the advent of laparoscopy, laparoscopic cholecystectomy (LC) became the gold standard technique. During these years, a lot of reports, case series, and RCTs have been published in order to define which is the

better timing for laparoscopic cholecystectomy in AC, early (ELC) or delayed (DLC).

Tokyo Guidelines

The TG suggested a treatment flowchart based on the clinical classification of AC [22]:

(a) Grade I AC: antibiotic therapy plus ELC is recommended.
(b) Grade II AC: the TG recommend to treat conservatively the acute inflammation with antibiotic therapy and program DLC; a percutaneous gallbladder drainage (percutaneous cholecystostomy, PC) is recommended if antibiotic therapy fails; surgery is recommended only if essential in emergency. ELC in this setting is contemplated only if advanced laparoscopic expertise is available.
(c) Grade III AC: PC plus antibiotic therapy is indicated.

In the TG the treatment indications were based more on the acute inflammatory process than on the patient clinical conditions. However, the advocated association between inflammatory status and difficulty of surgery was supported by weak evidences. Furthermore, the indications to PC in TG were not clear [23] because it was recommended in Grade III AC and sometimes in Grade II AC [22], but also as a safe option in high-risk patients with less severe AC who were considered poor surgical candidates or when a difficult dissection was encountered. Lastly the TG didn't give any indications on CBD stone management.

WSES Guidelines

WSES proposed an evidence-based flowchart for the treatment of AC [8] (Fig. 6.1).

According to WSES guidelines, surgery is recommended as a decisive treatment during the first hospital admission unless contraindicated. All the cholecystectomies should be started with laparoscopic technique unless there are contraindications; for the optimal timing for surgery, evidences show that there is not a strict limit, so ELC should be performed on an "as soon as possible" basis. If the patient is unfit for surgery, he/she should receive a conservative medical treatment with antibiotic. In patients where surgery is not indicated, if there isn't a resolution of the clinical setting after 48 h of medical therapy, PC with the percutaneous transhepatic technique is indicated, and a later surgical evaluation after 60 days from discharge for possible cholecystectomy should be planned.

Regarding the assessment of the risk for choledocholithiasis, after an evaluation for the presence of peritonitis, a condition that leads the patient to an emergency operation, WSES guidelines suggest to consider the ASGE guidelines. With a low risk, if the patient is eligible for surgery, ELC should be performed as soon as possible. If the patient is unfit for surgery, he/she should receive antibiotic therapy and eventually PC, if the medical treatment is ineffective after 48 h. Patient at high risk for choledocholithiasis should undergo directly ERCP or, if ERCP is ineffective, a surgical exploration of the CBD. Patients with intermediate risk have to be evaluated with MRCP or endoscopic US, based on the availability of the staff, to select patients who should receive ERCP. Either patients at high risk or those at

intermediate one, after diagnostic evaluation, if fit for surgery, should receive ELC or should be treated conservatively with antibiotic therapy if unfit [8].

Patients Selection for Surgery

In AC the severity of clinical setting and its life-threatening potential are strongly determined by the general status of the patient. For example, the patient's age above 80 and the coexistence of diabetes mellitus are major risk factors for worse clinical outcome, morbidity, and mortality. Currently, there is no evidence of the existence of any accurate scores in identifying patient's risk in surgery for AC in order to declare a patient fit or unfit for ELC. The only available risk assessment scores comparison (ASA vs APACHE II vs POSSUM) is limited to the perforated AC, and it found a significant association of the three scores with morbidity and mortality. APACHE II seems to be the best risk predictor [24], but it is built to predict morbidity and mortality in patients admitted to the ICU: its use as a preoperative score should be considered as an extension usage from the original concept. Therefore, prospective and multicenter studies to compare different risk factors and scores are necessary [8].

Timing for Surgery

Several randomized controlled trials have investigated ELC versus DLC [25–33]. The problem is that early and delayed laparoscopic cholecystectomies have been defined differently in different trials. In general, ELC has been defined variably as performed in patients with symptoms from less than 72 h or from less than 7 days but within 4–6 days from diagnosis. This roughly translates to 10 days from onset of symptoms. The DLC is defined variably as performed between 7 days to 45 days and performed at least 6 weeks after initial diagnosis. According to several meta-analyses [34–37], ELC and DLC aren't different in terms of conversion rate to open cholecystectomy or in terms of CBD injury, but a significant decrease in total hospital stay and a more cost-effective approach were found in the ELC group.

A great debate still exists regarding the best timing for ELC: historically the limit of 72 h for its performance has been reported. However it is not always clear if it is considered from the onset of symptoms or from hospital admission. Despite the presence of large studies showing that better results could be obtained with a limit of 48 h from admission [38, 39], other studies cannot individuate an exact time limit [40–43]. However, it should be noted that earlier surgery is associated with shorter hospital stay and fewer complications, and it is cost-effective [8, 38, 44–47].

WSES guidelines stated that ELC is preferable to DLC, and ELC should be performed as soon as possible up to 10 days from the onset of symptoms [8].

Conversely ELC should not be offered for patients beyond 10 days from the onset of symptoms unless there is worsening peritonitis or sepsis warrants an emergency surgical intervention. In people with more than 10 days of symptoms history, delaying cholecystectomy after 45 days is better than immediate surgery [8].

Despite the presence of these evidences, up to 80% of patients with AC do not receive the definitive surgical treatment during the first hospital admission [48–52], increasing costs and hospitalization without clinical advantages.

Type of Surgery

According to both Tokyo and WSES guidelines in AC, a laparoscopic approach should initially be attempted except in case of absolute anesthesiology contraindications or septic shock [8]. Laparoscopic cholecystectomy (LC) for AC is safe, feasible, with a low complication rate, and associated with shorter hospital stay [53–62]. Among high-risk patients, in those with Child A and B cirrhosis, in those with advanced age > 80, or in pregnant women, laparoscopic cholecystectomy is feasible and safe [8]. Indication to LC in patients with Child C cirrhosis is not clear [63–66], and as a first recommendation, cholecystectomy should be avoided in these patients, unless clearly indicated, such as in AC not responding to antibiotics [66].

According to WSES guidelines, subtotal cholecystectomy (laparoscopic or laparotomic) is a valid option for advanced inflammation, gangrenous gallbladder, or in any situations in which anatomy is difficult to recognize and main bile duct injuries are more likely.

Furthermore in case of local severe inflammation, adhesions, bleeding in Calot's triangle, or suspected bile duct injury, conversion to open surgery should be strongly considered.

6.4.3.2 Antibiotic Therapy

Although surgery is the gold standard in the treatment of AC, antibiotics are an important component in its management, in association with ELC or DLC for fit-for-surgery patients or alone for high-risk patients [67, 68].

In association with surgery, antibiotics are always recommended in complicated cholecystitis and in delayed management of uncomplicated cholecystitis. Patients with uncomplicated cholecystitis can be treated without postoperative antibiotics when the focus of infection is controlled by cholecystectomy. In complicated cholecystitis, the antimicrobial regimens depend on presumed pathogens involved and risk factors for major resistance patterns [8]. Organisms most often involved in biliary infections are the gram-negative aerobes, *Escherichia coli* and *Klebsiella pneumoniae*, and anaerobes, especially *Bacteroides fragilis* [69, 70]. In immunosuppressed patients, enterococcal infection should always be presumed and treated [71]. Healthcare-related infections are commonly caused by more resistant strains. For these infections, complex regimens with broader spectra are recommended as adequate empiric therapy appears to be a crucial factor affecting postoperative complications and mortality rates, especially in critically ill patients [71]. In Table 6.3 are reported antimicrobial regimen suggested by WSES for AC.

However, microbiological analyses are helpful in designing targeted therapeutic strategies for individual patients, mostly in patients at high risk for antimicrobial resistance [8].

6.4.3.3 Percutaneous Cholecystostomy

Gallbladder drainage decompresses the infected bile or pus in the gallbladder, removing the infected collection without removing the gallbladder. The removal of the infected material, in addition to antimicrobial therapy, can result in a reduced inflammation with an improvement of the clinical condition [8]. The TG considered

Table 6.3 Antimicrobial regimens suggested for acute calculous cholecystitis

Community acquired	
Beta-lactam/beta-lactamase inhibitor combination-based regimens	Amoxicillin/clavulanate (in stable patients) Ticarcillin/clavulanate (in stable patients) Piperacillin/tazobactam (in unstable patients)
Cephalosporin-based regimens	Ceftriaxone + metronidazole (in stable patients) Cefepime + metronidazole (in stable patients) Ceftazidime + metronidazole (in stable patients) Cefozopran + metronidazole (in stable patients)
Carbapenem-based regimens	Ertapenem (in stable patients) Imipenem/cilastatin (only in unstable patients) Meropenem (only in unstable patients) Doripenem (only in unstable patients)
Fluoroquinolone-based regimens (in case of allergy to beta-lactams)	Ciprofloxacin + metronidazole (only in stable patients) Levofloxacin + metronidazole (only in stable patients) Moxifloxacin (only in stable patients)
Glycylcycline-based regimen	Tigecycline (in stable patients if risk factors for ESBLs)
Healthcare associated	
In stable patients	Tigecycline + piperacillin/tazobactam
In unstable patients	Imipenem/cilastatin ± teicoplanin Meropenem ± teicoplanin Doripenem ± teicoplanin

the gallbladder drainage as mandatory in severe grade AC and also suggested its use in the moderate grade if conservative treatment fails. Furthermore the TG stated PC as an effective option in critically ill patients, especially in elderly patients and in patients with complications. However the role of PC is difficult to be determined because the "high-risk patients" definition is still unclear.

According to WSES guidelines, gallbladder drainage, and in particular percutaneous transhepatic gallbladder drainage (PTGBD), together with antibiotics, can convert a septic cholecystitis into a non-septic condition. It could be considered as a possible alternative to surgery after the failure of conservative treatment, after a variable time of 24–48 h, in a small subset of patients unfit for emergency surgery due to their severe comorbidities [8]. However the level of evidence is poor [8]. At

the moment a randomized controlled trial comparing PC with ELC in critically ill patients (APACHE score 7–14) with AC (the CHOCOLATE trial) is ongoing [72]: this will clarify the real role of PC (1a).

Mortality following the procedure is high (15%) but generally it is related to the severity of the underlying disease process [23]. The need for delayed cholecystectomy after PC also remains controversial: because approximately 40% of patients will have recurrent biliary tract disease within 1 year following PC [73], the surgical approach could be considered as an option.

6.5 Acute Acalculous Cholecystitis (AAC)

AAC is an acute inflammatory disease of the gallbladder without evidence of gallstones and represents 2–15% of all AC. The first case was reported in 1844 by Ducan et al. This disease is burdened with a higher mortality than AC that ranges from 10% to 90% (in opposite to 1% of AC) that is often related to the delay in diagnosis [74].

6.5.1 Pathogenesis and Diagnosis

AAC occurs often in hospitalized patients and arises in 0.2–0.4% of all critically ill patients. It is due to two main mechanisms: ischemia and bile stasis. There are many possible causes: shock, hypovolemia, heart failure, myocardial ischemia, dehydration, diabetes mellitus, abdominal vasculitis, malignant diseases, abdominal surgery, cholesterol embolization, sepsis with visceral arterial hypoperfusion, and cerebrovascular disease. Moreover, also fever, fasting, and dehydration alone (typical conditions of the ICU patients) can result in concentration of biliary salts, bile stasis, and consequent AAC [74]. Diagnosis is often difficult because it can be masked by the patient's concomitant or primary diseases [75]. Some authors emphasized the difficulty of differential diagnosis from cardiovascular disease due to symptom overlapping. Ultrasound plays a key role in AAC diagnosis. Complications of AAC, such as empyema, gangrene, abscess, and perforation are more common than in ACC with an incidence ranging from 37% to 81% [74–76].

6.5.2 Treatment

Although cholecystectomy is generally the gold standard in any infectious disease of the gallbladder, there is only a low level of evidence about a surgical or nonsurgical approach to critically ill patients with AAC [75]. The treatment decision depends mainly on the patient's comorbidities and conditions. In low-risk patients, when the risks under general anesthesia are low, a laparoscopic approach should be the preferred surgical intervention. However, in critically ill patients with multiple comorbidities, PC provides better outcomes with lower cost, lower morbidity, and lower mortality than laparoscopic and open cholecystectomy [76]. PC is safe, rapid, and

highly efficacious in treating AAC, and it can be performed at the bedside under local anesthesia. It can represent a definitive treatment or a bridge until cholecystectomy may be safely performed. PC is contraindicated in cases of gangrene or gallbladder perforation [76]. Regarding antimicrobial therapy, these critically ill patients are more prone to infections with multiresistant bacteria [75].

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Acute Cholangitis

7

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7.1 Introduction

Acute cholangitis (AC) is a clinical syndrome, first described by Jean-Martin Charcot in 1877. AC is typically characterized by the triad of right upper quadrant abdominal pain, fever and jaundice. It is known to be the result of biliary stasis and biliary sepsis. It is also often referred to as ascending cholangitis or acute pyogenic cholangitis. AC can present as a wide spectrum of severity, from mild up to severe and life threatening. In severe cases, early diagnosis, prompt resuscitation and urgent intervention are essential to improve clinical outcomes.

7.2 Pathophysiology

AC is caused primarily by bacterial infection in a patient with biliary obstruction. Organisms typically ascend from the duodenum, hence the term ascending cholangitis. The sphincter of Oddi is a mechanical barrier to duodenal reflux and prevents ascending bacterial translocation. Bacteria are able to translocate into the biliary tract from the duodenum when normal protective mechanisms of the sphincter are disrupted. Alternatively, a hematogenous spread from the portal vein can also result in AC [1]. Bile salts themselves are also inherently bacteriostatic [2]. Its continuous flushing effect down the common bile duct (CBD) is hence protective. Bacterial colonization may also be prevented by secretory immunoglobulin A (IgA) present in bile and biliary mucous secretions.

Biliary obstruction with stasis and sepsis is the most important factor that contributes to the pathogenesis of AC. The common causes of biliary obstruction are

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biliary calculi (28–70%), benign stenosis (5–28%) and malignancy (10–57%) [3]. AC is also a common complication resulting from biliary stenting for malignant biliary obstruction [4]. When biliary obstruction occurs, there is raised intrabiliary pressure which leads to increased permeability of bile ductules and translocation of bacteria and toxins from the biliary tract into the portal circulation [3]. Elevated pressure also favours migration of bacteria from the bile into the systemic circulation, increasing the risk of septicaemia. In addition, increased biliary pressure adversely affects a number of host defence mechanisms including Kupffer cells, IgA production and bile flow [1].

The presence of CBD stone increases the risk of bacterial colonization with or without the presence of obstruction. It was found that patients with CBD stones have a higher probability of bile culture positivity than those with gallstones [5]. Culture of bile, stones and biliary stents is positive in over 90% of patients with AC, yielding a mixed growth of gram-negative and gram-positive bacteria, most commonly gut strains [6]. *Escherichia coli* is the common gram-negative bacterium isolation (25–50%), followed by *Klebsiella* (15–20%) and *Enterobacter* species (5–10%). A higher prevalence of ESBL-producing *E. coli* can also be observed in patients with hospital-acquired cholangitis [7]. The most common gram-positive bacteria are *Enterococcus* species (10–20%). Anaerobes, such as *Bacteroides* and Clostridia, are usually present as part of a mixed infection. They are rarely the sole-infecting organisms. Recovery of anaerobes appears to be more common after repeated infections or surgery on the biliary tree. The frequency of anaerobic infection is underestimated by standard culture techniques. In patients with AC who have undergone previous biliary decompression, a history of previous stent therapy was found to be a risk factor for increased antimicrobial resistance, particularly those who had undergone numerous interventional procedures prior to onset of AC [8].

7.3 Clinical Features

As described by Jean-Martin Charcot, the classic presentation of AC consists of the triad of abdominal pain, fever and jaundice. However, only 50–70% of patients present classically with all three components [9]. Charcot's triad has high specificity but low sensitivity [10]. As a result, using Charcot's triad as criteria for the diagnosis of AC is not reliable in daily clinical practice [11]. Benjamin M. Reynolds added on two more symptoms: confusion and hypotension. Reynolds pentad, as it came to be known as, is suggestive of greater severity of AC and is associated with significant mortality [12]. The higher complication rates are due to multi-organ failure. Elderly and immunocompromised patients manifest atypical presentations as they are unable to mount inflammatory response. On examination, pyrexia, tachycardia, tachypnoea, right upper abdominal tenderness and icterus are variably evident. In extreme presentations, patient may be severely dehydrated and appear as moribund. In a study involving 182 patients with AC, Lee et al. have shown that pre-existing renal dysfunction is a risk factor for organ failure [13].

7.4 Diagnosis

Reliance on Charcot's triad to diagnose AC is flawed by its low sensitivity. Hence, the Tokyo International Consensus Meeting proposed a diagnostic criteria using a combination of Charcot's triad with biochemical and imaging tests. These diagnostic criteria were then established as 'Tokyo Guidelines' TG07 [3]. However, multicentre TG07 validation study reported only a sensitivity of 82.6% and specificity of 79.8% for diagnosis of AC [14]. TG07 was then revised and is currently known as the revised Tokyo Guidelines TG13 [14]. The new criterion uses three components: (1) systemic inflammation as evidenced by fever or raised inflammatory markers, (2) cholestasis (clinical jaundice or abnormal liver function) and (3) imaging proof of biliary dilatation or evidence of aetiology on imaging. Japanese multicentre retrospective study compared new TG13 diagnostic criteria with Charcot's triad and TG07. TG13 had 91.8% sensitivity for the diagnosis of AC compared to 26.4% and 86.2% for Charcot's triad and TG07, respectively [14]. The specificity of TG13 was however 77.7% versus 95.9% and 79.8% for Charcot's triad and TG07, respectively. We foresee that these criteria are likely to be revised again in light of new 'Sepsis-3' definition and widespread adoption of the quick Sequential Organ Failure Assessment (qSOFA) score in routine clinical practice. The senior author attended the 'Updating Tokyo Guidelines Public Hearing" on 9th June 2017 at the recently concluded Joint congress of The 6th Biennial Congresss of Asian-Pacific Hepato-Pancreato-Biliary Association and the 29th Meeting of The Japanese Society of Hepato-Biliary-Pancreatic Surgery at Yokohama, Japan. It is anticipated that the revision in the form of Tokyo Guidelines 2018 (TG18) will have minor modifications. For interested physicians, video recording of Public Hearing session is available via the link http://www.aphpba2017.com/contents/updating.html. Serum procalcitonin has been shown to discriminate between mild, moderate and severe AC [15]. In a study involving 110 patients with AC, Shinya et al. have shown that high procalcitonin levels can signify the need to perform emergency biliary drainage even in patients who are categorized as mild severity by TG13 system [16]. Recently, presepsin is being reported as a biomarker for inflammation, and in a study involving 119 patients with AC, Lin et al. have shown that presepsin has good discriminatory ability to predict the severity of AC [17]. An important clinical component along with the diagnosis of AC is the identification of the offending bacteria to allow for targeted antibiotic therapy. However aerobic blood cultures are often positive in only 20–30% of patients [18, 19]. This low bacterial yield is not specific to AC but is also reported in patient with pyogenic liver abscess (PLA) [20]. In a study including 528 patients with PLA, outcomes of patients with *Klebsiella pneumoniae* infection were similar to patients with negative cultures despite demographic and clinical differences [21]. Hence it is likely that empirical treatment based on the common etiologic microorganism and local antibiogram is a reasonable clinical practice. The blood culture-positive rates are significantly lower when compared to bile culture. Bile culture is positive in around 70% of cases [18]. In addition to the rates of positive cultures, the organism species identified also vary. Blood culture usually yields monomicrobial results (*Escherichia coli* being the most frequently identified), while bile culture results are often polymicrobial [22]. Serious attempts to

identify the offending bacteria should be made because although the bacteriological profile of AC has remained stable over the last few decades, antibiotic sensitivity pattern has changed [23, 24]. In view of growing concern of global antimicrobial resistance with the emergence of multidrug resistance organisms, a task force of specialists from 79 countries recently published a position paper to actively raise awareness of healthcare workers and improve prescribing behaviours [25]. Hence each hospital should have a local antibiogram made periodically available to clinicians to guide rational and targeted antibiotic use. It is known that host antimicrobial flora can be altered with the use of proton pump inhibitor therapy. Proton pump inhibitors have been widely used for its ulcer-protective effects, and overuse or abuse can alter host microbial flora [26]. In a retrospective study including 278 patients with 318 episodes of AC, Schneider et al. have reported that the use of proton pump inhibitor therapy is associated with a 23% increase in the number of biliary pathogens, more rates of polymicrobial infections, higher incidence of oropharyngeal flora and increased need for combination antimicrobial therapy [27]. In a recently published evidence-based guidelines for management of *Clostridium difficile* infection, discontinuation of unnecessary antimicrobial agents and proton pump inhibitory therapy is recommended when *Clostridium difficile* infection is suspected (Grade 1C) [28]. Carbohydrate antigen 19-9 (CA19-9) levels are frequently performed in patients with hepatobiliary diseases, and high levels are correlated with biliary obstruction or sepsis. In a study involving 209 patient of primary sclerosing cholangitis which included 23 patients with bacterial cholangitis, Wannhoff et al. concluded that inflammation but not biliary obstruction is associated with increased CA 19-9 levels in patients with primary sclerosing cholangitis. Hence CA19-9 has no role in the diagnosis and management of patients with AC but plays the role of a complementary adjunct in cholangitis patients with biliary malignancy [29].

7.5 Causes and Severity Classification

Beyond making an accurate diagnosis of AC, it is invaluable to determine the degree of severity so as to properly triage the patient and allocate sufficient resources in line with the severity. AC has a wide spectrum of severity ranging from a self-limiting disease requiring minimal intervention to a potentially life-threatening condition with high morbidity and mortality. It has been reported that approximately 70% of patients with AC are able to achieve improvement with medical therapy alone [30]. However patients with severe AC have an estimated 10% mortality despite antimicrobial therapy and biliary drainage [31, 32]. The TG13 criteria re-evaluated the severity classification of the TG07 guidelines so as to improve its severity assessment strategies upon diagnosis, to allow for the provision of immediate source control of the infection among patients with AC [14]. The severity of AC is classified as follows: Grade III (severe), the presence of organ dysfunction; Grade II (moderate), risk of increased severity without early biliary drainage; and Grade I (mild) which is the absence of more severe grades. The severity assessment criteria are very important for determining the treatment strategy for AC, especially for

Grade II cases which may progress to Grade III without immediate intervention. Treatment of AC requires 'treatment for causes' along with the administration of antimicrobial agents and biliary drainage [14].

Another way to classify severity in patients with AC is to acknowledge its overall systemic impact as per any complicated intra-abdominal infection (cIAIs) and risk stratify them accordingly. Suitable scoring systems must be able to identify serious patients requiring care in intensive care unit (ICU), easy to calculate and have high accuracy. WSES Sepsis Severity Score is specific for cIAIs and easy to calculate and may be relevant in AC; however, it needs prospective validation [33]. In a recent study, Kim et al. evaluated the usefulness of delta neutrophil index (DNI), which reflects the fraction of circulating immature granulocytes, using specific automated blood cell analysers, as a prognostic marker for early severity in patients with AC. They found that higher DNI at admission, day 1 and day 2 post admissions were significant risk factors for 28-day mortality [34]. Schwed et al. reported that a white blood cell count greater than 20,000 cells/μL and total bilirubin level greater than 10 mg/dL (171 μmol/L) were independent prognostic factors for adverse outcomes in AC [35]. AC is surgical emergency with various causative factors, resulting in a common pathway of biliary stasis and sepsis ultimately resulting in a wide spectrum of local and systemic complications. Figure 7.1 shows classification schema of AC with distinction of primary and secondary aetiologies. Primary aetiology can be further subdivided into the more common lithiatic biliary obstruction

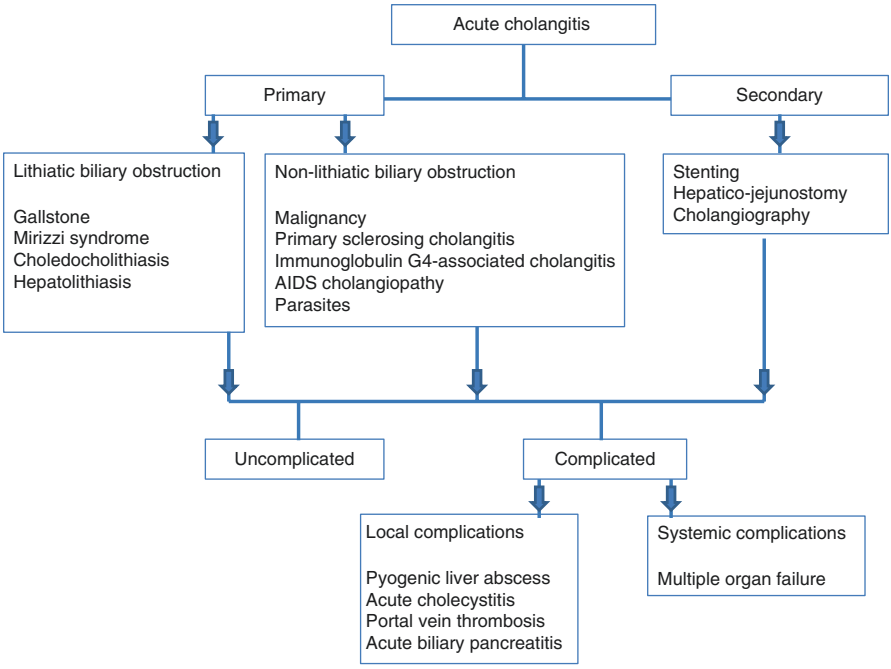

Fig. 7.1 Aetiologic classification of acute cholangitis

or the less common non-lithiatic biliary obstruction. Malignancy, either primary with origin from a hepato-pancreaticoduodenal complex or secondary nodal metastasis, can result in biliary obstruction. AC may result from biliary stricturing resulting from transarterial chemoembolization therapy for hepatocellular carcinoma.

Primary sclerosing cholangitis (PSC) is an idiopathic inflammatory process of the biliary system which will lead to fibrosis and obstruction. Elevated serum alkaline phosphatase and IgM levels are commonly detected [36]. Elevations of serum IgG4 are noted in ~10% of patients and are associated with a more rapidly progressing disease and poor response to corticosteroids [36, 37]. Anti-smooth muscle, antinuclear and anti-neutrophil cytoplasmic antibodies can be detected [37–39]. Ultrasound (US), computed tomography (CT) scan and magnetic resonance cholangiopancreatography (MRCP) scan can all demonstrate the typical obstructive picture. Liver biopsy is now seldom done to establish the diagnosis of PSC and is generally not considered necessary to establish the diagnosis [40].

7.5.1 Acquired Immunodeficiency Syndrome (AIDS)-Associated Cholangiopathy

AIDS cholangiopathy has been reported in patients infected with human immunodeficiency virus. AIDS cholangiopathy can have four distinct patterns on imaging [41, 42]. The majority (50%) present with a combination of sclerosing cholangitis and papillary stenosis. The next most common (20%) pattern is isolated intrahepatic sclerosing cholangitis like appearance. The last two patterns accounting for 15% of cases each are isolated papillary stenosis and long-segment extrahepatic duct stricture with or without concurrent intrahepatic disease.

Rarely parasitic infection such as *Ascaris lumbricoides* and *Clonorchis sinensis* may also result in biliary obstruction and dilatation and recurrent cholangitis/pancreatitis. In very rare cases, these patients may even present with AC many decades after initial parasitic infection [43, 44]. Secondary aetiologic causes of AC are prior instrumentation or biliary procedure/surgery such as biliary stenting, cholangiography or hepaticojejunostomy.

Resulting from primary or secondary causative pathways, the course of AC can be uncomplicated, necessitating minimal supportive management to a complicated course with local or systemic complications (Fig. 7.1).

7.6 Management

AC is a surgical emergency in which emergency surgery is contraindicated. Patients with AC should be admitted to hospital for close monitoring and treatment. Intravenous antibiotics and drainage of the biliary tree are the two pillars. Severe AC may be fatal if appropriate, and early medical care is not instituted. Therefore severity stratification guides in resource allocation [11]. In general, patient with mild AC may be managed with antibiotics alone. Biliary decompression is reserved for either nonresponders or more severe grades. For patients with moderate AC, early biliary decompression should be performed. In severe AC patients, an urgent

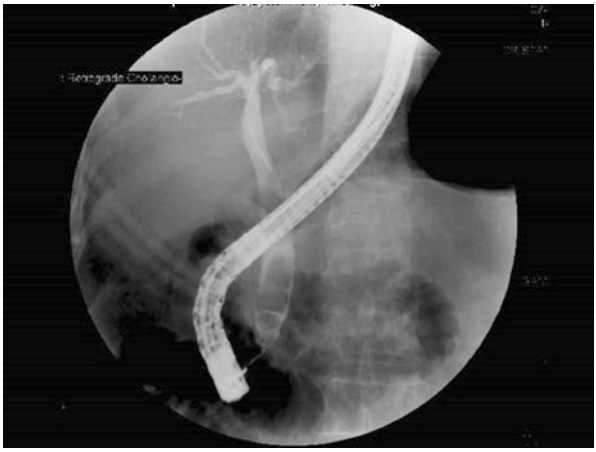

Fig. 7.2 ERCP showing multiple stones in the common bile duct

biliary decompression by endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic biliary drainage is mandatory, and this is ideally done following an initial haemodynamic resuscitation. In some instances, treatment for the etiology of AC such as choledocholithiasis can be done concurrently. Figure 7.2 shows an ERCP image of a patient with AC secondary to CBD stones. It is our policy to consider biliary decompression as a part of ongoing resuscitation in the septic patient, and we do not advocate delay in biliary decompression in hope of achieving haemodynamic normality and restoration of deranged serum biochemistry. Precious time may be lost in futile attempts to 'catch up with the haemodynamics' or 'restore the deranged serum biochemistry' or 'correct the coagulopathy'. One needs to recognize that biliary decompression is the ultimate treatment that would aid in achieving the 'normality'. Managing patients with AC needs the highest degree of attention with prompt engagement of multidisciplinary team of specialists, and quick decisions should be taken according to local resources and expertise. Multimodal care has been shown to improve outcomes in acute care surgery, and AC is no exception [20, 45–49]. The lead author advocates that sick patients should not be refuted biliary decompression citing high procedure risk for E RCP as the risk is only going to magnify with time and delay. Hence instead of 'singing the tune' of risk involved with prone position, moderate sedation, coagulopathy etc, the team should actively engage critical care specialist to secure airway, optimize oxygenation and proceed with ERCP at the immediate available opportunity.

7.6.1 Medical Management

Patients with AC may present with sepsis and even septic shock. Severe sepsis is generally managed according to the surviving sepsis guidelines [50]**.** This encompasses stabilising and supporting patient's airway, breathing and circulation, fluids and vasopressors as part of goal-directed therapies and starting empirical antibiotics after taking blood cultures. Patients with septic shock and organ dysfunction typically require high dependency or intensive care facilities to provide appropriate organ support.

7.6.2 Antibiotics

The decision on the choice of empirical antibiotics is dependent on the efficacy of the antibiotics against the common microorganisms in the biliary system, pharmacokinetic properties of the drug, severity of disease, comorbidities of patient such as renal or hepatic failure and local resistance patterns [25, 51]. In patients with biliary-enteric anastomosis, adequate anaerobic coverage is essential. In patients who have hospital-acquired infections, resistant bacteria such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci may be cultured and should be covered. As soon as the blood and bile cultures become available, more selective narrow-spectrum antibiotics should be prescribed. The duration of treatment will depend on the clinical response and guided by the trend of inflammatory markers. 70–80% of patients respond to conservative management with antibiotic therapy alone [52]. The decision regarding the initiation of antibiotics, de-escalation, duration and conversion from intravenous to oral forms should be governed by the antimicrobial stewardship programme (ASP) in the local hospital. There is now mounting evidence that adherence to ASP achieves optimum clinical outcomes in a cost-effectiveness way and at the same time reducing the harmful side-effects of drugs and importantly the emergence of antibiotic resistance. A recent meta-analysis revealed that empirical therapy based on guidelines and de-escalation achieves significant reduction in mortality [53]. For the majority of patients responding to antibiotics alone, biliary decompression is still required to eliminate the underlying aetiology, and hence early multidisciplinary engagement is vital.

7.6.3 Invasive Procedures

Biliary decompression can be achieved either by endoscopic, percutaneous or surgical means. The choice of procedure should be based on simplicity, risk, patient profile, body anatomy, local resources, available expertise and disease pathology.

7.6.3.1 Endoscopic Retrograde Cholangiopancreatography (ERCP)

ERCP is the default procedure of choice. ERCP has lower morbidity and mortality as compared to surgical options [31]. However, ERCP is an invasive procedure with risks of bleeding, pancreatitis and perforation. In addition, ERCP requires sedation and hence should not be utilized as a diagnostic procedure. Early ERCP is indicated in patients with mild or moderate AC, while emergency ERCP is mandatory in severe AC. According to one study, maximum heart rate more than 100/min, albumin of less than 30 g/L, bilirubin of more than 50 μmol/L and prothrombin time of more than 14 s on admission were associated with failure of medical treatment, and authors suggested that these patients need emergency ERCP [52].

Options during ERCP are guided by the etiology of AC, local expertise and patient physiology. Biliary stent placement and nasobiliary drain placement can be done with or without biliary sphincterotomy. Patients who have severe AC may also have coagulopathy, and sphincterotomy is a relative contraindication in these patients. In other patients without coagulopathy or severe sepsis, wide

sphincterotomy can achieve biliary decompression and stone clearance. Immediate sphincterotomy was found to be as safe as elective sphincterotomy in patients with AC as long as patients did not have platelet levels below 50,000 × 10^3/μL, coagulopathy or ongoing anticoagulation therapy [54]. In a prospective randomized study involving 94 patients, Zhang et al. have compared endoscopic nasobiliary drainage with endoscopic stenting, and they have shown increased rate of blockage in the stenting group and a greater decrease in liver enzyme levels in the endoscopic nasobiliary drainage group [55]. In a single-centre case series of 80 patients, Park et al. have reported that both stenting and nasobiliary drainage are effective treatment. They reported frequent hyperamylasemia with endoscopic stenting and sphincterotomy [56]. In a large prospective randomized control study including 150 patients with severe AC, Sharma et al. used seven Fr tubes and concluded that both—endoscopic stenting and nasobiliary drainage—are equally safe and effective treatments for patients with severe AC [57]. Occlusive cholangiogram required to 'clear' the common bile duct (CBD) of stones is not recommended in overtly septic patients as injection of the contrast may aggravate sepsis. ERCP performed in septic patients is usually not definitive but rather temporising and aiming to achieve decompression. Prolonged ERCP and extensive manipulation with multiple attempts at trawling of stones should be avoided. During the conduct of the ERCP for AC, the primary aim is to achieve decompression of the biliary system, and it should be accomplished in the shortest time and safest manner possible. The secondary aim of clearing the biliary system, such as the removal of stones, is a more time-consuming procedure and should be reserved for more stable patients. Surgeons and gastroenterologists who perform ERCP often employ various adjuncts in the form of balloons or baskets to help in the retrieval of CBD stones. The choice is determined by number of stones, size of stones and bile duct and experience of the endoscopist. The general rule of thumb is that balloons are used in non-dilated ducts with a free-floating stone, while baskets are more successful in clearing stones in dilated ducts with impacted stones [58]. In a study reporting on 276 patients with AC, Schneider et al. have reported that stent therapy is a risk factor for increased antimicrobial resistance, and multiple procedures increase the risk [8]. Hence, in a stable patient, all the attempts should be made to ensure that further ERCP needs are avoided. In a study reporting on 43 patients with laparoscopic common bile duct explorations at our institute, we have shown that laparoscopic exploration can salvage a failed endoscopic bile duct stone extraction [59]. Laparoscopic bile duct exploration is a technically challenging procedure, and expertise may not be available outside specialist units [60]. Hence treatment algorithms should be tailored to local resources and expertise.

7.6.3.2 Percutaneous Transhepatic Cholangiography and Drainage (PTCD)

PTCD is often a second-line intervention. This is because it is a more invasive procedure with potential higher morbidity [51]. The known complications include bleeding, biliary peritonitis and fluid-electrolyte imbalance. PTCD is useful in patients who have failed endoscopic attempts at decompression, altered gastrointestinal anatomy rendering them unsuitable for ERCP (e.g. Billroth II gastrectomy), those who are overtly septic despite aggressive medical therapy and in those with malignant

hilar lesions. A major advantage of PTCD over ERCP or surgery is that the procedure can be done with minimal or no sedation. If the patient is unwell or overtly septic, it is prudent not to prolong the procedure by making multiple attempts to cross the lesion but rather to proceed with quick decompression. Also, with refinement of interventional radiology techniques and introduction of fine-needle cholangiography, the procedure-related complications have decreased. As with ERCP, care must be taken to avoid injection of contrast under pressure in an overtly septic patient. In patients with AC on a background of malignant hilar obstruction, ERCP may not be able to achieve decompression of all parts, and multiple drains can be inserted by PTCD. In a local audit of managing 134 patients with cholangiocarcinoma, up to 25% of patients still required PTCD after an ERCP (unpublished data).

7.6.3.3 Endoscopic Ultrasound-Guided Biliary Drainage (EUS-BD)

EUS-BD is a relatively new procedure, first described by Giovannini et al. in 2001 [61]. The procedure involves assessment of the biliary anatomy by EUS, and under imaging guidance a fistula is created from the gastrointestinal tract into the biliary system through guidewire placement, dilatation of the tract and finally stent placement to ensure permanent continuity. It is a useful and safe salvage alternative to PTCD. Advantages of the EUS-BD approach over the PTCD approach are avoidance of external drain. This eliminates problems of fluid loss, electrolyte derangements, skin irritation and infection and pain. However, EUS-BD is technically difficult and has a steep learning curve. High-volume centres have reported up to 90% and lower-volume centres report 60% technical success rate and up to 30% complication rates [62]. Hence, beginners should have first 20 cases supervised by a proctor [63]. In a randomized trial comparing EUS-BD with PTCD involving 25 patients with unresectable malignant obstruction, there was no difference in complication rate (15 vs 25%, $p = 0.44$) [64]. It is likely that this study was not adequately powered due to small sample. Other studies have found somewhat similar technical success rates in both PTCD and EUS-BD but with slightly higher complication rate in the PTCD group. In future, with technological advance and increasing familiarity, EUS-BD will witness reduction in complication rates and may be more widely adopted. EUS-BD may improve the quality of life by avoiding an external drain.

7.6.4 Surgical Management

Emergency surgical intervention for AC carries high mortality [65]. Therefore, emergency surgical intervention is a last resort procedure when all the other options are exhausted. In the event surgical intervention is necessary, the aim is to decompress the biliary system in the safest and quickest way. Prolonged procedures should be avoided. In our experience, nonoperative modalities are universally successful in controlling the sepsis, and surgery is reserved as a definitive therapy after patient is stable. Contrary, in patients with choledocholithiasis, without concomitant AC, single-stage laparoscopic common bile duct exploration (LCBDE) and cholecystectomy are possible. LCBDE offers a high success rate and short length of stay and obviates the risks associated with ERCP [60]. Advanced age in itself is not a

contraindication to surgery; CBDE by open or laparoscopic techniques can be performed safely in the elderly with accepted morbidity and mortality [66]. In situations where AC was caused by gallstones, laparoscopic cholecystectomy is offered after endoscopic stone clearance. This is because up to 25% of patients with gallbladder in situ may experience recurrent biliary symptoms [67]. When interval laparoscopic cholecystectomy is performed for AC due to gallstones, the performing surgeon needs to be aware of possible continual passage of stones [60]. This risk is lower in patients with previous sphincterotomy and in patients with prohibitive surgical risk; ERCP and wide sphincterotomy may be sufficient definitive treatment [68]. A proposed algorithm for the management of AC can be found in the Fig. 7.3.

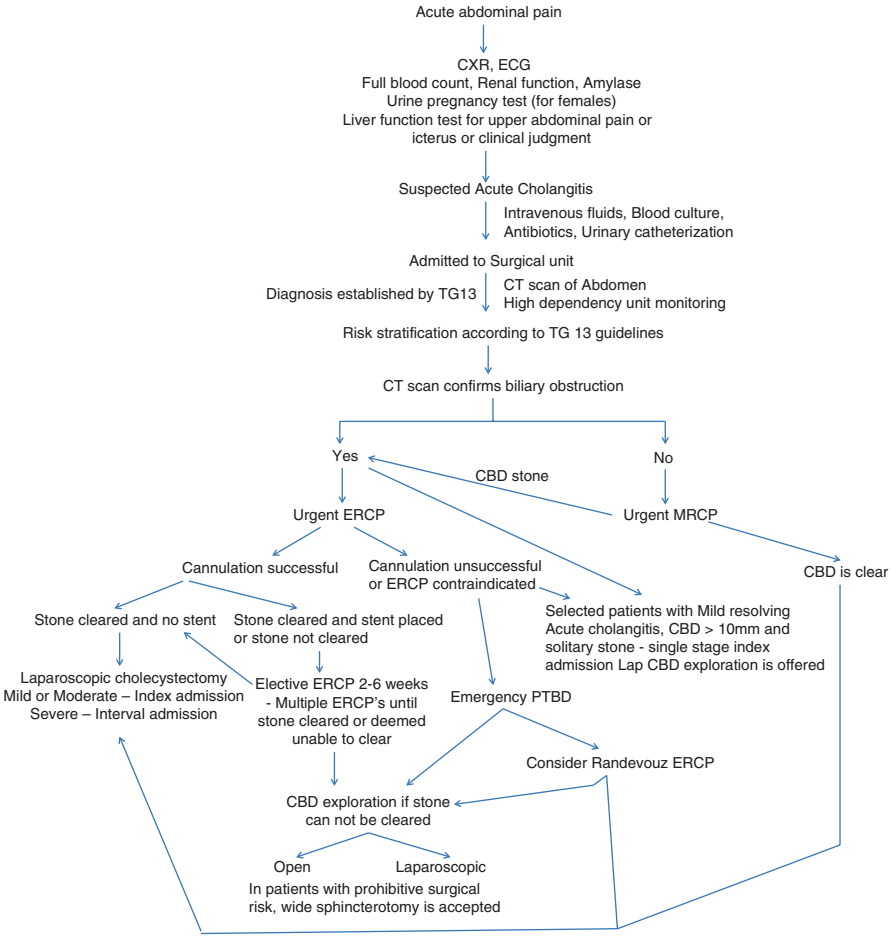

Fig. 7.3 Tan Tock Seng Hospital algorithm of management of acute cholangitis. *CXR* chest X-ray, *ECG* electrocardiogram, *TG13* Tokyo Guideline 13, *CT* computed tomography, *CBD* common bile duct, *ERCP* endoscopic retrograde cholangiopancreatography, *MRCP* magnetic retrograde cholangiopancreatography, *PTC* percutaneous transhepatic cholangiography

It is clear that ERCP, PTCD and surgery are not competing therapeutic modalities but rather complementary, each having its distinct role. Multimodal and multidisciplinary care is vital to the successful treatment and management of AC. Beyond the management of AC, one also needs to pay attention to special patient groups. One such special group is the elderly. Although current clinical guidelines support cholecystectomy after an initial biliary event, such recommendations have often poor compliance in the elderly due to multiple factors such as comorbidity, surgical risk and patient choice. ERCP should be offered as an alternative when surgery is contraindicated or refused after discharge. Relapse of AC is more frequent in patients managed without any invasive procedures [69].

7.7 Management of Secondary Causes of Ascending Cholangitis

7.7.1 Post Stenting

Since the 1970, biliary stenting via endoscopic or percutaneous methods has provided effective relief of obstructive diseases of biliary tree [70]. Today, stenting via endoscopic approach remains the most common form of palliation in patients who present with obstructive jaundice due to unresectable malignancy and has obviated the need for surgical bypass in many patients. Figure 7.4 shows PTBD with

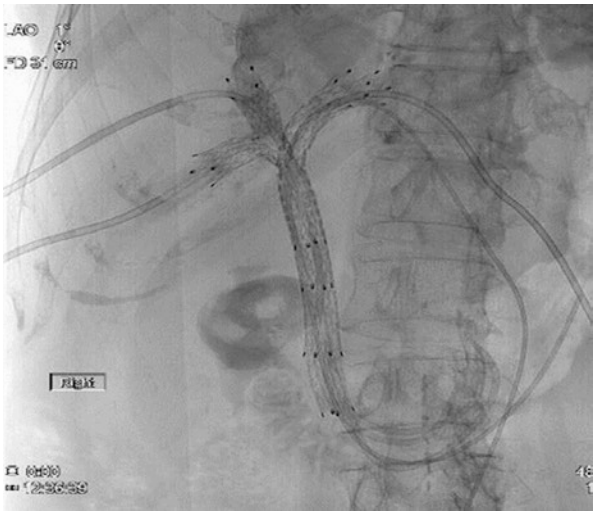

Fig. 7.4 A 73-year-old female patient with bismuth type IV cholangiocarcinoma and ascending cholangitis managed with multiple PTCD, and four metallic biliary stents were inserted to achieve decompression

palliative metallic endobiliary stents in patient with inoperable hilar cholangiocarcinoma. Recurrent cholangitis is a major complication of biliary stents due to blockage by microbial biofilm growth and biliary sludge formation. Larger diameter stents have a longer patency rate. Maximal stent size is limited by the inner diameter of duodenoscopes. Stent side holes may enhance patency; however comparative studies have not found any difference in patency [71]. Other techniques to improve patency include new biomaterials and coating such as hydrophilic polymer-coated polyurethane stents, silver-coated stents and impregnation of polymeric biliary stents with antimicrobial agents [72–74]. Metal biliary stent has higher patency rates compared to plastic stents and is therefore considered choice stents in patients with malignant obstruction with longer life expectancy [75]. Prophylactic antibiotics have been proposed as a means to reduce stent occlusion and incidence of AC [76]. Ciprofloxacin shows good tissue penetration, reaches high concentrations in the bile and is able to reduce bacterial adhesions. A multicentre, double-blinded study showed that patients receiving ciprofloxacin after plastic biliary stent insertion were less likely to have cholangitis episodes [77].

7.7.2 Post Hepaticojejunostomy (HJ)

AC may occur in patients with HJ due to anastomotic stricture or biliary stasis secondary to jejunal motility failure and reflux of intestinal contents into the biliary tree [78]. Imaging modalities such as hepatobiliary scintigraphy help to differentiate between the two. For anastomotic strictures, endoscopic or percutaneous balloon dilatation or stent placement is the first choice of treatment, and revision of HJ is reserved for selected patients. Biliary access loops facilitate endoscopic intervention and can be prophylactically done at the time of HJ. Purse-string anastomosis with an intra-anastomotic biodegradable biliary stent placement can reduce the rate of stricture [79, 80]. If AC is recurrent despite medications, surgical options such as extension of the afferent loop jejunum, creation of an antireflux valve to the afferent loop jejunum or revision of the biliary reconstruction are all valid surgical options [81–83].

7.7.3 Cholangiography

Cholangiography, via ERCP, PTBD or intraoperatively all, bears risks of AC. The risk factors for post-ERCP cholangitis include insufficient drainage of biliary system, Klatskin's tumour, PSC, jaundice and low-volume centre. Disinfection of endoscope and accessories, the use of low volume of contrast, decompression of obstruction and prophylactic use of intravenous antibiotics reduce the risk of AC [84]. A double-blind randomized controlled trial that evaluated the effect of adding gentamicin to contrast media for preventing post-ERCP cholangitis did not show any difference [85].

Conclusion

AC is a common surgical emergency. Charcot's triad has minimal role in establishing diagnosis. Early diagnosis by prompt abdominal imaging is essential. Prompt physiologic restoration, broad-spectrum antibiotics tailored according to local antibiogram and urgent biliary decompression are essential pillars of care. ERCP, PTBD, EUS-BD and surgical modalities are complimentary and not competing. In primary AC with lithiatic biliary obstruction, definitive surgery is essential to reduce risk of recurrent biliary events. In primary AC without lithiatic biliary obstruction and secondary AC, definitive treatment is tailored according to the underlying aetiology. Multidisciplinary care tailored to local resources and expertise is important to improve outcomes.

Conflict of interest None

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Pyogenic Liver Abscess

8

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8.1 Introduction

A hepatic abscess is a suppurated cavity caused by the invasion and multiplication of microorganisms within the liver parenchyma [1]. It can be bacterial (pyogenic), parasitic (amebic), mixed (pyogenic superinfection of parasitic abscess), or rarely fungal. Adult pyogenic liver abscess (PLA) is a major hepatobiliary infection with mortality of up to 46% [2–4]. The recent improvement in mortality can be attributed to improved understanding of sepsis with advances in interventional radiology and critical care. The cornerstone of PLA treatment remains antibiotic therapy with percutaneous drainage/aspiration. The first significant study on PLAs was performed by Ochsner in 1938, and he reported association with young men, portal pyemia, and 77% mortality [5].

8.2 Epidemiology

Incidence of PLA is increasing globally [2]. Prevalence is more common in Asia than in the West. Taiwan has a prevalence of 18/100,000 compared to up to 4/100,000 in the West [6–8]. The characteristics of PLA in the Asian and Western population also differ [9]. A greater proportion of Western patients have underlying malignancy or hepatobiliary-pancreatic pathologies, while Asian patients present with cryptogenic PLA or biliary pathologies. *Staphylococcus* or *Streptococcus* species were the more common causative organisms in the West, as opposed to *Klebsiella pneumoniae* in Asia. Alarmingly, there is an increasing prevalence of

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extended-spectrum beta-lactamases (ESBL)-producing *Klebsiella pneumoniae*, from 1.6% of initial blood cultures in 2001 to 14.3% in 2011 [2]. This increase in resistance is likely to be due to widespread use of broad-spectrum third-generation cephalosporins. PLA patients are more likely to have type 2 diabetes mellitus (DM), and there is a significant rise in malignancy as an etiology [2]. A recent case control study from Taiwan has reported that proton pump inhibitor use is associated with greater risk of PLA [10].

8.3 Etiology

PLA arises due to the invasion of the liver parenchyma by microorganisms via the blood stream (hematogenous, most often portal), bile ducts, or contiguously especially via the gallbladder bed [11]. Hematogenous spread can occur via the portal venous system infections such as appendicitis, enteritis, or colitis. PLA may also arise from extra-abdominal infections or preexisting liver lesions (biliary cysts, hydatid cysts, or necrotic metastases). Biliary spread may result in the course of intra-abdominal biliary infections that contaminate the biliary tract. PLA may complicate surgical procedures that involve bilio-enteric anastomosis (pancreaticoduodenectomy) and immunosuppression (liver transplantation). Widespread adoption of interventional radiology procedures such as radiofrequency ablation (RFA) or trans-arterial chemoembolization (TACE) for hepatocellular carcinoma (HCC) is also associated with PLA. In a local study reporting on 103 patients with acute cholecystitis treated with percutaneous cholecystostomy, 12.6% of patients had contiguous PLA on imaging [12]. PLA is also known to complicate patients with recurrent pyogenic cholangitis (RPC) [13]. In a study reporting on 319 patients with RPC, Law ST et al. reported that PLA in patients with RPC has distinct clinical, microbiologic, and radiologic patterns; however, outcomes with antibiotics and percutaneous drainage are comparable [14].

8.4 Bacteriology

The mainstay of the treatment of PLA is antibiotics. Ideally all patients should receive targeted antibiotic therapy [15]. In PLA patients, blood culture is the prime source for microbial identification. The pus from percutaneous aspiration or drainage also allows for microbial isolation.

8.4.1 *Klebsiella pneumoniae* Pyogenic Liver Abscess (KPPLA)

The past two decades have seen an increasing prevalence of *Klebsiella pneumoniae* as the leading pathogen, especially in Asian countries [16]. KPPLA is reported to be associated with larger size of PLA [17, 18]. In a study involving 288 patients, we have reported that KPPLA is ten times more common as compared to *Escherichia coli* PLA. Also, KPPLA tends to be larger in size (6 cm vs. 4 cm, $p = 0.006$). Due to large size, KPPLA was more likely treated with percutaneous drainage [16].

8.4.2 *Escherichia coli* Pyogenic Liver Abscess (ECPLA)

ECPLA occurs more commonly in older patients with ischemic heart disease and is more likely to be associated with an underlying biliary disease [16, 17]. Hence the management of ECPLA poses distinct challenges. We have reported on adversaries associated with ECPLA and concluded that despite demographic and clinical differences, in the era of multimodal care, the outcomes of ECPLA are comparable to KPPLA [16]. Due to increased association with gallstone disease and biliary pathology, we advocate routine abdominal ultrasound scan of patients with ECPLA.

8.4.3 Culture-Negative Pyogenic Liver Abscess (CNPLA)

While blood cultures are the main source for microbial identification, the sensitivity to isolate the culprit microorganism is less than 40% [2, 19, 20]. In patients who undergo PLA aspiration or drainage, only 60% have positive pus cultures [2]. This is likely due to the starting of antibiotics prior to drainage. Other methods such as polymerase chain reaction (PCR) can be used to improve the diagnostic yield or obtain results earlier.

CNPLA is often underreported, yet is not uncommon. There is limited data on the outcomes of CNPLA. The management of CNPLA poses unique challenges when patients fail to respond to treatment. We have reported that the prevalence of CNPLA was the same as KPPLA over a 9-year period [20]. CNPLA patients were treated with the same empirical antibiotics targeted to *Klebsiella pneumoniae*, and the overall outcomes (length of hospital stay and 30-day mortality) of CNPLA patients were similar to KPPLA patients. CNPLA patients who had undergone percutaneous drainage have better outcomes compared to those treated with antibiotics alone. The empirical antibiotic of choice in CNPLA patients should be tailored to the most prevalent microorganism in local geography and antibiogram of the institution.

8.5 Clinical Presentation

The diagnosis of PLA requires a high index of clinical suspicion, as symptoms are often nonspecific and highly variable. The common symptoms of PLA are fever with chills, abdominal pain, and malaise. The common signs are pyrexia and right upper quadrant tenderness (two thirds of PLA are located in the right hemiliver). In a study by Chen et al., there was no difference in the presentation of KPPLA as compared to PLA from infection with other microbes [21]. PLA can occur on background of abdominal sepsis, and patient may manifest with clinical symptoms and signs of primary underlying disease. In patients treated with RFA or TACE for HCC, persistent pyrexia and abdominal pain should be investigated for possible PLA. In patient with TACE, high index of suspicion is essential as fever can be discounted as post-embolization syndrome. Possible complications of PLA include rupture, endophthalmitis, and multi-organ failure [21].

8.5.1 Rupture

Rupture of PLA is uncommon, occurring in up to 6% of PLA [22, 23]. Risk factors for rupture include DM, liver cirrhosis, *Klebsiella pneumoniae*, gas formation, size >6 cm, and left lobe involvement [24, 25]. Diabetes mellitus and liver cirrhosis compromise phagocytic and bactericidal functions with severe local inflammation and predisposing to rupture. PLA rupture is a surgical emergency. Free rupture with peritonitis requires surgical intervention, while localized rupture without peritonitis can be treated with percutaneous drainage and antibiotics [26]. Patients with ruptured PLA will have longer duration of hospital stay and use of antibiotics, higher rates of intervention (percutaneous or surgical drainage), and risk of metastatic infection. In a study reporting on 23 patients with ruptured PLA, Jun CH et al. have reported 4.3% mortality [24].

8.6 Investigations

8.6.1 Biochemistry

There is no specific serum biochemical test for establishing diagnosis of PLA. Routine serum biochemistry aids in diagnosis of sepsis, and on a background of clinical presentation, PLA can be suspected. Raised total white blood cell count, elevated urea, coagulopathy, and deranged liver enzymes aid in clinical judgment. Serum biochemical tests assist in monitoring the response to treatment and also guide duration of treatment. In the process of abscess formation, hepatocytes undergo necrosis and secrete cytokines to stimulate the growth of adjacent fibrous stroma tissue to form the abscess wall [27]. C-reactive protein (CRP) is an acute-phase protein synthesized primarily in the liver and is stimulated by cytokine release, especially interleukin-6. Law et al. calculated the CRP ratio in relation to the CRP concentration at week 1. They showed that a CRP ratio of 0.278 or less at week 3 is a marker of response and the PLA will likely be eradicated by a 5-week antibiotic regime, while a CRP ratio of greater than 0.57 at week 3 indicates possible treatment failure, progression of abscess, and a higher risk of mortality [27]. This results need to be validated.

8.6.2 Imaging

Ultrasound (US), computerized tomography (CT), and magnetic resonance imaging (MRI) scans are highly sensitive in the diagnosis of PLA. However, imaging findings are often nonspecific and may mimic hepatic cysts or necrotic tumors. US is simple and readily available and, in addition to diagnosis of PLA, assists in detection of gallstones. In patients presenting with septic shock and acute kidney injury, US can help reduce the risk of contrast-induced nephropathy. CT scan is helpful in detailing the enhancement pattern, as well as the presence of gas or calcifications.

MRI scan has multiplanar capability and has high specificity for differentiating hydatid cysts [4, 28]. On MRI scan, PLA may have perilesional edema and increased signal intensity seen on T2-weighted images and exhibit variable signal intensity on T1- and T2-weighted images, depending on their protein content. Imaging features can assist in the identification of underlying microorganism. Widely scattered microabscesses are seen in staphylococcal infections and usually involve both the liver and spleen. PLA may also manifest as a cluster of microabscesses that appear to coalesce focally. The cluster pattern is associated with coliform bacteria and enteric organisms and may represent an early stage in the evolution of a large PLA cavity. Gas formation is suggestive of clostridial infection; however, even in patients with gas formation, *Klebsiella pneumoniae* remains the predominant pathogen. In a study by Alsaif et al., gas was only seen in 17% of PLA on CT scan [29]. KPPLA is more likely solitary and appear solid and multilocular as compared to PLA caused by other bacteria. Imaging is typically considered the treatment end point and is a core component of diagnosis and treatment monitoring.

8.6.3 Size of the Abscess

Antibiotics are the mainstay of treatment of PLA; however, parenteral antibiotics alone may not be sufficient to treat large PLA because of the higher bacterial load, inadequate penetration of antibiotics, and ineffective medium for bacterial elimination [30, 31]. Drainage of PLA may shorten the duration of parenteral antibiotics. The size of an abscess that necessitates drainage and the modality of drainage are subject to much debate. Liao et al. [32] showed that an abscess larger than 7.3 cm predicts failure of percutaneous drainage. Other authors advocate operative drainage for larger PLA [30, 33]. There is currently no consensus on what defines a "large" abscess. We have defined a "giant" PLA as an abscess that is equal to or greater than 10 cm in diameter [34]. In that retrospective study, only 7% of PLA were giant and only 2.6% of giant PLA failed percutaneous drainage. This study demonstrated that percutaneous drainage with parenteral antibiotics is a safe and sufficient treatment for giant PLA, and operative drainage is only rarely needed. Size of the abscess does not affect the overall mortality [34]. Size is not the only factor that determines the success of percutaneous drainage. Multiloculation also leads to higher failure rates of percutaneous drainage because of the compartmentalization of the abscess. Multiloculated PLA is associated with increased morbidity and hospital stay [35, 36]. Only 55% of giant PLA were found to be multiloculated in the series by Ahmed et al. [34]. The relatively lower rates of multiloculated PLA in this series could have contributed to the high success rate of percutaneous drainage.

8.6.3.1 Gas Formation

Gas-forming PLA has higher rates of septic shock, occurring in 32.5% as compared to 11.7% in non-gas-forming PLA [37]. Gas formation is also an independent risk factor for spontaneous rupture [24]. The presence of gas on imaging is

associated with high mortality [22, 32]. The threshold to escalate therapy should be lowered in patients with gas-forming PLA that do not respond to percutaneous drainage. While percutaneous drainage is not contraindicated in gas-forming PLA, a study by Liao et al. [32] showed that the presence of gas was the most important radiological predictor for percutaneous drainage failure. *Klebsiella pneumoniae* is the most common bacteria isolated from gas-forming PLA, both from liver pus aspirates and from blood cultures [29]. *Klebsiella pneumoniae* is found in 81–100% of positive liver pus cultures in gas-forming PLA compared to 28–86% of non-gas-forming PLA [38–41]. Gas formation may be reliably diagnosed with either US or CT scan, with detection rates up to 100% [40]. On US, gas formation may appear as diffuse hyperechoic spots with acoustic shadowing [38] or hyperechoic lesions with reverberation [37]. On CT scan, gas formation may be recognized as low attenuation areas with Hounsfield units similar to that of the lungs [38]. Gas-forming PLA is increasingly reported to be associated with TACE [42, 43].

8.7 Management

8.7.1 Pharmacologic

The mainstay of PLA treatment is antibiotic therapy, with or without percutaneous aspiration/drainage. Antibiotic therapy must be targeted according to the locally prevalent organism and to specimen culture and sensitivity. It may not always work due to the bacterial load and poor penetration of antibiotics. Factors that predict failure of antibiotics-only therapy include age ≥55 years, multiple abscesses, malignant etiology, and patients who underwent endoscopic intervention. Antibiotic duration and abscess size were not predictive of failure [2]. In a recent study, we have concluded that empiric treatment of patients with CNPLA is safe if the treatment is tailored according to local antibiogram [20]. Our local algorithm of management of PLA is showed in Fig. 8.1.

8.7.2 Percutaneous Aspiration/Drainage

While some authors believe that percutaneous drainage may be inadequate for large PLA [30], more recent evidence has shown that large size of the abscess is not a contraindication to percutaneous drainage. In a study by Ahmed et al., percutaneous drainage was successful in 97.4% of PLA greater than 10 cm [34]. Figure 8.2 shows a CT scan image of an elderly gentleman with gas-forming PLA. Figure 8.3 is the CT scan image of the same patient following treatment with antibiotics and percutaneous drainage. Percutaneous drainage requires local anesthesia and minimal sedation and can be performed under radiological guidance. Percutaneous drainage

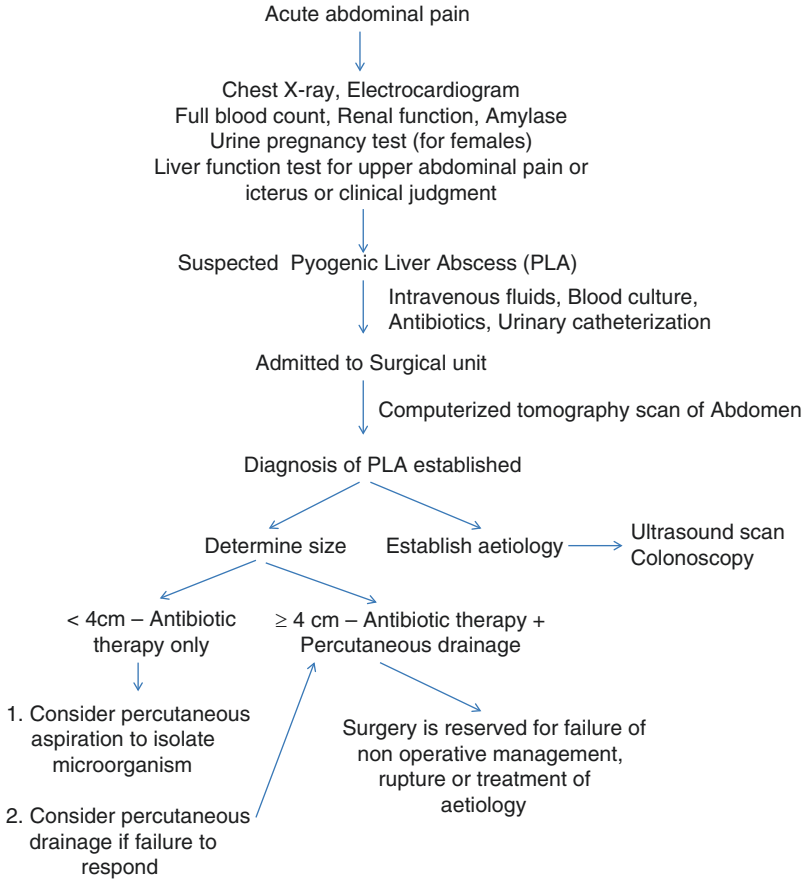

Fig. 8.1 Tan Tock Seng Hospital algorithm of management of pyogenic liver abscess

has a higher success rate compared to percutaneous aspiration and allows for controlled drainage of large abscesses with minimal hemodynamic and physiological stress to the patient [30, 44]. Factors that predicted the failure of antibiotics and percutaneous therapy include ECOG (Eastern Cooperative Oncology Group) performance status ≥2, hypertension, and raised serum bilirubin [2]. The presence of multiple abscesses and size were not predictive of failure of percutaneous therapy [2]. Failure of percutaneous drainage can lead to uncontrolled sepsis and eventually death. In giant or multiloculated PLA, sometimes multiple drainage catheters are warranted. Catheter site discomfort with pain, superficial infection, and dislodgement are common drawbacks. In patients with minimal drainage, it is safer to flush the catheter to ensure patency rather than prematurely remove it. It is authors practice to remove catheter only when clinical and biochemical improvement is established and drainage is <10 ml/24 h for 2 consecutive days.

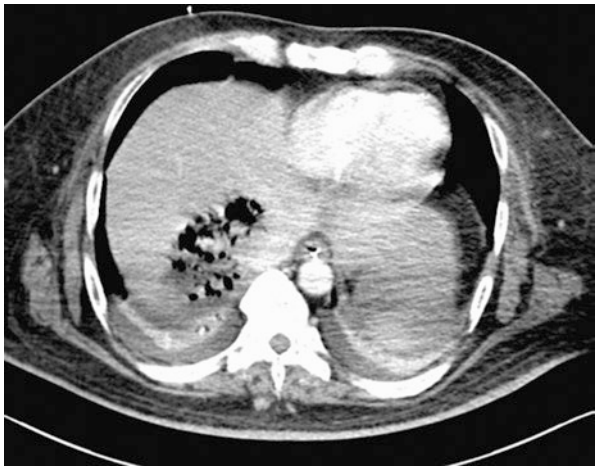

Fig. 8.2 Computerized tomography scan image showing gas-forming pyogenic liver abscess

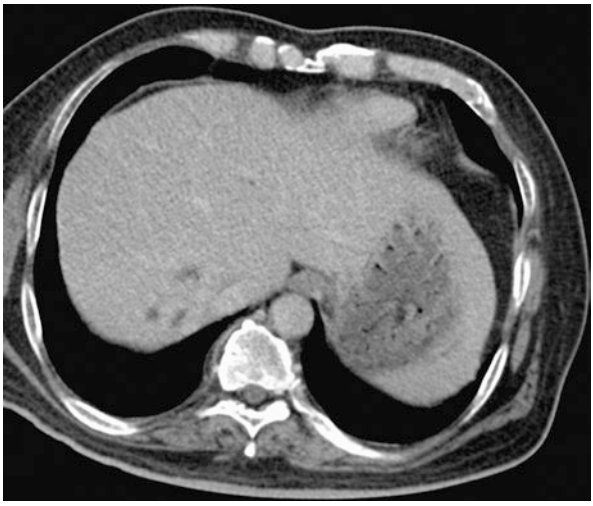

Fig. 8.3 Computerized tomography scan image of the same patient showing resolution of liver abscess following antibiotics and percutaneous drainage

8.7.3 Surgical Drainage

Surgery is indicated in patients with ruptured abscesses. Surgical drainage can be performed either open or laparoscopically. In most studies comparing percutaneous drainage to surgical drainage, percutaneous drainage has lower morbidity with comparable mortality [45, 46]. While laparoscopic drainage has a higher treatment success rate, operative and anesthesia-related morbidity remains high and hence only indicated in patients with failure of percutaneous drainage [47]. Open drainage allows the surgeon to use his fingers to break down the locules of the abscess effectively and subsequently places large-bore drains into the cavity. Open drainage may be better suited for abscess at difficult sites, such as the dome of the liver, as it allows more effective hemostasis in patients with severe coagulopathy [30].

However, with improvements in laparoscopic techniques and instruments, laparoscopic drainage may be as effective as open drainage. Recently, video-assisted drainage of PLA is reported in patients with failure of percutaneous drainage [48]. Hepatic resectional procedures are restricted to PLA in patients with recurrent pyogenic cholangitis.

Conclusion

PLA is a severe hepatobiliary infection with substantial morbidity and mortality. Widespread application of interventional radiology procedures for treatment of HCC has partly contributed to changing geographic trends. Imaging remains the cornerstone for diagnosis and treatment monitoring. Percutaneous drainage is essential in patients with large size and even sufficient in patients with multiloculated or giant PLA. Surgical therapy is indicated in patients with rupture, failure of percutaneous drainage, or for treatment of underlying etiology. Multimodal care is integral to ensure good outcomes.

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Gastroduodenal Perforations

9

Kjetil Søreide

9.1 Introduction

Perforation of a gastroduodenal ulcer represents a surgical emergency that is still associated with high mortality and morbidity worldwide [1]. While this condition was more frequently discussed and investigated some decades ago, the decline in overall peptic ulcer disease in the Western worlds due to a more defined aetiology and therapy (*Helicobacter pylori* and its eradication possibilities), a somewhat reduced incidence of smoking in populations, and the use of effective acid secreting medications (e.g., proton pump inhibitors) has decreased the overall incidence of peptic ulcer disease (PUD). Notably, the perforation rate in PUD has not declined to the same degree. Still, mortality is reported at high rates, with mortality numbers reported between 15% and 30% even in modern series. Thus, timely and appropriate management of this condition is needed in order to reduce risk of death and complicated outcomes. The strategy to accommodate an improved outcome involves preoperative, intraoperative, and postoperative initiatives (Fig. 9.1) to a range of factors that may or may not be amenable for modification [2]. Early recognition and treatment of the sepsis syndrome is crucial in this patient group, and dedicated care bundles should be considered to reduce mortality [3].

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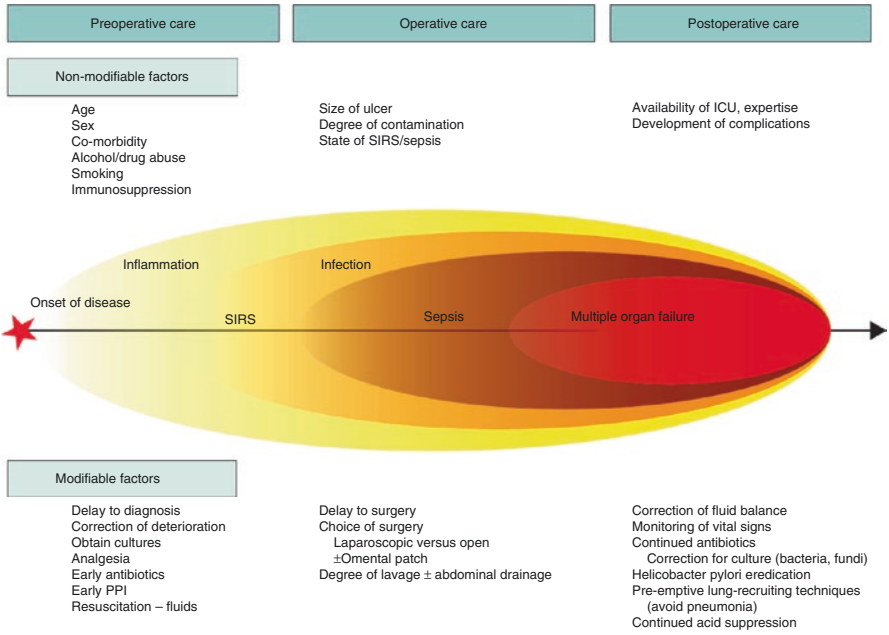

Fig. 9.1 Strategy to management of gastroduodenal ulcer perforation. Modifiable and non-modifiable risk factors in perforated ulcer disease are presented. *SIRS* systemic inflammatory response syndrome, *ICU* intensive care unit, *PPI* proton pump inhibitor (Reproduced with permissions from *Br J Surg. 2014;101(1):e51–64* © 2013 BJS Society Ltd., John Wiley and Sons)

9.2 Gastroduodenal Ulcer: Characteristics and Demographics

While mechanisms to PUD in general have been heavily explored, the pathomechanisms underlying a perforation (Fig. 9.2) are poorly understood and less well investigated [4]. Further, change in population demography has led to a shift in age- and gender distributions in patients presenting with perforated gastroduodenal ulcers. For example, the pattern of a predominant young, male population with duodenal ulcers reported in Western countries several decades ago [5] is still reported in most developing countries [6–8]. In contrast, an age- and gender-distribution change in many Western countries toward higher age, more women, and a predominant gastric location of ulcer perforations is seen [9, 10]. The wave of aging people will contribute to an increasing workload of emergency surgery conditions in the near future [11], which needs to be taken into account when considering both mortality and morbidity comparisons across regions and countries. The changing population characteristics over time also likely explain the lack of precision and accuracy of the available scoring systems suggested for gastroduodenal perforations [12, 13].

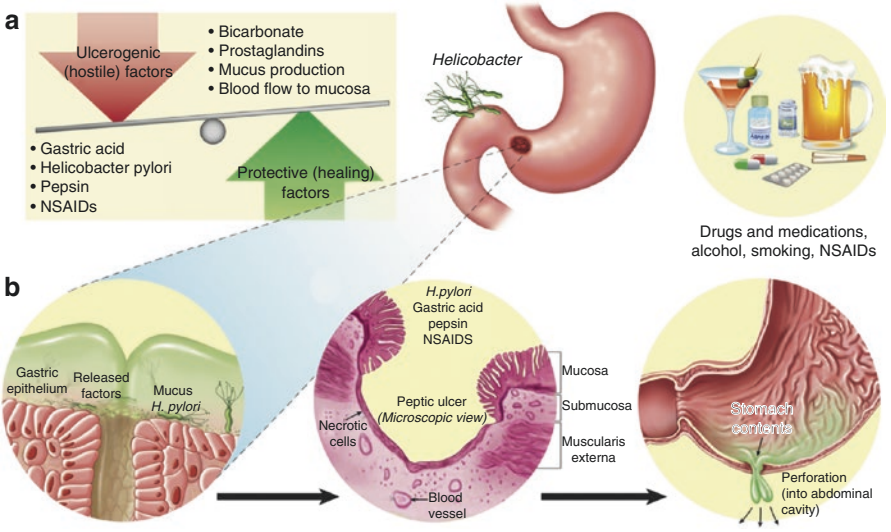

Fig. 9.2 Proposed pathomechanisms to perforation in a gastroduodenal ulcer. (*A*) The ulcer process starts with an imbalance between protective and hostile factors, most frequently represented by *Helicobacter* infection (for duodenal ulcers) or the excessive use of nonsteroidal anti-inflammatory drugs for gastric ulcers. Other modifiers include smoking, drinking, and several drugs. (*B*) As the protective mucosal barrier is broken, acidic exposure of the mucosa leads to tissue destruction. The exact mechanism of perforation remains a puzzle because most ulcers are small and localized in the anterior of the stomach or duodenum (Reproduced with permissions from *J Trauma Acute Care Surg* 2016;80(6):1045–8)

9.3 Diagnosis

The classical "textbook" description of rapid onset of intense, acute abdominal pain in the upper abdomen, associated with board-like rigidity indicative of peritonitis is typical for the predominantly young population. Leukocytosis may be present early on as an acute phase response, while C-reactive protein (CRP) may only be elevated if symptoms have endured for some while before presentation. Notably, the clinical presentation and abdominal signs in the elderly population are more subtle with fewer overt clinical signs (e.g., a less peritonitis) [14], lower or no leukocytosis, and a higher risk for diagnostic delay or misdiagnosis. Imaging with an erect, abdominal X-ray used to be standard imaging in the past [15] but has such a low specificity and high risk for misdiagnosis (sensitivity around 75%) and very little information regarding appropriate differentials, so this should not be the method of choice if alternatives exist. Thus, the superior sensitivity (>98%) of abdominal computed tomography (CT) has led to a change in diagnostic workup [16], and the majority of patients are now diagnosed by section scans [17]. Avoiding diagnostic delays as well as delay to surgical treatment is paramount [18, 19], as for every added hour of delay infers an additional 2.4% poorer risk of survival [19].

9.4 Early Resuscitation and Preoperative Management

In critically ill patients with an acute abdomen, the appropriate initiation of pain medications, fluid resuscitation, and early start of empiric intravenous broad-spectrum antibiotics should be entertained from the beginning of the clinical evaluation. In sick patients, the resuscitative measures should not be delayed until imaging results are ready, as imaging studies may take time even in emergency situations. As soon as the diagnosis is established and/or confirmed, the patient should be informed and prepared for surgery. It is important to inform the patient and next of kin of the perceived and possible outcomes and complications. In the very elderly (>80 years) with a high comorbidity burden, it should be made clear that the mortality risk is high (over 30%), independent of the technical success of surgery [14, 19]. Furthermore, in elderly patients with a high comorbidity burden and independent living status or with no or very limited cognitive capacity, the discussion to forego surgery or simply consider other conservative or palliative measures should be considered in order to avoid futile care [20, 21].

9.5 Management

In principle, a perforation can be managed by surgical suture, by resection, or by nonoperative (also called conservative) management. In addition, a few newcomer options have been reported, such as endoscopic management by means of clips or stents and natural orifice technologies (NOTES). However, the standard approach should be surgical suture for source control, and only occasionally resection may be entertained. The NOM and other techniques are to be viewed as experimental or only to be applied on rare occasions when other options, for any reason, may not apply.

9.5.1 Surgical Repair

Surgery for perforated gastroduodenal ulcer can be performed as either an open or a laparoscopic approach. The laparoscopic approach may provide for additional diagnostics in case of diagnostic uncertainty in patients with “free air” but with no clear focus or identified source. The choice to undertake the surgical repair laparoscopically or open should rest with the skills and proficiency under which this can be done, as there are no clear benefits to laparoscopy over open surgery for surgical repair [22–24]. Conversion from laparoscopy to open surgery usually occurs in complex patients, with advanced stage of disease, thus placing a bias on cases performed laparoscopically to those done with an open approach [25]. Proponents of laparoscopy will argue for a more rapid recovery, less pain, and fewer days in hospital, but when considering disease factors (contaminated abdomen, septic patient) and age and comorbidity, there is no documented advantage of laparoscopy in terms of difference in mortality or morbidity. Notably, the older the patients are, the longer they stay in hospital [14], and conversely, the young and fit population may easily be discharged early with an uneventful recovery [6].

Independent of surgical access (open or laparoscopical), the mode of repair should be that of a safe closure of the defect and usually adding an omentopexy to cover the perforation. The omental pedicle is usually sutured over the perforation site, but others have demonstrated that the omental patch also stays in place without sutures [26], likely due to inflammatory processes that adhere the tissue to the area. Some argue for placing the omental patch in the perforation without primary suture of the hole, but there is no evidence to support that choice other than the practical fact that larger holes may not easily be sutured in when friable, inflamed tissue edges do not easily approach.

There are a number of variants (Fig. 9.3) that have been proposed for primary suture repair and omental patch coverage, and no evidence exist to favor one over the other. However, one exception is the use of a free (non-pedicled) omental flap

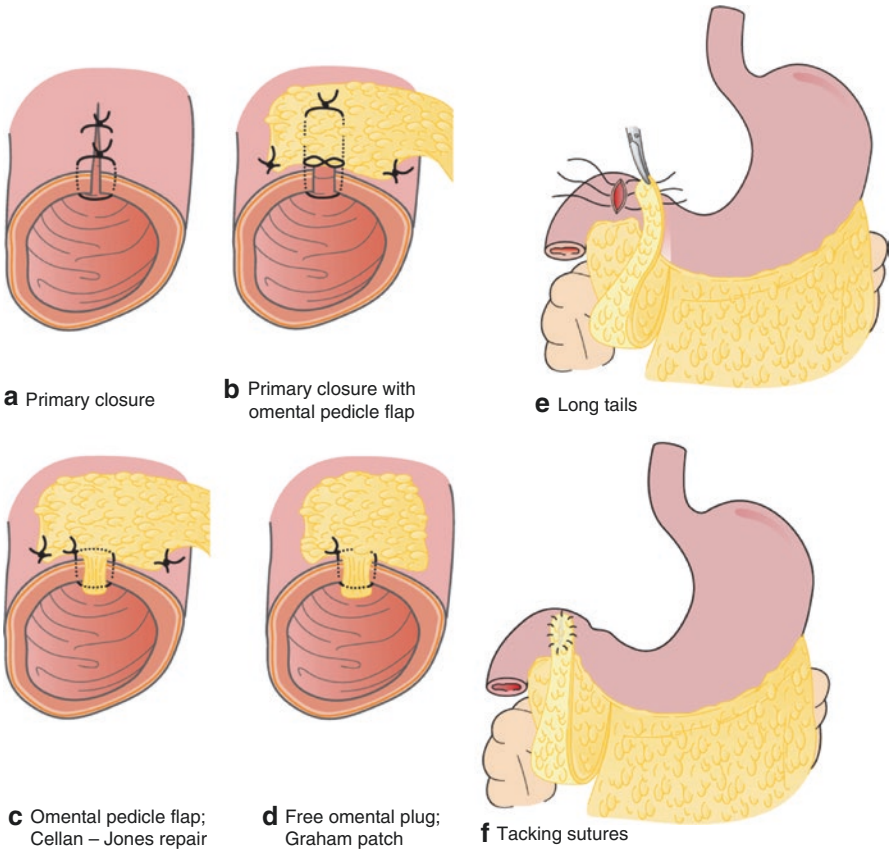

Fig. 9.3 Suture technique variations for closure of a perforated gastroduodenal ulcer. (**a**) Primary suture; (**b**) primary suture with pedicled omental flap; (**c**) pedicled omental flap sutured into the perforation (Cellan–Jones repair); (**d**) free omental plug sutured into the perforation (Graham patch; no longer recommended); (**e**) use of three long-tailed sutures to close the perforation and buttress with a pedicled omental flap; (**f**) use of tacking sutures around the perforation (e.g., when friable edges or a large perforation may not allow approximation of wound edges) (Reproduced with permissions from *Br J Surg. 2014;101(1):e51–64* © 2013 BJS Society Ltd., John Wiley and Sons)

(so-called Graham patch) that should be avoided as this nonvascularized piece of omentum is bound to necrotize and thus lead to a new leak. The so-called Cellan–Jones repair is the method of choice among the majority of studies reported. The local application glue products, the spray-application of a solution containing mesenchymal stem cells [27] to foster improved healing, or the use of a "biopatch" to close the perforation are all still experimental [28] and have no current routine clinical application to humans.

The need for reinterventions (either as percutaneous drainage or reoperations) after a primary repair occurs in about 11–17% of patients [10, 29]. Persistent leaks and wound dehiscence are the most frequent indications for reinterventions [29]. No difference in risk is seen between laparoscopy and open surgery, although open surgery is associated with the obvious risk for wound dehiscence (but this is biased toward selection of the sickest patients having open surgery) [29]. Obese male patients with coexisting diseases and high disease severity (e.g., shock on index operation; long delay to surgical repair) are at increased risk of reoperation [10].

9.5.2 Complex Ulcer Situations

Resectional surgery for perforated gastroduodenal ulcers is associated with particularly high mortality [30] but may be considered in certain situations. Resections are performed more frequently in Asian countries such as Japan [31], likely due to tradition but also possibly due to a higher incidence of gastric cancer, which must always be entertained as an underlying cause in perforations. This is different in Western countries where resections are only occasionally performed for perforated gastroduodenal ulcers and, when done, this is associated with higher mortality. However, in some situations—such as a very large ulcer or in reoperations for failed primary repair—the tissue may be so friable that primary closure of the defect is not possible nor are the sutures likely to hold. In such situations, the use of T-drains to create a controlled gastro/duodenal-cutaneous fistula has been reported with success [32, 33].

9.5.3 Nonoperative Management

The use of nonoperative management (NOM) consists of proper fluid resuscitation, placement of a nasogastric tube for decompression and drainage of the stomach, percutaneous intraabdominal drains per imaging findings, intravenous medications with proton pump inhibitor, intravenous antibiotics, and frequent monitoring of vital functions. The indication to NOM may be either one of two extreme presentations. For one, NOM may be entertained in the otherwise fit patient who presents with acute symptoms but else few clinical signs of high disease severity and for whom the imaging findings indicate a gastroduodenal perforation. Secondly, NOM may be considered in the very sick patient who is unlikely to tolerate surgery for other reasons (e.g., severe aortic stenosis; grade 4 pulmonary disease, or similar) and for whom an attempt at NOM may be a compromise between optimal and best

care. In both situations, the patient needs to be well informed about the risks and outcomes. Little hard evidence exists for this approach, and only one RCT exists, which was done in the pre-PPI era and dates back to the late 1980s [34]. Failure rate was particularly high in those aged >70 years, so elderly patients appear not to be very good candidates. One study demonstrated the utility of a risk score by combining clinical info (age <70 years), radiological parameters (US-detected fluid collections; extravasation of oral contrast), and APACHE II score (<8), the clinical score allowed early identification of PPU patients who could benefit from nonoperative management [35]. In patients with a low score (1 point or less), a high success rate (>80%) for NOM was achieved. However, this was not randomized and needs to be validated externally.

9.5.4 Experimental Therapies and Management Options

Endoscopic techniques and minimal-invasive options have been used to manage perforated gastroduodenal ulcers, but most are experimental and reviewed in detail elsewhere [1]. Endoscopic repair has been done by over-the-scope clips [36] and represents an option or adjunct to NOM where expertise and resources allow. Natural orifice transluminal endoscopic surgery (NOTES) techniques have been used with some success in smaller pilot trials [37, 38], but this requires the patient to be stable and tolerate the procedure as well as having a perforation that allows for closure by this combined laparoscopic/endoscopic technique. It is still experimental and should not be done outside trials.

Conclusions

Patients with perforated gastroduodenal ulcers are at high risk of death, and the condition is associated with considerable morbidity. Predicting who is at risk of death or complicated disease course has proven futile [12, 13, 39, 40] as no single score captures the risk across populations. Age is a major determinant for a poor outcome [14], as is diagnostic and therapeutic delays [19]. Length of stay is largely different between age groups, and typically two thirds of those aged >55 years may be discharged within a week after surgery, whereas only one-third of those aged >80 years will be able for this [14]. Strategies need to be tailored to the pre-, peri-, and postoperative management of these patients.

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Small Bowel Perforations

10

Sanjy Marwah

10.1 Introduction

Small bowel perforation is a serious complication of a variety of systemic as well as small bowel diseases. It usually leads to generalized peritonitis and complicated intra-abdominal infection that demands quick diagnosis and early management. However, many patients present late in a state of preestablished sepsis and multi-organ failure due to missed or delayed diagnosis. Despite surgical intervention, best of intensive care and antimicrobial therapy, these cases culminate unacceptably high morbidity and mortality [1, 2]. In a recently conducted observational study in the USA on more than two million patients undergoing emergency surgery, small bowel resection was one of the seven emergency surgical procedures that accounted for 80.0% of procedures, 80.3% of deaths, 78.9% of complications, and 80.2% of inpatient costs [3]. Thus, small bowel perforations are one of the most common life-threatening surgical emergencies as well as "bread and butter" for the surgeons [4]. Anatomically, the small bowel extends from gastroduodenal junction to ileocecal junction and comprises of the duodenum, jejunum, and ileum. This chapter covers the description of jejunal and ileal perforations only since duodenal perforations have already been covered in this book.

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10.2 Small Bowel Perforation: General Consideration (Box 10.1)

10.2.1 Spectrum of Small Bowel Perforation

Small bowel perforation presenting with generalized peritonitis is more commonly seen in the developing countries and less often in the West. In a review of 15 large series reported from Asia and Far East, small bowel perforation was the second most common cause (6–42% cases) of secondary peritonitis after gastroduodenal perforation [2]. In developing countries, typhoid fever is the commonest cause of small bowel perforation followed by tuberculosis, nonspecific perforations, intestinal obstruction, blunt abdominal trauma, and round worm infestation [2, 5]. In developed countries, the reported causes of small bowel perforation are Crohn's disease, trauma, ischemic enteritis, foreign bodies, radiotherapy, drugs, malignancies, and congenital malformations [6–9].

In oriental countries, apart from enteric fever and "nonspecific" ulcers, the other reported causes of small bowel perforations include Crohn's disease, Behcet's disease, radiation enteritis, adhesions, ischemic enteritis, SLE, and, very rarely, intestinal tuberculosis [10–14]. Free perforation is a rare complication of Crohn's disease, but its incidence is reported to be highest from Japan (3–10%) [12]. Similarly, the incidence of Behcet's disease is much higher in Japan, and perforation of the intestinal ulcers can occur in up to 56% of the cases [13].

Box 10.1 Salient Points: Small Bowel Perforation

- It is seen more commonly in the developing countries and less often in the West.
- Typhoid fever is the commonest cause followed by tuberculosis in developing countries.
- Classical features of underlying disease in a patient of peritonitis are sufficient to make the preoperative diagnosis.
- Chest X-ray has evidence of pneumoperitoneum in 50–80% cases.
- In stable patients, triple-contrast CT scan is the imaging modality of choice.
- In septic and unstable patients, bedside diagnostic laparoscopy helps in diagnosis and decision-making.
- The treatment is resuscitation followed by emergency exploratory laparotomy.
- The operative procedure is resection-anastomosis or ileostomy depending upon the patient's condition.
- Patients presenting with delayed perforation and severe peritonitis are best managed with laparostomy.
- If peritoneal lavage done during exploration is inadequate, patients may need re-laparotomy for doing re-lavage.
- The mortality in cases of perforation peritonitis ranges between 6% and 27%.

Table 10.1 describes the causes of small bowel perforations, and Table 10.2 gives the distribution of different etiologies of small bowel perforation reported in various series in the literature.

Table 10.1 Small bowel perforation—causes

Infections
Typhoid fever
Nonspecific
Tuberculosis
Amoebic
Clostridium
Histoplasmosis
Cytomegalovirus
Trauma
Blunt injury
Penetrating injury
Tumors
Primary tumors: lymphoma, GIST, adenocarcinoma, carcinoid, desmoid, angiosarcoma
Metastatic tumors: lung cancer, lymphoma, breast cancer, mesothelioma, melanoma
Mesenteric ischemia
Embolism
Arterial thrombosis
Venous thrombosis
Non-obstructive mesenteric ischemia
Crohn's disease
Diverticular disease
Meckel's diverticulum
Jejunal diverticulosis
Drugs
Steroids
NSAIDs
Potassium chloride
Cocaine
Oral contraceptives
Cytotoxic chemotherapy
Radiation enteritis
Foreign bodies
Dentures
Toothpick
Fishbone
Worms
Roundworm
Tapeworm
Pinworm
Iatrogenic
Laparoscopy (Veress needle, trocar, diathermy)
Enteroscopy
Peritoneal dialysis
Migrated biliary stents
Post-ESWL
Unsafe abortion
Abdominal drains
Gossypiboma

Table 10.2 Distribution of different etiologies of small bowel perforation reported in literature

Authors	Total cases	Typhoid *n* (%)	Nonspecific *n* (%)	Tubercular *n* (%)	Trauma *n* (%)	Malingnancy *n* (%)	Stangulation *n* (%)	Foreign body *n* (%)	Crohn's *n* (%)	Others *n* (%)
Bhansali [15]	46	29 (63)	–	7 (15.2)	–	–	–	–	–	–
Mehendale et al. [16]	32	9 (28.1)	2 (6.2)	13 (40.6)	–	–	–	–	–	–
Nadkarni et al. [17]	32	8 (25)	18 (56.2)	3 (9.3)	–	–	–	–	–	–
Rajagopalan and Pickleman [8]	16	–	–	–	–	3 (18.75)	–	2 (12.5)	4 (25)	7 (43.75)
Khanna and Mishra [5]	125	100 (80)	–	4 (3.2)	–	–	–	–	–	–
Bose et al. [18]	75	46 (61.33)	1 (1.3)	8 (10.6)	–	–	–	–	–	–
Sharma et al. [19]	62	42 (67.7)	5 (8.1)	12 (19.3)	–	–	–	–	–	–
Dorairajan et al. [20]	103	69 (66.9)	7 (6.8)	13 (12.6)	–	–	–	–	–	–
Chulakamontri and Hutachoke [10]	8	2 (25)	1 (12.5)	–	–	–	–	–	–	–
Ray et al. [21]	30	8 (26.7)	5 (16.7)	4 (13.3)	–	–	–	–	–	–
Chitkara et al. [22]	216	92 (42.6)	36 (16.7)	36 (16.7)	–	–	–	–	–	–
Chaterjee et al. [6, 23]	460	248 (53.9)	111 (24.1)	16 (3.5)	–	–	–	–	–	–
Khan et al. [24]	18	7 (38.9)	5 (27.8)	2 (11.1)	–	–	–	–	–	–
Jhobta et al. [25]	92	41 (44.5)	–	20 (21.7)	14 (15.2)	5 (5.4)	5 (5.4)	–	–	6 (6.5)
Wani et al. [26]	94	49 (52.1)	21 (22.3)	3 (3.2)	15 (16.0)	–	–	–	–	6 (9.3)
Afridi et al. [27]	120	51 (42.5)	–	63 (52.5)	–	–	–	–		6 (5.0)
Patil et al. [28]	60	38 (63.3)	11 (18.3)	10 (16.6)	1 (1.6)	–	–	–	–	–
Yadav and Garg [29]	40	23 (57.5)	–	9 (22.5)	–	–	–	–	–	8 (20.0)
Doklestic et al. [30]	25	–	–	–	5 (20.0)	–	15 (60)	2 (8.0)	3 (12)	–
Nekarakanti et al. [31]	105	5 (4.8)	30 (28.6)	4 (3.8)	36 (34.3)					14 (13.3)

Türkoğlu et al. [32]	30	2 (6.6)	14 (46.6)	2 (6.6)	–	8 (26.4)	2 (6.6)	1 (3.3)	1 (3.3)	–
Malhotra et al. [33]	36	27 (75)	–	3 (8.3)	6 (16.6)	–	–	–	–	–
Verma et al. [34]	41	10 (24.4)	23 (56)	8 (19.5)	–	–	–	–	–	–
Garg et al. [35]	98	84 (85.7)	7 (7.14)	7 (7.14)	–	–	–	–	–	–
Seth and Agrawal [36]	10	5 (50)	1 (10)	2 (20)	1 (10)	1 (10)	–	–	–	–

Others include idiopathic, jejunal diverticulosis, amyloidosis, obstruction, radiation enteritis, and hernia

10.2.2 Pathophysiology

Perforation in the small bowel can be spontaneous due to some underlying pathology or can occur following external trauma. Recent studies also support the hypothesis that perforation of the small intestine may be genetically based with different mutations causing altered connective tissue structure, synthesis, and repair [37]. In all the situations, the resultant leak from the small gut produces chemical inflammation during the first 6–8 h followed by a septic process due to secondary bacterial invasion (secondary peritonitis).

There is a difference between initial chemical peritonitis produced by jejunal leakage and the one due to ileal leakage. The jejunal juices are rich in pancreatic enzymes leading to intense chemical reaction in the peritoneal cavity similar to acute pancreatitis. Since pancreatic enzymes are inactivated by the time they reach the ileum, so ileal perforations produce less severe and localized peritoneal reaction. Due to this reason, ileal perforations are walled off much faster than jejunal perforations. Also, the clinical signs of peritonitis appear much later in distal perforations. However, these fine differences are lost when the underlying cause of perforation is septic in nature [38].

With the small bowel being an intraperitoneal structure, its perforation almost always leads to complicated intra-abdominal infection (IAI) causing localized or diffuse peritonitis [39]. The complicated IAIs, if not treated promptly, can lead to septicemia, multi-organ failure, and death [2, 40].

10.2.3 Clinical Features

The small bowel perforation leading to peritonitis mostly affects young males in the tropical countries [25–27, 41]. Majority of the patients present with the history of pain abdomen, distention, nausea, vomiting, altered bowel habits (usually obstipation), and fever. Abdominal pain may be acute or insidious. Initially, the pain may be dull and poorly localized due to involvement of visceral peritoneum and later progresses to steady, severe, and more localized pain once parietal peritoneum is involved. Other specific features depend upon underlying etiology and have been described separately under individual causes.

The clinical findings are that of localized or generalized peritonitis and depend upon the stage of presentation. However, majority of the patients in third world countries have a delayed presentation and come in a state of dehydration and shock. There is tachycardia, hypotension, decreased urine output, and tachypnea [25]. The patients having altered mental status are indicative of evolution to severe sepsis. On abdominal examination, there is distension, tenderness, and rigidity with masked liver dullness and absent bowel sounds.

10.2.4 Diagnosis

In endemic areas, the diagnosis of perforation peritonitis due to small bowel perforation is primarily a clinical diagnosis. The investigations aid in the diagnosis, but no single investigation is diagnostic. **Hematological investigations** reveal

polymorphonuclear leukocytosis, electrolyte imbalance (hypokalemia, hyponatremia), raised blood urea and creatinine, and metabolic acidosis. A **chest X-ray** in erect posture shows evidence of pneumoperitoneum in 50–80% cases as reported in various series [6, 20, 42–44]. Multiple air fluid levels on abdominal X-ray in erect position may be seen in 30% cases [27].

Abdominal ultrasound has the advantage of being portable and is helpful in the evaluation of the patients with suspected small bowel perforation. In most patients, much of the small bowel from duodenum to terminal ileum can be imagined with conventional sonography without any specific preparation [45]. However, the examination is sometimes limited because of patient discomfort, abdominal distension, and bowel gas interference [46]. The sonographic findings suggestive of small bowel perforation typically include the presence of extra-luminal air, a fluid collection, and inflammatory changes adjacent to a thickened small bowel segment [47].

In hemodynamically stable patients, **triple-contrast CT scan** (oral, rectal, and intravenous) is the imaging modality of choice for suspected small bowel perforation. In case of perforation, leaking of water-soluble contrast agent into the peritoneal cavity doesn't provoke inflammatory reaction as it is rapidly absorbed. CT scan provides excellent anatomical details of the intestinal wall, detects secondary signs of underlying bowel pathology within the surrounding mesentery, and picks up even small amounts of extra-luminal air or oral contrast leakage into the peritoneal cavity [48, 49]. Thus, abdominal CT plays an important role in its early diagnosis, with overall sensitivity of 64%, specificity of 97%, and accuracy of 82% [50]. However, from the safety perspective, the radiation associated with CT, especially in children, should be always kept in mind.

In recent times, **laparoscopy** is gaining wider acceptance in emergency surgery both as diagnostic and therapeutic modality [51]. In septic and unstable patients in ICU with uncertain preoperative diagnosis, bedside diagnostic laparoscopy helps in diagnosis and decision-making, thus shortening the observation period [52, 53]. The accuracy of diagnostic laparoscopy is very high and is reported to be 86–100% in unselected patients [54–56].

10.2.5 Principles of Treatment

The standard treatment after diagnosis of secondary peritonitis due to small bowel perforation is resuscitation followed by emergency exploratory laparotomy. All patients are resuscitated preoperatively with intravenous fluids (2–3 l of Ringer's lactate) along with nasogastric aspiration and urethral catheterization for monitoring of urine output. The broad-spectrum antibiotics covering gram positive, gram negative, and anaerobes are started, and electrolyte/acid-base imbalance, if any, is corrected. Midline laparotomy is performed, and the site and cause of perforation are identified and treated accordingly. The peritoneal fluid is sent for culture and sensitivity. After managing the small bowel perforation, the peritoneal cavity is irrigated with warm saline till effluent is clear and single, or multiple drains are put in the peritoneal cavity. The laparotomy wound is closed either in mass closure or in

layers depending upon the operator's preference. Patients are monitored postoperatively for recovery as well as detection and management of complications if any. The broad-spectrum antibiotics are continued in the postoperative period.

10.2.6 Source Control: Resection-Anastomosis Versus Ileostomy

The aim of surgery is "source control," and various options include primary repair of perforation, segmental resection and anastomosis, and primary ileostomy with or without resection of diseased bowel. Some authors have adopted laparoscopy as preferred surgical approach for the management of secondary peritonitis [57].

For a primary anastomosis following small gut resection, both the bowel ends should be healthy, and vascular and general condition of the patient should be good. This may not always be there especially in cases with delayed presentation having hemodynamic instability and generalized peritonitis. In such cases there is a high risk of anastomotic leak and its consequent morbidity and mortality. Therefore, diverting ileostomy is a much safer option that serves as a lifesaving procedure in these cases. Ileostomy should always be considered in cases with delayed presentation, severe fecal peritonitis, grossly inflamed gut with multiple perforations, multiorgan failure, poor mesenteric circulation, or dependence on high doses of vasopressors. After recovery of the patient, ileostomy closure is done as an elective procedure after 6–8 weeks that requires no further laparotomy. A study from India has reported significant decrease in leak rate from 13% to 4% after adopting ileostomy liberally in such cases [44].

Most of the authors have recommended loop ileostomy for fecal diversion in cases of small bowel perforations [58, 59]. A recent prospective study compared

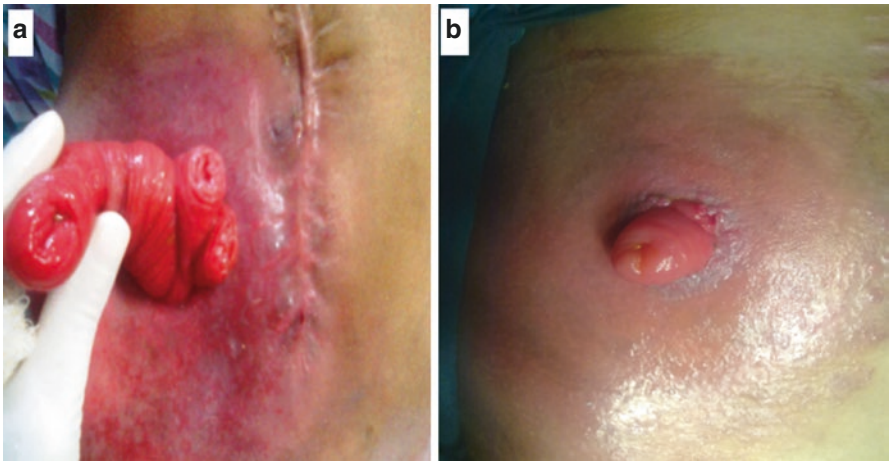


Fig. 10.1 Complications of ileostomy. (**a**) Ileostomy prolapsed. (**b**) Parastomal skin excoriation

loop vs. end ileostomy for small bowel perforations and observed end ileostomy as much easier to construct and manage postoperatively in edematous bowel [34].

However, apart from the need of second surgery for stoma closure, ileostomy has its own inherent complications in form of peristomal skin excoriation, fluid and electrolyte imbalance, and nutritional depletion [60]. Other complications are bleeding, ischemia, obstruction, prolapse, retraction, stenosis, parastomal hernia, fistula, residual abscess, wound infection, and incisional hernia (Fig. 10.1). In addition, ileostomy adds to financial burden and is also known to adversely affect the patient's quality of life due to physical restrictions and psychological problems [61].

10.2.7 Laparostomy, Planned/On-Demand Re-laparotomy

Patients presenting with delayed perforation develop a severe form of the peritonitis having a thick layer of fibrin, mesenterial abscesses, and edema of the bowel wall. Moreover, fluid infusion during resuscitation in a state of septic shock adds to the bowel edema. At the end of laparotomy, forced closure of the abdominal wall is likely to cause intra-abdominal hypertension (IAH) and consequently modify pulmonary, cardiovascular, renal, splanchnic, and central nervous system physiology causing significant morbidity and mortality. This has led to the evolution of therapeutic concept of open management of the laparotomy wound called "laparostomy" [62–67].

In cases with delayed presentation having severe purulent peritonitis, repeated peritoneal lavage every day or on alternate day is indicated for removal of slough and exudates. The lavage is done by re-laparotomy that can be "planned" or "on demand." The planned re-laparotomy is done 36–48 h after initial laparotomy, whereas on-demand re-laparotomy is done only if there is deterioration in patient's condition. Most of these patients need postoperative ventilatory support for variable periods.

Thus surgical approach that leaves the abdomen open may both facilitate re-laparotomy and prevent deleterious effects of abdominal compartment syndrome (ACS) [68]. However, serious complications like evisceration, fistula formation, and giant incisional hernia were observed following laparostomy. Therefore, the technique of open treatment was modified, leading to the concept of "covered laparostomy" [63, 69, 70]. Temporary closure of the abdomen may be achieved using simple gauze packing, impermeable and self-adhesive membrane dressing, absorbable or nonabsorbable meshes, plastic bag, zippers, and vacuum-assisted closure (VAC) devices. VAC has recently become a popular option for the treatment of open abdomen [71–74].

10.2.8 Antimicrobial Therapy

Ileal perforations, especially from the distal part, lead to peritoneal infection with gram-negative facultative and aerobic organisms. Initially, broad-spectrum empirical antimicrobials are given based on the severity of the infection, risk of resistant pathogens, and the local resistance epidemiology. The details of antimicrobial therapy are covered in Chaps. 16–21.

10.2.9 Outcome

Perforation peritonitis due to small bowel perforation bears a high mortality with the reported ranges between 6% and 27% [2, 75, 76]. Factors contributing to the high mortality and morbidity are delayed presentation, old age, delay in the treatment, septicemia, and associated comorbidities [27].

10.3 Typhoid Ileal Perforations (Box 10.2)

10.3.1 Introduction

Typhoid fever is a major health problem in third world countries most of which occurs in Asia and Africa. It is seen at places where food is contaminated, water supplies are polluted, and sanitation facilities are inadequate. However, increasing global travel to endemic regions, especially Indian subcontinent, has led to rise in number of such cases in developed nations as well [77]. The disease commonly causes typhoid enteritis that has serious complications such as small bowel perforation. It may lead to generalized peritonitis, intra-abdominal abscess, septicemia, fluid and electrolyte derangement, and severe malnutrition resulting in high mortality.

The reported incidence of small bowel perforation in cases of typhoid fever varies from region to region and ranges between 0.8% and 40% [78–83]. In West African region, the reported incidence of perforation is highest in the world (15–33%) [84]. Butler et al. in a review of 57,864 cases of typhoid fever in developing countries found the incidence of small bowel perforation to be 2.8% in pre-antibiotic era that was very much similar to the incidence of 2.5% in post-antibiotic era indicating that the incidence of perforation has remained almost unchanged despite use of the antibiotics [85].

10.3.2 Pathophysiology

Typhoid fever is caused by *Salmonella typhi*, and the pathogenesis of typhoid perforation in cases of typhoid fever is poorly understood. Everest et al. proposed a model explaining how bacterial factors and host immunological mediators within

Box 10.2 Salient Points: Typhoid Perforation

- Typhoid ileal perforation is caused by *S. typhi* infection, predominantly seen in young males in the age group of 20–30 years.
- It has definite seasonal prevalence being high during monsoon season.
- Intestinal perforation usually occurs during the late second or early third week of illness. In developing countries, cases are reported early within first week of illness.
- The perforation is usually single (may be multiple), oval in shape seen as "punched out hole" with erythematous mucosa, mostly located in terminal ileum that is inflamed and friable.
- Omentum does not migrate to the site of perforation due to delayed peritoneal response leading to generalized fecal peritonitis.
- The preoperative diagnosis in endemic areas is primarily clinical, based on history of prolonged fever and clinical findings suggestive of peritonitis.
- The positive Widal test is seen in 25–75% cases.
- Erect chest X-ray shows free sub-diaphragmatic air in 33–83% cases.
- CT scan is useful in evaluating patients with delayed presentation, sealed perforation, or less specific manifestations of the illness.
- Intraoperative findings almost confirm the diagnosis in endemic areas.
- All cases are treated surgically after adequate preoperative resuscitation.
- Primary closure of perforation is done in cases of single perforation with healthy bowel.
- Multiple perforations with unhealthy gangrenous small bowel segment are managed with resection-anastomosis.
- In moribund patients presenting late and having severe inflammation and edema of the bowel, primary ileostomy is done.
- Postoperative mortality rates are 9.9–62%.

infected tissue might contribute to the occurrence of typhoid ileal perforation [86]. It has also been hypothesized that the ileal perforation occurs during the second or third infection with *S. typhi* [87]. To prove this point, Nguyen in a study of 27 patients with typhoid ileal perforation observed culture of *S. typhi* was positive in only four perforation biopsy samples indicating an exaggerated host response to a limited number of bacteria within the Peyer's patches contributing to the development of perforation. This inappropriate or exaggerated host response might be due to immunological priming of the Peyer's patches as a result of prior exposure to *S. typhi* [88]. Thus it has been suggested that the necrosis of the Peyer's patches is caused by a mechanism similar to the Shwartzman and Koch reactions [86]. Shwartzman reaction involves clumping of reactive macrophages and lymphocytes around vascular tissues, resulting in intravascular thrombi and necrosis of venules. These effects occur because bacterial products prepare tissue sites in such a way that they become extremely sensitive to cytokine-mediated tissue damage on re-exposure to a cytokine-triggering stimulus [89].

Typhoid intestinal perforation generally occurs in second to third week of illness, but in developing countries cases are reported early within the first week of illness [82]. It has been attributed to hypersensitivity of the Peyer's patches, low immunity, high virulence of *S. typhi*, and ileal contents of bacteria [90–92].

10.3.3 Morphology

Preoperatively, the GI tract is found to be inflamed primarily involving terminal ileum and cecum. The bowel wall is friable, and bowel loops are matted together with purulent exudate on serosal surface near the site of perforation. Single or multiple perforations having variable diameter (mean 5 mm) are seen as "punched out holes" in the distal ileum, majority occurring within 30 cm of ileocecal junction on anti-mesenteric border (Fig. 10.2). The mucosa at the perforation site is erythematous, swollen, and fragile with occasional areas of "paper" thin wall around the perforation. Mesenteric nodes are enlarged and inflamed [88, 90].

Characteristically, unlike other intestinal perforations, the omentum does not migrate to the site of perforation due to delayed peritoneal response, and there is no attempt to localize the typhoid ileal perforation. Henceforth large quantities of small bowel contents continue to pour into the peritoneal cavity leading to generalized fecal peritonitis that can result in overwhelming sepsis and consequent mortality [81, 83].

On histopathological examination, the microscopic picture of typhoid perforation is one of a chronic, but discrete, inflammation around the perforation site, with relatively mild-to-moderate mucosal changes. There is marked proliferation of reticuloendothelial cells of the lymphoid follicles locally and systemically. There is

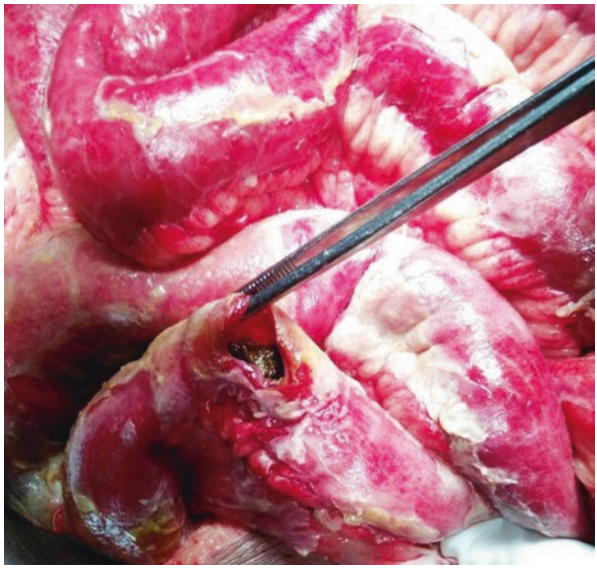


Fig. 10.2 Operative photograph showing longitudinally placed typhoid perforation in the terminal ileum with enteritis

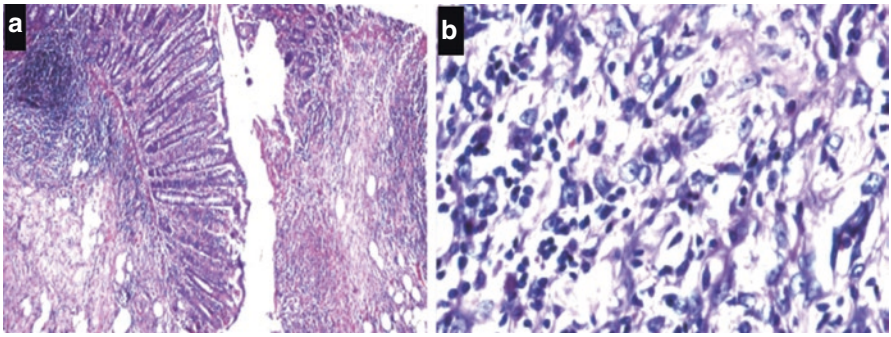


Fig. 10.3 Photomicrograph of the typhoid ileal perforation. (**a**) Mucosal ulceration and inflammation of the wall (H&E × 40X). (**b**) Inflammation predominantly composed of lymphocytes and histiocytes (H&E × 400X)

accumulation of histiocytes and mononuclear phagocytes. The macrophages characteristically form small nodular aggregates filled with red cells (erythrophagocytosis) [93] (Fig. 10.3).

10.3.4 Clinical Features

Typhoid perforation is predominantly seen in young males in the age group of 20–30 years, who have significant contribution to the economy of third world countries [94–96]. It is rarely seen in <5 years or >50 years of age [92, 97, 98]. There is a definite seasonal prevalence of typhoid perforation reflecting the incidence of typhoid fever, with majority of cases occurring in either summer or autumn.

The small bowel perforation may occur in a case of typhoid fever despite being on treatment for typhoid fever [81]. The cases typically present in emergency with history of constant, high-grade fever for the past 2–3 weeks. It is followed by sudden-onset central abdominal pain that is severe in intensity and gets generalized all over the abdomen along with distension abdomen, bilious vomiting, and obstipation. On examination, there are features of perforation peritonitis as described in Sect. 10.1.3.

In many cases classical clinical features may be masked due to late presentation and misuse of antibiotics. Another problem in endemic areas is that most of the cases presenting with persistent high-grade fever may initially be labeled as resistant malaria and need differentiation [99]. In such cases, high index of suspicion is warranted since delayed intervention can lead to high morbidity and mortality.

10.3.5 Diagnosis

The preoperative diagnosis of typhoid perforation in endemic areas is mainly clinical based on the history of prolonged fever and clinical findings suggestive of peritonitis.

Full blood count: In typhoid fever, there is anemia and leukopenia with neutropenia. However, leukocytosis occurs once there is ileal perforation.

Widal test: Widal test may be negative in the early course of the disease, and a positive diagnosis can be made from seventh to tenth day. The positive Widal test reported in cases of typhoid perforation in various studies range between 25% and 75% [100, 101]. Thus positive Widal test is useful for the diagnosis, but negative test doesn't rule out the diagnosis.

Blood and stool cultures: The blood culture and stool culture can pick up the organisms, but these are usually negative since majority of the patients have already taken antibiotics for persistent fever [81].

Erect chest X-ray: Including both domes of the diaphragm shows free subdiaphragmatic air in majority of the cases. The free gas under the right dome of the diaphragm has been reported to be seen in 33–83% cases of typhoid perforation in various studies [82, 85, 95, 99, 101, 102].

Abdominal ultrasound: Reveals free intraperitoneal fluid with specks of air suggestive of peritonitis in large number of cases. Free peritoneal collections were seen in 85.7% and 97% cases in different studies [82, 99].

Abdominal computed tomography (CT): Enteric perforation is a common emergency in endemic areas; however, its CT findings are rarely described in the literature. CT is useful in evaluating patients with delayed presentation, sealed perforation, or less specific manifestations of the illness. CT findings in enteric perforation include splenomegaly, mesenteric lymphadenopathy, circumferential bowel thickening of terminal ileum, free fluid, and pneumoperitoneum [103].

Intraoperative findings: In endemic areas, laparotomy findings of inflamed, edematous distal ileum with single or multiple oval perforations on anti-mesenteric border of the gut along with fecal peritonitis almost confirm the diagnosis of enteric perforation [81].

10.3.6 Treatment

Enteric perforation is best managed surgically. Preoperatively, adequate resuscitation is done as described in Sect. 10.1.4. Nowadays, it has been proven that mortality and morbidity is significantly decreased with aggressive preoperative resuscitation for 4–6 h [42, 80]. The serological and bacteriological reports are usually available in 1–3 days, so they act as a "post facto" aid to subsequent management after surgery. Exploration is done with lower midline laparotomy and, in most cases, on opening the abdomen; there is escape of foul smelling gas, pus, and fecal material. After draining the peritoneal contents, the site of perforation is localized. Several options are available for the management of perforation, and the most appropriate operative procedure should be chosen judiciously depending upon the general condition of the patient, site and number of perforations, degree of enteritis, and the degree of peritoneal soiling. Various options are:

Primary closure: The necrosed edges of the perforation are excised, and simple transverse closure of the perforation is done in one or two layers [104, 105]. Many a times, reperforation lesions are seen adjoining to the site of perforation. Uba et al. recommended that such lesions should be prophylactically buried, using Lambert's sutures on the surrounding seromuscular bowel wall [90].

Majority of the surgeons recommend that primary closure should be reserved for single perforations [106–109]. However, primary repair is also recommended in cases with multiple perforations where short bowel syndrome is likely to develop following gut resection [110, 111]. The argument given in favor of primary closure is that it is a quick procedure suited for seriously ill patients, gives good results, and is cost-effective. However, primary repair also carries a significant risk of reperforation and peritonitis leading to high morbidity and mortality [88].

Reperforation or perforation from another ulcer usually presents with peritonitis and fecal fistula generally leading to fatal outcome [112, 113]. It is difficult to differentiate the two without re-exploration which is usually not possible due to poor general condition of the patient [81, 106]. In such a situation, peritoneal drainage is done to remove the feco-purulent material, and once the patient is stabilized, ileostomy with peritoneal lavage is done as a lifesaving measure.

Recently, **laparoscopic treatment** of typhoid perforation with primary closure has also been reported successfully, but there are no comparative studies [114, 115]. Sinha et al. observed a port-site infection rate of 8% in laparoscopically managed cases [115].

Wedge resection and closure: A wedge of ileal tissue is resected around the perforation, and the defect is closed transversely in two layers [43, 98, 113]. Ameh et al. however reported that a wedge resection is associated with a very high mortality rate [116]. Therefore, it is no longer a popular procedure.

Resection-anastomosis: On exploration, if there are multiple perforations, large perforation with hemorrhage, and gangrenous or severely diseased terminal ileum, it is best managed with resection of diseased small bowel with end-to-end anastomosis [82, 96]. Athié et al. recommended a 10 cm resection from both ends of the perforation and anastomosis [117].

Ileo-transverse anastomosis: Primary closure of perforation with proximal ileotransverse anastomosis is sometimes performed in moribund cases as bypass procedure so as to decrease the chances of leak [81, 99].

Right hemicolectomy: It is performed in cases where terminal ileum and cecum are involved with gangrenous changes and multiple perforations [82, 83, 113]. Some authors have recommended limited hemicolectomy in such cases [99].

Ileostomy: In moribund patients presenting late in the course of illness, there is severe inflammation and edema of the bowel making it friable, and there is increased difficulty in handling and suturing the bowel. In such cases, primary ileostomy enhances intestinal decompression with improved healing, early resolution of ileus and helps in early start to enteral feeding [83, 101, 105, 118, 119].

Drainage of peritoneal cavity: It is done under local anesthesia in moribund patients as a lifesaving procedure [95, 102, 120–125].

Antibiotics in typhoid perforation: The emergence of multidrug-resistant (MDR) organisms in typhoid perforation is a major global health threat in endemic areas. In the past, chloramphenicol, ampicillin, or trimethoprim-sulfamethoxazole along with metronidazole was the treatment of choice, but multidrug resistance to these antibiotics started to emerge in 1990 [126]. It led to a shift toward the prescription

of fluoroquinolones or third-generation cephalosporins with metronidazole added for the anaerobes and gentamicin for the gram-negative pathogens.

Singhal et al. reported the trends in antimicrobial susceptibility of *S. typhi* from North India over a period of 12 years (2001–2012). In 852 isolates of *S. typhi*, a statistically significant decreased ($p < 0.001$) resistance to chloramphenicol, ampicillin, and cotrimoxazole was observed. Resistance to nalidixic acid was found to be highest among all the antibiotics; it has been rising since 2005 and is presently 100%. Ciprofloxacin resistance was relatively stable over the time period studied with a drastic increase from 5.8% in 2008 to 10% in 2009; since then it has increased in 2011–2012 to 18.2% [127]. Recent studies have shown high sensitivity of *S. typhi* to imipenem and meropenem [128].

10.3.7 Outcome

Despite surgical intervention, the cases of typhoid perforation have high morbidity and mortality.

The most common morbidity is wound infection, while the most serious is formation of a fecal fistula. The reported incidence of wound sepsis is 40–60% [83, 129–131] and that of fecal fistula resulting from repair leaks is 3.8–16.5% [83, 105, 132, 133]. Burst abdomen, intra-abdominal abscess, empyema, bleeding diathesis, and psychosis are other reported complications [129].

There is great variation in the reports of postoperative mortality rates ranging from 9.9% to 62% [80–82, 99, 105, 112, 119, 121, 129, 134, 135]. The reported mortality is higher in developing countries [83]. However, mortality rates as low as 1.5–2% have been reported from some parts of the developed world, where socioeconomic infrastructures are well developed [136].

10.4 Tubercular Small Bowel Perforation (Box 10.3)

10.4.1 Introduction

Tuberculosis primarily involves lungs and is prevalent in developing countries. However, its incidence is increasing the world over due to emergence of multidrug resistance, aging population, and pandemic of HIV infection. The incidence is also rising in Western countries due to immigration from third world countries [137].

Abdominal tuberculosis usually involves intestines, peritoneum, and mesenteric lymph nodes, commonest site being ileocecal region. It has varied presentation and can mimic variety of abdominal conditions. Its diagnostic confirmation is not always possible due to limited accuracy of biochemical and radiological investigations. The delay in the diagnosis can lead to complications like intestinal obstruction and gut perforation. The mainstay of treatment is antitubercular drugs, whereas surgery is indicated for the management of complications.

Box 10.3 Salient Points: Tubercular Perforation

- Abdominal tuberculosis is prevalent in developing countries, but its incidence is increasing the world over due to high incidence of HIV infection, aging population, and immunosuppressive drugs.
- Abdominal tuberculosis commonly involves ileocecal region that presents with constitutional symptoms and features of subacute intestinal obstruction.
- Intestinal perforation occurs in 1–15% of patients with abdominal tuberculosis.
- Perforation is usually single and occurs within or proximal to ileal stricture that presents with generalized peritonitis in 3/4th of the cases.
- Perforation can also develop 2 days to 4 months after start of antitubercular treatment.
- The diagnosis is usually based on clinical and radiological findings that require emergency laparotomy.
- Intestinal resection and anastomosis should be preferred over primary closure of perforation due to high risk of leak.
- Multiple strictures far apart from the site of perforation are managed with strictureplasty.
- For ileocecal tuberculosis, conservative ileocecal resection is preferred over right hemicolectomy.
- The moribund cases with perforation are best managed with diverting ileostomy with or without resection of perforated segment.
- Six months antitubercular chemotherapy is given in all the cases. The role of steroids is controversial.
- Cases of tubercular ileal perforation with HIV coinfection need urgent surgical intervention with antitubercular as well as antiretroviral therapy.
- The mortality rate in tubercular gut perforation ranges from 25% to 100%.

10.4.2 Incidence

Tuberculosis involves extra-pulmonary sites in 15–20% cases, and abdominal tuberculosis is the sixth most frequent site of occurrence [138, 139]. The incidence of abdominal tuberculosis was as high as 55–90% in patients with active pulmonary lesion before the advent of specific antitubercular drugs and got reduced to 25% after the development of specific chemotherapy [140].

However, in recent years, its incidence has increased, and one of its most feared complications is intestinal perforation seen in 1–15% cases [141–144]. In India, after enteric perforation, abdominal tuberculosis is the second commonest cause of small gut perforation and accounts for 5–12% of all gut perforations [20, 145, 146].

10.4.3 Pathophysiology

The gastrointestinal tuberculosis usually begins with direct ingestion of infected material. The most common site of involvement is ileocecal region due to

physiological stasis, high rate of fluid and electrolyte absorption, minimal digestive activity, and abundance of the lymphoid tissue in this area. Further spread occurs to the regional lymph nodes and peritoneum. The granuloma formation, fibrosis, and stricture formation in the gut occurs consequently over a period of time. The perforation usually occurs as a complication in long-standing cases having tubercular stricture in ileocecal region. Its usual site is within or proximal to the site of stricture; it may be single or multiple, but is usually single in 90% of the cases [146, 147] (Fig. 10.4). Along with stricture, there can be multiple yellowish white small tubercles diffusely distributed on the serosal gut surface (Fig. 10.5).

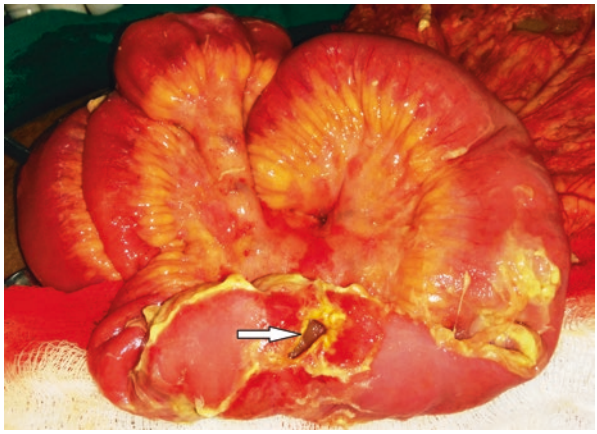


Fig. 10.4 Operative photograph showing transversely placed tubercular perforation in the distal ileum (*arrow*) with pus flakes on serosal surface

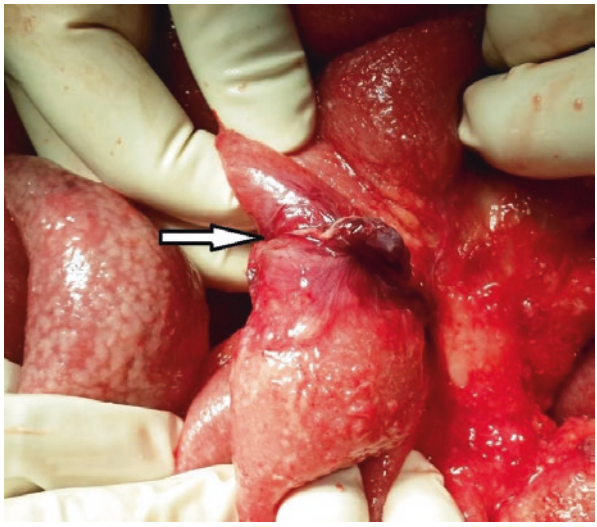


Fig. 10.5 Multiple small tubercles on serosal surface of the gut with distal ileal stricture (*arrow*)

The small bowel perforation can also develop following antitubercular treatment that can occur between 2 days and 4 months following start of the treatment [137, 148–150]. The early perforation is believed to be either due to natural progression of the disease or due to the effect of antitubercular treatment leading to decreased inflammatory response, impaired ulcer healing, and reduced reinforcement of mesentery [143]. The delayed cases have initial improvement with antitubercular treatment and then develop perforation possibly due to improved delayed hypersensitivity response of the host as well as high levels of mycobacterial antigens due to bacterial killing by effective drugs. This phenomenon is labeled as "paradoxical response" and is seen more often in HIV-positive patients taking both antitubercular and antiretroviral therapy [151]. Another possible mechanism described for delayed perforation could be underlying primary immunodeficiency [152]. However, as rightly pointed out by Leung et al., before accepting various mechanisms for delayed perforation, an inadequate response to antituberculous therapy due to drug resistance or poor drug compliance must always be excluded [153].

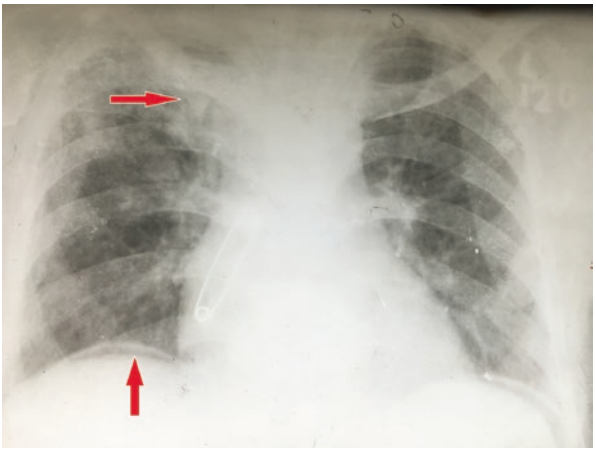
10.4.4 Clinical Features

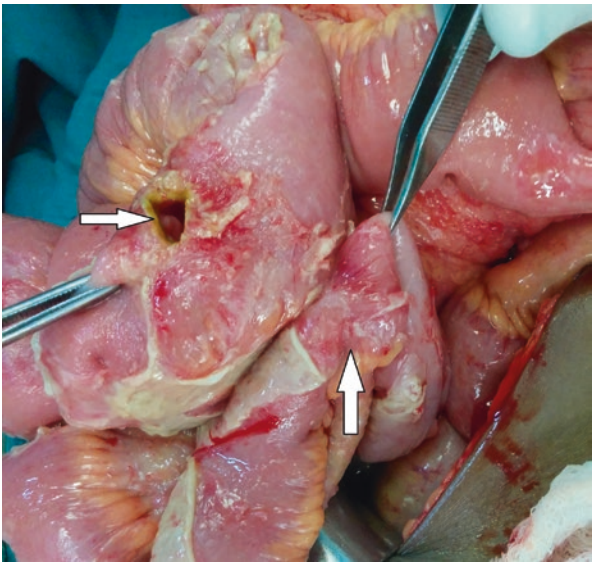
Abdominal tuberculosis is commonly seen in young adults between second and fourth decades due to abundant Peyer's patches at this age. It usually involves ileocecal region and presents in acute, subacute, or chronic forms, the last being most common. Majority of the patients have symptoms for a few weeks to months, sometimes years. The classical presentation is with the features of subacute intestinal obstruction in the form of colicky pain abdomen, distension after meals, vomiting, moving ball of wind, and diarrhea alternating with constipation. The associated constitutional symptoms are seen in about one-third of patients in form of low-grade fever with evening rise of temperature, malaise, night sweats, and loss of weight and appetite [154].

Sometimes, cases of abdominal tuberculosis may present in emergency as acute abdomen, and the cause may be acute intestinal obstruction, perforation peritonitis, acute mesenteric lymphadenitis, or acute tubercular appendicitis [139]. The tubercular small bowel perforation usually presents with localized or generalized peritonitis depending upon the severity of obstruction, size of perforation, and extent of adhesions.

In such cases, past history of subacute intestinal obstruction and evidence of tuberculosis on chest X-ray with pneumoperitoneum are important clues for the diagnosis (Case Summary 10.1).

Case Summary 10.1 A 30-year-old female with 3-month history of subacute intestinal obstruction presented in emergency with acute abdomen. Chest skiagram revealed air under the diaphragm (*arrow*) with fibro-cavitatory lesion in the right apex (*arrow*). Exploration revealed perforation in terminal ileum (*transverse arrow*) with stricture distal to perforation (*vertical arrow*) that was managed with resection-anastomosis. Diagnosis of tubercular perforation was confirmed on histopathology, and the patient responded to antitubercular chemotherapy.





10.4.5 Diagnosis

Majority of the cases with tubercular small bowel perforation present as an acute abdomen in the emergency, and the diagnosis of gut perforation is primarily based on radiological investigations.

Chest X-ray: The fibro-cavitatory lesions in the lungs are seen in only 15% patients of abdominal tuberculosis [155].

Abdominal erect skiagram: It may show free air under the diaphragm in 30–50% of the cases [146, 156, 157]. It may also show dilated intestinal loops, air fluid levels, and calcified lymph nodes.

Abdominal ultrasound: It may show specks of air with free fluid or septated collection with echogenic debris (due to particulate matter), matted small bowel loops with thickened walls, and rolled up omentum. The localized inter-gut loop fluid seen on ultrasound is described as "club sandwich" sign. Discrete or conglomerated (matted) lymphadenopathy with heterogenous echotexture may be seen, and central anechoic areas in the lymph nodes represent caseation necrosis. The ileocecal region is thickened and pulled up toward subhepatic region and is described as "pseudokidney sign" [138, 158].

CECT abdomen: It is the imaging modality of choice in the detection of abdominal tuberculosis and its complications like gut perforation. Apart from picking up even small volumes of free air due to perforation, it shows high- or low-density ascites, asymmetrical bowel wall thickening, luminal narrowing with proximal dilatation, adherent bowel loops, and thickened omentum. The finding of enlarged mesenteric lymph nodes with central caseation (central low-density with high-density periphery) in endemic areas is highly suggestive of tubercular abdomen [138, 159].

MRI: When compared to CT, it has no added advantage in the diagnosis of abdominal tuberculosis; hence, its utility in abdominal TB is limited.

Laparoscopy: It is an effective method of diagnosis in cases of tubercular peritonitis. However, its role in tubercular small gut perforation is not established.

Microbiological/histopathological diagnosis: Histopathological examination of biopsy specimens (small gut, lymph node, omentum) obtained during laparotomy for small gut perforation can reveal caseating granulomas (Fig. 10.6). Rarely, acid-fast bacilli may be picked up in the ZN staining of the biopsy tissues.

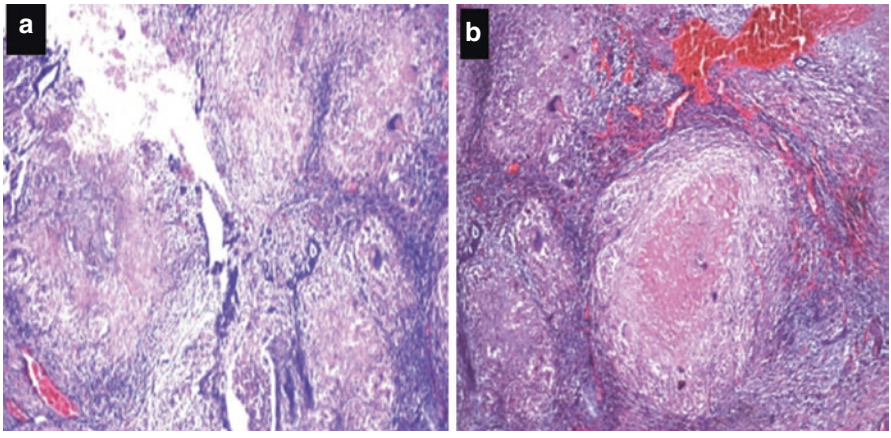


Fig. 10.6 Photomicrograph of tubercular small gut perforation showing. (**a**) Mucosal ulceration and granulomatous inflammation in the wall (H&E × 40X). (**b**) Epithelioid cell granulomas with Langhans' giant cells and central caseous necrosis (H&E × 100X)

10.4.6 Treatment

The treatment of tubercular small bowel perforation is primarily emergency laparotomy. It can sometimes be difficult for a surgeon to make an appropriate intraoperative decision on how to treat the perforation so as to achieve the best results. The operative procedures are decided based on the extent of disease and general condition of the patient. On exploration, intestinal **resection and anastomosis** should be preferred over **primary closure** of the perforation because of high risk of leak in primary closure cases [137, 146].

Tubercular perforations are usually ileal and are associated with distal strictures; if the two are close to each other, the segment should be resected followed by end-to-end anastomosis [160]. If there are multiple strictures far apart from the site of perforation, they may be managed with a separate resection and anastomosis or treated with **strictureplasty** [161]. In strictureplasty, a 5–6 cm-long incision is made along the anti-mesenteric side in the strictured area of the small gut and closed transversely in two layers.

Previously, more radical procedures like **right hemicolectomy** have been performed in cases of distal ileal perforation with ileocecal tuberculosis (Fig. 10.7).

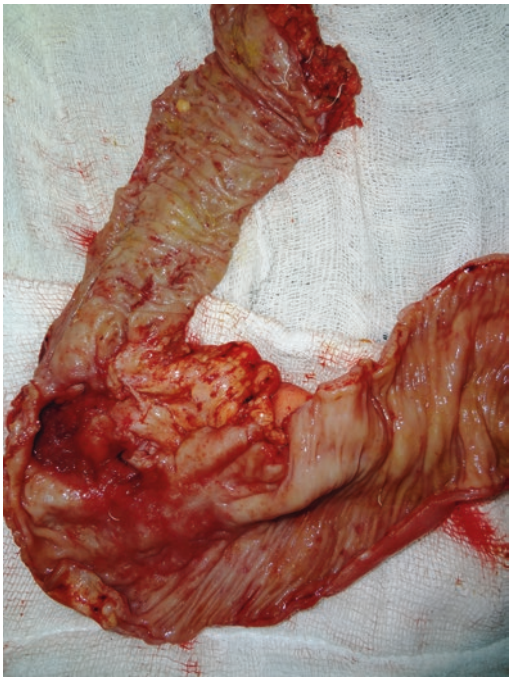


Fig. 10.7 Opened up right hemicolectomy specimen showing ulcero-hyperplastic ileocecal tuberculosis

These procedures were often not tolerated well by the malnourished patients leading to high morbidity and mortality. Over the years, it has been realized that tuberculosis is a systemic disease and cannot be eradicated by surgery alone. Hence, **conservative ileocecal resection** with a 5 cm margin on both sides and end-to-end anastomosis is preferred so as to minimize postoperative complications [162].

Bypass procedures like **ileo-transverse anastomosis** are no longer preferred to resections these days since residual disease might cause complications like obstruction, fistulae, and blind loop syndrome leading to malabsorption [139].

Many a times, patients of tubercular perforation have poor general condition and are not fit enough for resection and end-to-end anastomosis in emergency setting. Such cases are best suited for fecal diversion by exteriorizing the site of perforation in form of **ileostomy** or resection of diseased segment and ileostomy.

Sometimes, tubercular ileal perforation is associated with formation of "**abdominal cocoon**." In this condition, the entire intestine is plastered with very dense omental and bowel adhesions. During surgery, it is difficult to make out proximal from distal intestinal loop, and it is almost impossible to separate them without injuring the bowel (Fig. 10.8). These adhesions have recently been described as

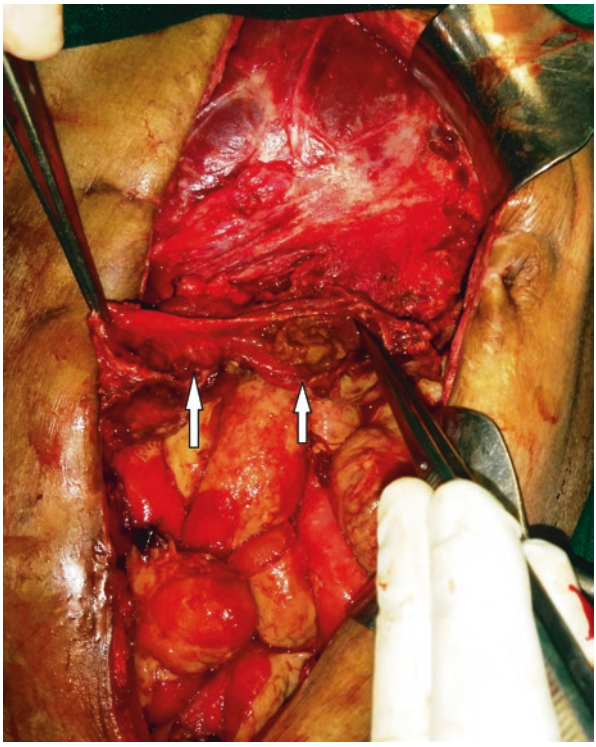


Fig. 10.8 Stretched out and perforated small bowel (*arrows*) during dissection of abdominal cocoon

"Jalebi adhesions" due to their similarity with an Indian dessert [163]. The surgical treatment includes extensive adhesiolysis that should be performed very gently so as to avoid postoperative fistula formation. The ileal perforation should be managed with ileostomy since resection and primary anastomosis have high chances of leak in these cases.

Antitubercular drugs: Apart from surgical intervention, the patients should receive conventional antitubercular therapy for at least 6 months. The treatment consists of initial 2 months of rifampicin, isoniazid, pyrazinamide, and ethambutol/streptomycin followed by 4 months of rifampicin and isoniazid. Pyridoxine should always be added to prevent peripheral neuropathy due to isoniazid toxicity. Some authors also recommend empirical addition of steroids for 2 months so as to reduce the degree of cicatrization during healing [147, 164], but others observed higher incidence of mortality in patients on steroids [152].

Second-line chemotherapy is necessary for a longer period if one or more of these first-line drugs cannot be used because of intolerance or drug resistance [165]. The second-line drugs include fluoroquinolones, amikacin, kanamycin, azithromycin, and clindamycin.

Some of the reports recommend antitubercular treatment for 12–18 months in such cases [146, 147, 166]. However, Balasubramanian et al. [167] performed a randomized comparison of 6-month short-course chemotherapy with a 12-month course in 193 adult cases of abdominal tuberculosis. Cure was observed in 99% and 94% in patients given short-course and the 12-month regimen, respectively [167].

It is most important to administer a correct and complete course of antitubercular treatment, as inadequate drugs, dosage, or duration is the most important cause of recurrent disease and emergence of multidrug-resistant tuberculosis [139].

10.4.7 HIV and Tubercular Perforation

Tuberculosis is the most common opportunistic infection among HIV-infected individuals. The cases of tubercular ileal perforation with HIV coinfection present with features of peritonitis and require urgent surgical intervention. However emergency surgery in such cases bears high mortality [168]. Regarding medical therapy, treatment of tuberculosis in HIV-infected patients is same as in non-HIV cases, but multi-drug-resistant tuberculosis is more common in the former group [169, 170]. For HIV infection, a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) along with one non-nucleoside reverse transcriptase inhibitor (NNRTI) is recommended for first-line therapy [171].

10.4.8 Outcome

Postoperative complications in cases of tubercular small bowel perforation include fecal fistula due to anastomotic leak, peritonitis, intra-abdominal abscess,

paralytic ileus, wound infection, and burst abdomen [172, 173]. Short bowel syndrome may occur as a delayed complication. Re-laparotomy may be required during follow-up period for recurrent intestinal obstruction due to strictures or adhesions [174, 175].

The reported mortality rate in tubercular gut perforation is very high ranging from 25% to 100% [137, 142, 143, 157, 176]. The factors associated with high mortality include old age, cachexia, delayed operation (36 h), multiple perforations, multiple strictures, primary closure of the perforation, anastomotic leakage, and steroid therapy [146, 152, 157].

10.5 Nonspecific Perforations

The small bowel perforations are labeled as "nonspecific" when these can't be classified on the basis of clinical features, serology, culture, operative findings, and histopathological examination into any specific disease such as typhoid, tuberculosis, or malignancy [10, 17, 23, 26]. Ulcers in such cases are usually single and commonly involve terminal ileum [23]. Wani et al. observed that the operative findings in these cases were similar to that of typhoid fever, but no laboratory evidence of the disease was found [26].

The proposed mechanisms for their occurrence are submucus vascular embolism [177], chronic mesenteric ischemia due to atherosclerosis or arteritis [178], or drugs such as enteric-coated potassium tablets [179].

Most of the series reporting cases of "nonspecific" perforations are from the Asian countries. These occur next to typhoid perforations and are closely followed by tubercular perforations in the small intestine [2]. The management is similar to typhoid perforation.

10.6 Other Intestinal Infections

Cytomegalovirus (CMV): In immunocompromised patients, CMV may affect GI tract, commonly involving the colon (47%) and rarely the small bowel (4.3%). Perforation is the most lethal complication and is commonly seen between ileum and splenic flexure [180–184]. The small bowel perforation presents with acute abdominal crisis in the setting of long-standing pain, wasting, weight loss, chronic diarrhea, and fever [185]. On exploration, the appearance of the perforated intestine reveals multiple brownish discolorations on the serosal surface that correspond to the underlying ulcers with one or more full-thickness perforations through an ulcer base [184, 186]. The diagnosis of CMV infection is usually based on pathology results, especially in cases where the lesions may appear grossly normal [187]. In view of multifocal nature of CMV, distal small bowel perforations should be treated by segmental resection with an end stoma and mucous fistula [188]. The anti-CMV

agent, ganciclovir, is given in postoperative period [189]. Overall, reported mortality following emergency laparotomy is 54–87% [184, 188].

Other intestinal infections that can rarely cause small bowel perforation are ***Entamoeba histolytica*** [190], ***Clostridium difficile*** [191], and **histoplasmosis** infection [192]. The latter is usually seen in cases with underlying HIV infection.

10.7 Traumatic Small Bowel Perforation (Box 10.4)

Small bowel perforation may occur following blunt or penetrating abdominal trauma. It has been reported to be the most commonly injured hollow viscus and the third most commonly injured organ in blunt abdominal trauma [193, 194].

Box 10.4 Salient Points: Traumatic Small Bowel Perforation

- It may occur following blunt or penetrating abdominal trauma.
- Mostly seen in younger age groups due to road traffic accidents.
- Mechanisms of injury in blunt abdominal trauma are compression and deceleration injury.
- Physical signs are reliable in only 30% of blunt trauma cases.
- Focused assessment with sonography in trauma (FAST) is an initial step of assessment of hemodynamically unstable patients and is useful in decision-making for urgent laparotomy.
- Diagnostic peritoneal lavage (DPL) can identify small bowel perforation with great sensitivity (up to 100%) but relatively low specificity.
- Abdominal CT scan is the diagnostic modality of choice in hemodynamically stable patients and shows contrast extravasation and/or extraluminal air.
- Laparoscopy is useful in hemodynamically stable patients and can avoid laparotomy in 40% cases.
- Absolute indications for operative intervention include hemodynamic instability, diffuse peritonitis, or radiological findings of gastrointestinal perforation.
- Priority of treatment for the small bowel perforation should be lower than the limb-threatening injuries.
- Simple closure is adequate for single perforation, whereas more extensive injuries require resection-anastomosis.
- Delayed presentation of blunt abdominal trauma needs constant clinical monitoring and serial imaging with urgent exploration if indicated.

10.7.1 Injury Mechanism

The mechanism of small bowel injury is straightforward in cases of penetrating abdominal trauma that usually presents with multiple perforations (Fig. 10.9). However, in cases of blunt abdominal trauma, the two primary mechanisms of injury are compression force and deceleration force. The deceleration injury commonly occurs following high-speed motor accident in which there is stretching and linear shearing between relatively fixed and free objects. As bowel loops travel from their mesenteric attachments, mesenteric tears leading to splanchnic vessel injuries and thrombosis may occur. In compression injury, the small bowel is compressed against a fixed point like vertebral column or seat belt. It causes rapid increase in intraluminal pressure leading to gut perforation on anti-mesenteric border, where the bowel is usually weaker [195–197].

10.7.2 Clinical Features

These injuries are seen in younger age groups and usually occur due to road traffic accidents [193, 197, 198]. The patients usually complain of continuous abdominal pain following trauma. On examination, wound of entry and exit can be assessed in penetrating trauma. In blunt trauma cases, "seat belt sign" (ecchymosis across the abdomen inflicted by seat belt) may be seen. Other clinical signs like abdominal distension, tenderness, and guarding may be present [199–201]. However, physical signs are reliable in only 30% of blunt trauma injuries [202].

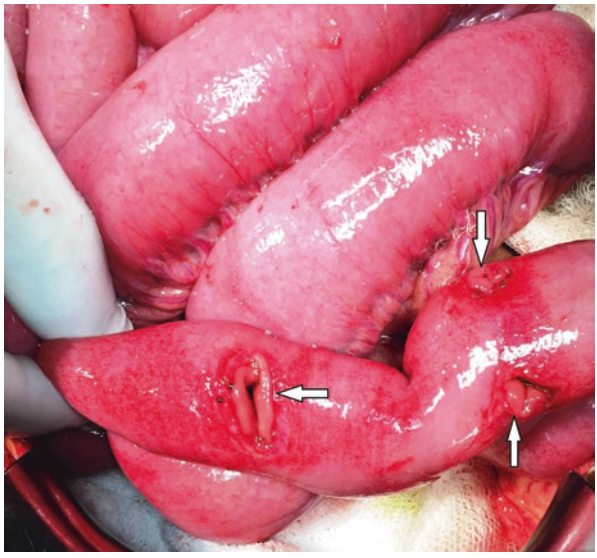


Fig. 10.9 Multiple traumatic ileal perforations (*arrows*) following stab abdomen

10.7.3 Diagnosis

There are no specific laboratory tests diagnostic for small bowel injury. In conjunction with history and physical findings, the raised white blood cell (WBC) count and serum amylase levels could be suggestive of bowel injury. However, neither WBC nor red blood cell (RBC) counts are reported to be significantly different between patients with or without small bowel perforation [195, 200].

Plain abdominal skiagram: It may show free subhepatic air indicative of hollow viscus injury, but it is reported to lead to an early diagnosis in only 7–8% of the cases with small bowel perforation [195, 203, 204]. Other findings that can be picked up with plain film are trajectory of a missile (gunshot) or presence of a foreign body (bullet, shrapnel).

Focused assessment with sonography in trauma (FAST): It is an initial step in assessment of hemodynamically unstable patients with blunt abdominal injury. It can detect free intraperitoneal fluid in a rapid, noninvasive, and repeatable way, with a sensitivity of 91–100%. It is very useful in decision-making for urgent exploratory laparotomy. In majority of the cases, it detects the presence of free fluid but identifies only 8% of cases of small bowel perforation with direct sonographic evidence [201].

Diagnostic peritoneal lavage (DPL): It can identify small bowel perforation with great sensitivity (up to 100%) but relatively low specificity [205]. The diagnosis is based on the findings of cell count ratio of ≥1, increased lavage amylase activity, presence of particulate matter, and/or bacteria in the lavage fluid [195]. With easy availability of CT scan, FAST and DPL have been reserved mainly for patients with hemodynamic instability who can't be transported to radiology department [196].

Abdominal computed tomographic (CT) scan: It is accepted as the primary diagnostic modality for identifying specific intra-abdominal injuries in hemodynamically stable patients. It is useful in differentiating patients needing abdominal exploration from those with injuries that can be managed nonoperatively.

In penetrating abdominal trauma, leaking of contrast is the most specific finding of bowel injury especially when the external wound track extends up to the injured bowel. The presence of pneumoperitoneum alone is not diagnostic as it can enter the peritoneal cavity along the penetrating wound [206].

In blunt abdominal trauma, CT findings considered diagnostic for bowel perforation are contrast extravasation and/or extra-luminal air. Findings which are non-diagnostic but suggestive are free fluid without solid organ injury, small bowel thickening, mesenteric streaking, and dilated bowel loops [207]. CT alone cannot reliably exclude small bowel perforation. However, any unexplained abnormality on CT after blunt abdominal trauma may signal the presence of intestinal perforation and warrant close clinical observation and further diagnostic tests. Patients with persistence of abdominal signs should undergo diagnostic peritoneal lavage or laparoscopy.

Laparoscopy: It is increasingly being used in recent years as an alternative modality for the diagnosis and treatment of small bowel perforation in hemodynamically stable patients. With emergency laparoscopy, laparotomy can be avoided in 40% of the cases [204], while in the absence of peritonitis, the laparoscopy-related morbidity rate is <1% [208].

10.7.4 Treatment

Patients diagnosed with small bowel injury should undergo urgent abdominal exploration. Absolute indications for operative intervention include continuing hemodynamic instability, diffuse peritonitis, or radiological evidence of gastrointestinal perforation such as pneumoperitoneum, spilled intraluminal contrast, and bowel infarction. However, the principle of "rushing to the operation suite" for a stable blunt abdominal trauma patients without detailed systemic examination is not justified. In a retrospective review of 111 cases of small bowel perforations caused by blunt abdominal trauma, delay in surgery for more than 24 h did not significantly increase the mortality with modern method of treatment; however, complications increased dramatically [195]. Therefore, priority of the treatment for small bowel perforation should be lower than the limb-threatening injuries.

On exploratory laparotomy, drainage of septic peritoneal fluid and warm saline lavage are done. Simple closure is usually adequate for single perforation of the small intestine, but more extensive injuries such as multiple perforations and gangrene from mesenteric injuries require resection and anastomosis [209].

10.7.5 Blunt Abdominal Trauma: Delayed Presentation

Delayed presentation of small bowel perforation following blunt abdominal trauma is extremely rare entity and is difficult to diagnose [210]. Following blunt abdominal trauma, there is mesenteric tear or formation of hematoma, which progressively affects the small bowel vascularity resulting in ischemia of the adjacent bowel segment (partial or full thickness), mucosal ulceration, and submucosal inflammation. The progressive ischemia and ulceration might result in delayed bowel perforation as late as 2 weeks to 3 months [211].

In such cases, the diagnosis of mesenteric hematoma is initially picked up on CECT abdomen. Most of the times, hemodynamically stable and asymptomatic cases can be managed conservatively. However, such cases need constant clinical monitoring and serial imaging in form of X-ray, ultrasound, and repeat CECT abdomen if indicated. If delayed perforation is diagnosed and the condition of the patient is deteriorating, an urgent exploration is indicated [210].

10.8 Small Bowel Tumors

A variety of small bowel tumors can present with spontaneous perforation, and majority of them are malignant in nature. Various mechanisms proposed for the perforation are [212–217]:

1. Neoplastic infiltration of the bowel wall with rapid growth of tumor, necrosis, and perforation.

2. Vascular occlusion by tumor cell infiltration leading to ischemic necrosis of bowel wall and perforation.
3. Tumor obstructing bowel with increased intraluminal pressure and perforation proximal to obstruction.

10.8.1 Lymphoma

Perforation and peritonitis are known complications of GI lymphomas, and vast majority of them occur in the small bowel [214, 216, 218–221]. The perforation can occur either at diagnosis or during the course of treatment, and the patients present with acute abdomen. However, the perforation occurs at the end of the first month or beyond the time of initial therapy and is likely to be missed. So clinical awareness and early evaluation of this clinical entity helps in prompt diagnosis. Plain X-ray abdomen shows pneumoperitoneum. On CECT abdomen, along with the morphological characteristics of lymphoma in the bowel wall, multifocal bowel involvement, peritoneal fat infiltration, ascites, lymphadenopathy, hepatosplenomegaly, and free air indicative of perforated GI lymphoma can be picked up [222]. The treatment is early surgical intervention.

10.8.2 Gastrointestinal Stromal Tumors (GIST)

A rare but important complication of GIST is tumor rupture with accompanying hemoperitoneum; and majority of ruptures occur spontaneously and are located in the stomach and small bowel [212, 214, 215]. The large-sized, exophytic GISTs with internal necrosis or cystic degeneration have an increased risk of developing spontaneous rupture [212, 215]. The clinical features are that of perforation peritonitis, and many a time, the diagnosis is made after exploration (Fig. 10.10).

During follow-up imaging, rapid growth of mass is a feature indicative of increased risk of spontaneous perforation [215]. The ultrasonography and CT scan findings of heterogenic tumor of laminated or whirled appearance, associated with echogenic or dense ascites, are indicative of a ruptured GIST. However, there is no relation between histologic criteria of malignancy and the rupture [212]. The treatment is early surgical intervention; however long term survival is poor.

10.8.3 Gastrointestinal Metastasis

The metastatic disease in the small intestine usually from an extra-abdominal site, including lymphoma, coming through hematogenous route may present with gut perforation [223, 224]. The most common primary malignancy causing small bowel perforation is lung cancer [217, 225]. The jejunum is more commonly affected by

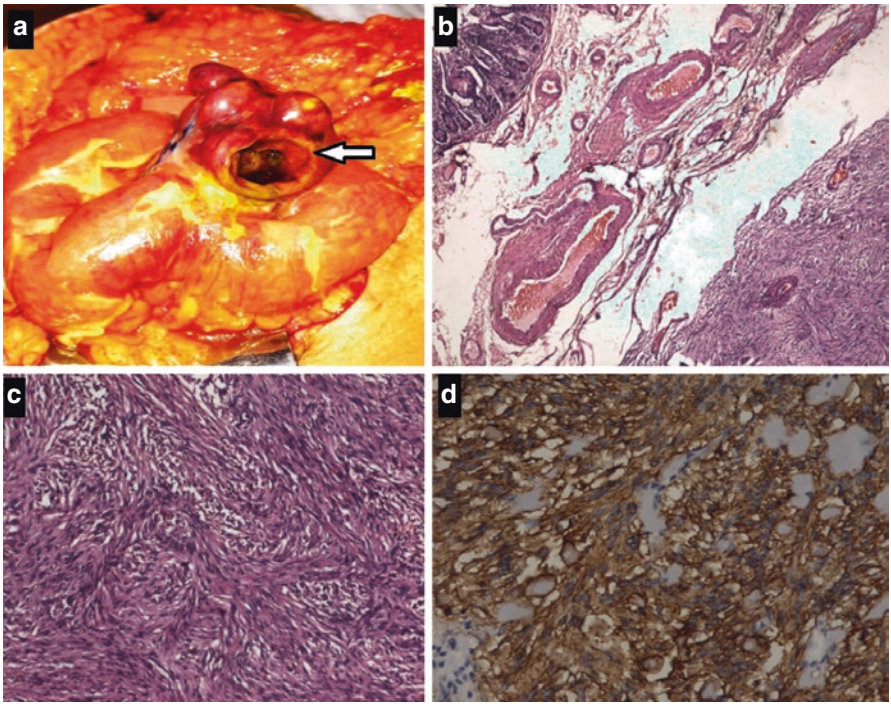


Fig. 10.10 Perforated gastrointestinal stromal tumor. (**a**) Operative photograph showing exophytic GIST on antimesenteric border of the jejunum presenting with perforation (*arrow*). (**b**) Microphotograph showing tumor centered in the muscle layer separated from the normal mucosa by a preserved muscularis mucosae and submucosa (H&E × 40X). (**c**) Microphotograph showing fascicles and intersecting bundles of tumor cells (H&E × 100X). (**d**) Microphotograph showing strong CD117 immunoreactivity in the GIST (IHC × 200X)

perforation than the ileum [214]. Other rare extra-intestinal causes are rhabdomyosarcoma [226], breast carcinoma [227], pleural mesothelioma [228], tongue squamous cell carcinoma [224], cutaneous malignant melanoma [229], and scalp angiosarcoma [230]. Perforated GI metastasis needs urgent surgical intervention. There is high operative mortality and poor outcome [214, 217].

10.9 **Acute Mesenteric Ischemia** (Box 10.5)

Acute mesenteric ischemia is a rapidly progressing disease that usually affects elderly population having serious comorbidities, and the diagnosis is often delayed due to nonspecific features. Small gut perforation can occur in cases of acute mesenteric ischemia leading to intestinal necrosis.

Box 10.5 Salient Points: Acute Mesenteric Ischemia

- Small bowel perforation occurs due to acute mesenteric thrombosis, acute embolism, non-occlusive mesenteric ischemia and mesenteric venous thrombosis.
- It has sudden onset with nonspecific symptoms, rapid clinical deterioration, and minimal abdominal signs leading to delay in diagnosis.
- CECT abdomen is the investigation of choice showing focal bowel wall thickening, lack of bowel wall enhancement, submucosal hemorrhage, air in portal venous system, intra-mural gas, and pneumoperitoneum.
- Volume resuscitation is the first and foremost step in management.
- The presence of peritoneal signs is an indication of surgical exploration.
- Resection of infarcted bowel with embolectomy is performed for embolism.
- Revascularization in arterial thrombosis is performed by bypass grafting or thrombo-endarterectomy.
- In non-occlusive mesenteric ischemia, the diagnosis is mostly made at exploratory laparotomy. Papaverine is useful in producing local vasodilatation and salvaging the compromised bowel.
- In mesenteric venous thrombosis, anticoagulants are given for 3–6 months.
- In extensive bowel involvement, second-look laparotomy after 24 h is done for salvaging bowel with doubtful viability.
- Mortality in acute mesenteric ischemia is 60%, maximum being for non-occlusive mesenteric ischemia.

10.9.1 Etiology

Acute mesenteric ischemia occurs due to the following conditions:

1. *Acute arterial embolism*: It is the commonest cause of acute mesenteric ischemia and occurs in more than half of the cases [231]. Most of the emboli are cardiac in origin coming from the left ventricle (following myocardial infarction) or left atrium (following atrial fibrillation). There are usually no preceding abdominal symptoms.
2. *Acute thrombosis*: It constitutes 25% of the cases, and it usually occurs over preexisting atherosclerotic lesions present on ostia of mesenteric arteries. Many of these patients give history of chronic symptoms consistent with previous transient mesenteric ischemia.
3. *Non-occlusive mesenteric ischemia*: It constitutes 20–30% of the cases and there is no occlusion of mesenteric arteries. The impaired blood supply occurs due to vasoconstriction following decreased cardiac output and renal or hepatic disease [232]. Most of these patients are critically ill and difficult to assess clinically.
4. *Mesenteric venous thrombosis*: It accounts for 5–15% of the cases and can be primary thrombosis due to hypercoagulation disorders (deficiency of protein C, protein S, antithrombin III, and factor V Leidin) or secondary thrombosis due to oral contraceptives, inflammatory bowel disease, pancreatitis, trauma,

malignancies, portal hypertension, or cirrhosis [233, 234]. The abdominal pain of acute mesenteric venous thrombosis is less severe, mid-abdominal, and colicky, suggesting an origin in the small bowel.

10.9.2 Clinical Features

The acute mesenteric ischemia usually has sudden onset, having nonspecific symptoms, and there is rapid clinical deterioration. To begin with, there is severe abdominal pain that persists beyond 2–3 h, but physical findings in the abdomen are unremarkable. The absence of clinical findings is usually responsible for delay in the diagnosis. The patient may also complain of nausea, vomiting, anorexia, diarrhea, and fever. Hematochezia is reported to occur in about 15% of the cases [235]. In delayed cases, gangrenous changes set in leading to small bowel perforation and peritonitis. The patient develops tachycardia, hypotension along with distension, tenderness and rigidity of the abdomen, and absence of bowel sounds.

10.9.3 Diagnosis

Lab investigations are not very helpful in making the diagnosis and are primarily meant for exclusion of other causes of acute abdomen. Plain X-ray abdomen usually has nonspecific findings, but the presence of free air makes the diagnosis of gut perforation. In delayed cases, thumb printing, intramural pneumatosis, and air in the portal venous system may be seen [236].

Duplex ultrasonography may demonstrate blood flow in the mesenteric circulation. But its role is limited due to the presence of bowel gas, need for technical expertise, and poor sensitivity for low-flow vessel disease [237].

Contrast-enhanced CT scan of the abdomen is the investigation of choice. The findings suggestive of the diagnosis include focal bowel wall thickening, lack of bowel wall enhancement, submucosal hemorrhage, air in portal venous system, intramural gas, and free air in the peritoneal cavity [238]. CT angiography can clearly delineate pathology in mesenteric vessels.

Magnetic resonance angiography has equal sensitivity and specificity to CT angiography, with the additional advantage of prevention of exposure to ionizing radiation. It is very useful for chronic mesenteric ischemia, but its utility in acute mesenteric ischemia is not established due to inadequate visualization of distal emboli and non-occlusive low-flow states [239, 240].

10.9.4 Treatment

The first and foremost step in the management is volume resuscitation that is guided by urine output and CVP monitoring. Dopamine can be used as vasopressor since it acts as mesenteric vasodilator in low doses.

The presence of peritoneal signs is an indication of surgical exploration, as bowel infarction has probably occurred. Resection of infarcted bowel as well as embolectomy

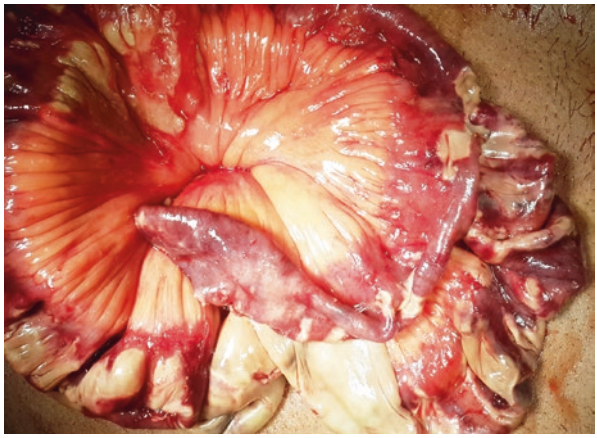


Fig. 10.11 Operative photograph showing extensive small gut gangrene due to acute mesenteric ischemia

can be performed during this process. Revascularization is more complex in arterial thrombosis and can be performed by either bypass grafting or thrombo-endarterectomy.

In case of non-occlusive mesenteric ischemia, the diagnosis is mostly made at exploratory laparotomy. The use of papaverine has been found to be useful in producing local vasodilatation and salvaging the compromised bowel [241].

In case of mesenteric venous thrombosis, the treatment with anticoagulants should be initiated as soon as the diagnosis is made or confirmed intraoperatively and continued for 3–6 months. On exploration, the aim of resection is to conserve as much bowel as possible. In cases with extensive bowel involvement, second-look laparotomy after 24 h should be considered with the aim to preserve the bowel with doubtful viability [242, 243] (Fig. 10.11).

Despite improvement in diagnostic and therapeutic modalities, mortality of acute mesenteric ischemia is about 60%, maximum being for non-occlusive mesenteric ischemia.

10.10 Crohn's Disease

Free perforation is a rare complication in Crohn's disease [244]. Majority of the cases involve ileum with a smaller number occurring in the jejunum or colon [245]. Many of the reports include secondary abscess perforation in their statistics, but this event is not a true free perforation. The incidence of free perforation in Crohn's disease is 1–3% in Western countries [245–249]. European and North American Jews are considered to be three–five times more susceptible to Crohn's disease than non-Jews. One study from Israel has reported the incidence of free perforation in Crohn's disease to be 15.6% [246].

The exact mechanism of free perforation in Crohn's disease is not known, but several hypotheses have been postulated. Greenstein et al. [245] observed that the

mean disease duration was 3.3 years before free perforation which was much shorter than duration of development of other complications like ruptured abscess or internal fistula [245]. This relatively short duration indicates that free perforation occurs before the protective granulomatous fibrotic and cicatrizing reactions have taken place [250]. Another factor could be bowel distension with increased intraluminal pressure proximal to an obstruction [245, 247–249]. The perforation may also occur in the absence of colonic dilatation due to ischemia or in cases of toxic colitis [251–254]. The use of steroids in Crohn's disease has not been found to be associated with higher incidence of free perforation [12, 245, 247–249].

Free perforation as a first sign of disease is seen in 23–30% cases [245, 246]. The patient of Crohn's disease will have sudden worsening in the clinical course, and there will be abdominal signs of generalized peritonitis. A high index of suspicion is required for making the diagnosis.

Plain X-ray abdomen (erect film) may rarely show free air under the diaphragm [255]. CECT abdomen demonstrates extra-luminal air or leaking oral contrast with typical findings of active Crohn's disease in form of thickened small bowel loop with multilayer enhancement and hypervascularity at its mesenteric side [206].

Free bowel perforation is an indication for emergency surgery in Crohn's disease. One should avoid debridement and simple suture of the perforation due to high rate of morbidity and mortality [245, 247–249]. For ileal perforation, limited resection of the most severely affected bowel segment with primary anastomosis is the treatment of choice. In moribund patients with generalized peritonitis, proximal diverting ileostomy should be done [12]. For jejunal perforations, Menguy recommended resection of the diseased loop and end-to-end anastomosis without temporary jejunostomy [244]. The latter is avoided due to serious metabolic problems associated with it and greater safety of jejunal anastomosis in general. The mortality rate of free perforations in Crohn's disease has decreased from 41% to 4% ever since the simple suture modality is replaced with resection [245].

10.11 Diverticular Disease

10.11.1 Perforated Meckel's Diverticulum

Perforation is a very rare complication of Meckel's diverticulum and is reported to be seen in 0.5% of symptomatic diverticula [256]. The factors and mechanisms leading to perforation of Meckel's diverticulum described in the literature are:

1. Progressive diverticulitis leading to spontaneous perforation
2. Foreign body in the diverticulum causing pressure necrosis and perforation [257–262]
3. Peptic ulceration and perforation due to acid secreted by ectopic gastric mucosa
4. Tumorlike leiomyoma in Meckel's diverticulum getting perforated [263]

5. Blunt abdominal trauma [264–267]

The perforation of a Meckel's diverticulum usually presents as acute abdomen mimicking acute appendicitis [268]. The diagnosis is usually made at operation, and it is managed with diverticulectomy or segmental resection along with peritoneal irrigation [269]. There are reports describing successful management of perforated Meckel's diverticulum with laparoscopic approach [270–272].

10.11.2 Jejunoileal Diverticulosis

These are seen in 0.25–1% of the population and can rarely perforate. These usually cause localized peritonitis because of their location on mesenteric border that readily gets sealed. The treatment is segmental intestinal resection with primary anastomosis including noninflamed diverticula [273–275].

10.12 Drugs Causing Small Bowel Perforation

The small and large intestines are the sites accounting for 20–40% of all drug-related side effects [276]. The common gastrointestinal drug-induced side effects include dyspepsia, nausea, vomiting, diarrhea, and constipation. However, of greater concern is drug-induced mucosal ulceration that can manifest as gastrointestinal hemorrhage, stricture, and perforation.

10.12.1 Steroids

Prolonged use of glucocorticosteroid may cause gastric and small bowel perforations that have high mortality (27–100%) [277–281]. The perforation usually occurs during the first 3 weeks of steroid therapy, and due to the masking effect of steroids, clinical presentation is vague, and abdominal discomfort is the only presenting symptom. The persistent pain is an indication of aggressive diagnostic work-up for gut perforation, and if diagnosed, it warrants early abdominal exploration [282].

10.12.2 Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs-induced small intestinal damage is diagnosed with video capsule endoscopy (VCE) and balloon enteroscopy (BE) in more than 50% of patients taking long-term NSAIDs. It mainly occurs in the distal small bowel and colon, most commonly in the ileocecal region [283–285]. Long-term NSAID therapy usually induces clinically silent enteropathy characterized by increased intestinal permeability and inflammation. Chronic occult bleeding and protein loss may result in iron-deficiency anemia and hypoalbuminemia. NSAIDs can also induce small

bowel ulcers that infrequently lead to acute bleeding, perforation, or chronic scarring responsible for diaphragm-like strictures [286]. Clinical presentation of diaphragm-like strictures is nonspecific and may produce obstructive symptoms, GI blood loss, or abdominal pain [287–290]. The cases with perforation present with features of peritonitis. Endoscopic balloon dilatation can be used for accessible strictures, but most cases of massive bleeding, obstruction, or perforation require surgical intervention [291].

10.12.3 Potassium Chloride Tablets

The high local concentration of potassium chloride due to breaking of enteric coating of the tablet in the small gut causes edema, hemorrhage, erosion, and cicatrizing stenosis of the gut wall. The gut perforation can occur with or without associated stenosis of the wall [292–294]. The reported mortality is as high as 27% [292].

10.12.4 Cocaine

Cocaine abuse can cause mesenteric ischemia and gangrene, which results in small and large bowel perforation as well as intraperitoneal hemorrhage [295–297]. Distal ileum is the most commonly affected site, but there are reports of gangrene involving almost any part of the small bowel [298].

10.12.5 Oral Contraceptives

Oral contraceptives can cause enterocolitis to small intestinal perforation and peritonitis due to mesenteric vascular thrombosis [299–302]. Estrogen component of oral contraceptives is associated with both arterial and venous occlusion, while progestin is related only with arterial occlusion [302].

10.12.6 Post-chemotherapy

The small bowel perforation is known to occur during chemotherapy for GI lymphomas as mentioned earlier. Other primary tumor sites like head and neck cancer, carcinoma breast, and acute monocytic myeloid leukemia are also reported to present with small bowel perforation [303–310]. The possible mechanism of intestinal perforation during chemotherapy can be necrotizing enteritis in the presence of neutropenia, metastatic tumor infiltration, and tumor lysis by chemotherapeutic agent [305, 311, 312]. Bevacizumab has been shown to cause bowel perforation in 1–4% cases [313]. The gut perforation usually occurs 2–3 weeks after giving the first cycle of chemotherapy [305, 309, 314]. Making diagnosis of gut perforation in such cases is often difficult since chemotoxicity itself leads to nausea, vomiting, and

abdominal pain mimicking features of acute abdomen. Hence a strong suspicion and awareness of the possibility of gut perforation is warranted so as to prevent delay in diagnosis and management [304].

10.12.7 Post-radiotherapy

Radiotherapy to pelvis has been occasionally reported to cause small gut perforation [315, 316]. The mechanism of perforation is previous abdominal surgery leading to adhesions, decreased bowel motility, and holding a segment of bowel in an unfavorable position during radiotherapy [317]. The treatment is surgical exploration with resection and anastomosis or stoma creation. There is high incidence of anastomotic leak following primary anastomosis [316].

10.13 Worms

Intraluminal worms can sometimes lead to intestinal obstruction and small bowel perforation. It is commonly caused by *Ascaris lumbricoides* (roundworm) [318]. Other worms like *Taenia solium* (tapeworm), *Enterobius vermicularis* (pinworm), and *Trichuris trichiura* (whipworm) can also rarely result in similar picture [319].

The mechanism of small bowel perforation is either due to pressure necrosis caused by heavy worm load or worms eroding the underlying ulcers in the small bowel that are commonly encountered in tropical countries due to typhoid, tuberculosis, and amebiasis [320, 321].

A small bowel perforation due to worms presents with acute abdomen and diagnosis is usually made with finding of pneumoperitoneum on plain X-ray abdomen. Management is emergency laparotomy and resection-anastomosis of the involved gut segment. The bunch of worms is gently milked out of the enterotomy site before anastomosis (Fig. 10.12).

For roundworm infestation, oral chewable tablet albendazole 400 mg single dose is the drug of choice. Paralyzing antihelminthics (e.g., pyrantel pamoate, piperazine, ivermectin) should be avoided in patients with intestinal obstruction since the paralyzed worms may further complicate surgery. For tapeworm, the drug of choice is a single dose of praziquantel 10–20 mg/kg or niclosamide 2 g as a single-dose chewable tablet [322]. In endemic areas, patients should be reevaluated in 3–6 months and retreated if stool ova persist.

10.14 Foreign Bodies

The foreign bodies in the small intestine may rarely cause obstruction and perforation.

The causes of foreign body ingestion include careless eating (among children and elders), psychiatric problems, and drug addiction [323, 324]. Pointed foreign bodies have higher risk of perforation, not because they directly penetrate the bowel wall but because their passage through the gut tends to be arrested, a process that initiates necrosis of the wall [325]. The common sites of involvement are areas of gut strictures or sites of anatomical narrowing (distal ileum and ileocecal junction) [326, 327].

The clinical presentation of small bowel perforation may vary from localized abscess formation to generalized peritonitis [328, 329]. On plain X-ray, free pneumoperitoneum is rarely seen since foreign body is gradually impacted and the perforation is locally covered with fibrin. CT scan shows segmental bowel thickening with localized pneumoperitoneum seen as extra-luminal gas bubbles. Demonstration of foreign body on CT scan establishes the diagnosis [206]. The treatment is urgent surgical intervention.

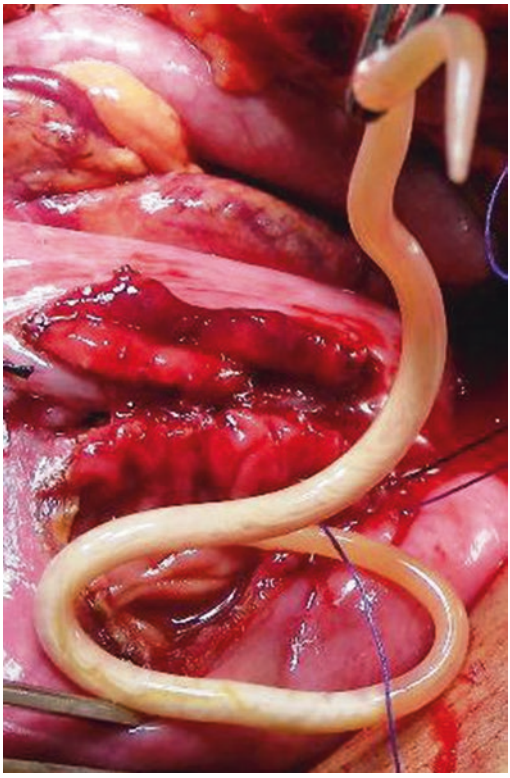


Fig. 10.12 Roundworm in small gut delivered through enterotomy at the site of perforation

10.15 Iatrogenic Perforations

10.15.1 Laparoscopic Surgery

Small bowel injury is a rare but serious complication of laparoscopic surgery. Small bowel perforation is likely to occur during creation of pneumoperitoneum by Veress needle or while blind insertion of first trocar. Umbilical piercing done for creating pneumoperitoneum is a particular risk factor for small bowel perforation due to adhesions between bowel and anterior abdominal wall [330]. Sometimes bowel injury might occur during cautery dissection due to inadvertent contact of diathermy to the adjoining gut wall in a direct or indirect manner. The small bowel injury is usually noted during surgery provided operating surgeon is careful. It is managed with primary repair with good outcome. However, if it is missed during surgery, the diagnosis might be difficult in postoperative period, because the features of the ensuing peritonitis are obscured by postoperative pain. In cases of intestinal anastomosis, the finding of extra-luminal oral contrast with intact anastomotic site seen on CECT abdomen indicates iatrogenic bowel injury [206]. In delayed cases, diagnosis may also be made by finding of gut contents in the abdominal drain [331]. The treatment is primary closure of perforation after freshening the perforation margins or gut exteriorization depending upon condition of the patient and severity of peritonitis. The mortality of bowel perforation during laparoscopy is reported to be 3.6% [332].

10.15.2 Enteroscopy

These days, double balloon enteroscopy is being used for diagnosis of obscure intestinal bleeding. In order to advance the long enteroscope through the small bowel, two balloons are alternatively inflated, a potential hazard for perforation. Perforations have also been described after capsule endoscopy, when the capsule is caught in a stricture [333].

10.15.3 Unsafe Abortion

Bowel perforation is a rare but serious complication of unsafe abortion [334]. Although rare and uncommon in developed world, it is a significant and major cause of maternal morbidity and mortality in third world countries [335]. In fact, the incidence of abortion-related bowel injuries is increasing in developing countries [336]. The reported rate of bowel perforation is 5–18% of all abortion-related complications [337–339]. The exact incidence is expected to be much higher since many cases go unreported due to its medicolegal implications [340, 341].

During unsafe abortion, bowel perforation occurs due to rupture of posterior vaginal wall by operating instrument (curette, ovum forceps, uterine sound, plastic

cannula) that damages the adjoining pelvic viscera [342]. The ileum and sigmoid colon are the most commonly injured parts due to relative fixity of these portions [335, 340, 342–346]. The diagnosis is based on clinical findings of peritonitis, X-ray abdomen showing pneumoperitoneum, ultrasound, and CECT abdomen showing free peritoneal collections. After resuscitation, early surgical intervention in form of resection/repair of the injured organs is done [347]. The awareness and early diagnosis of this clinical entity is of paramount importance in avoiding high morbidity and mortality.

10.15.4 Abdominal Drains

Small bowel perforation caused by drainage tubes following abdominal surgery is a rare complication with occasional case reports in the literature [348–354]. The suction drains can draw the bowel wall in the side holes due to high negative pressure [349, 350], whereas open drains due to long-term placement may cause perforation owing to pressure necrosis by the tip of the drain [348, 353].

The patients having abdominal drain in situ in the postoperative period may complain of high-grade fever with pain in the abdomen. On examination, there can be features of localized or generalized peritonitis. The small bowel contents coming through the drainage tube make the diagnosis obvious. Ultrasonography of the abdomen may reveal collections of mixed echogenic fluid. A fistulogram through the drain reveals that the tip of the drain had entered the gut [353, 355] (Fig. 10.13).

In patients without signs of peritonitis, discontinuation of the vacuum in suction drain and withdrawal of tube from the perforation site in an open drain invariably leads to healing of perforation site [350, 353]. The patients with generalized peritonitis need repeat laparotomy for management of perforation. It is recommended that to avoid this complication, drains should be placed carefully and removed early after the drainage has decreased [353].

10.15.5 Gossypiboma

Retained surgical sponge accidently left inside the body during surgery is known as gossypiboma. If left inside the abdomen during laparotomy, it can sometimes erode small bowel leading to its perforation. Gawande et al. in the largest retrospective study of 60 cases over a period of 7 years analyzed the risk factors for retained sponges after surgery. The incidence of retained surgical sponge was one per 1000–15,000 abdominal operations. The operations performed under emergency conditions ($p < 0.001$), unexpected change in procedure ($p < 0.01$), high BMI ($p < 0.01$), long duration of procedures, multiple surgical teams, and

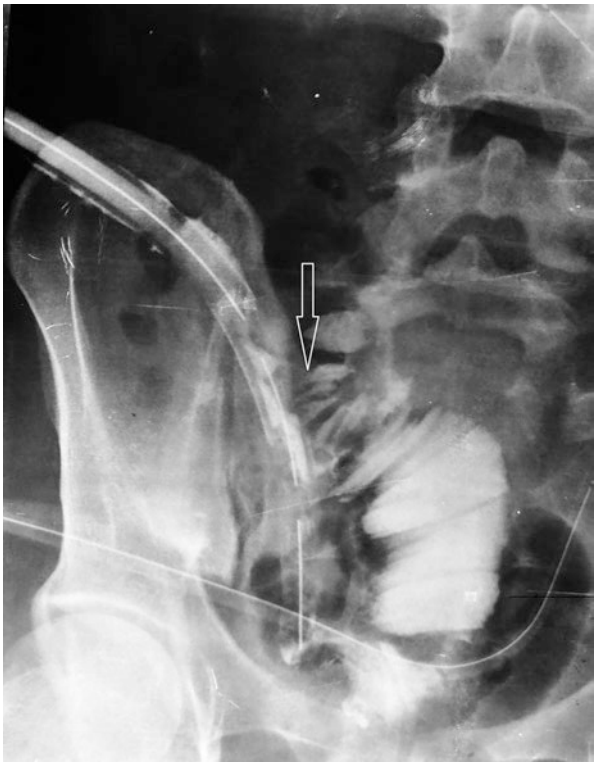


Fig. 10.13 Drain sinugram showing contrast entering into the jejunum (*arrow*) due to pressure necrosis by the drain causing gut erosion

change in assistant staff during operation were the risk factors for retained sponge [356].

Following laparotomy, persistent pain in the abdomen, fever, and wound infection should lead one to suspect a retained foreign body. The diagnosis needs awareness and high index of suspicion. If sponge contains radio-opaque marker, it can be seen in plain X-ray abdomen. Ultrasound abdomen may show intense acoustic collection in the mass in operation area. CECT abdomen is the investigation of choice. Surgery is the recommended treatment and is usually done through the previous operative site. Resection and anastomosis of the eroded segment of the gut is performed along with sponge removal and peritoneal lavage (Fig. 10.14). Laparoscopic removal of sponge has also been reported in some cases [357].

10.15.6 Miscellaneous causes

Extracorporeal shock wave lithotripsy (ESWL) for impacted ureteric stones, **migrated biliary stents**, and insertion of catheters for **peritoneal dialysis** are other rare iatrogenic causes for small bowel perforation [358–360].

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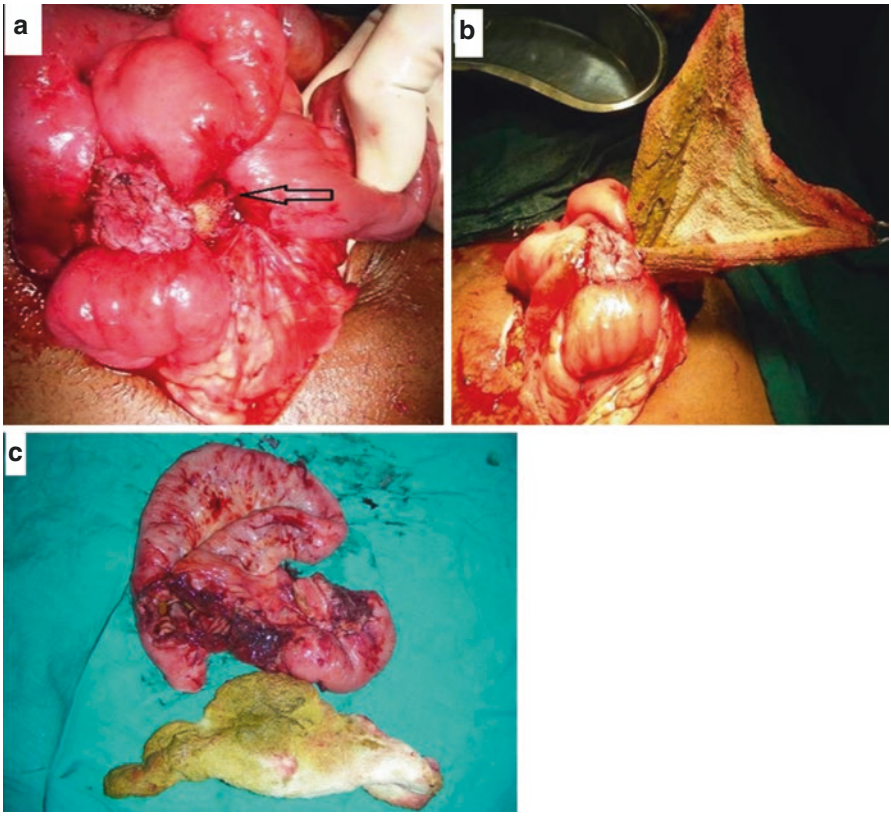

Fig. 10.14 Gossypiboma causing small bowel perforation. (**a**) Operative photograph showing sponge eroding small gut leading to sealed perforation (*arrow*). (**b**) Sponge being delivered through small gut. (**c**) Resected segment of terminal ileum with sponge

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Acute Colonic Diverticulitis

11

Jan Ulrych

11.1 Introduction

Acute colonic diverticulitis is defined as an inflammation of one or more diverticula located in the large bowel. The diverticula can develop anywhere in the large intestine. The colon may be affected by a single diverticulum or by diverticulosis. Diverticulosis is a condition characterized by the presence of numerous diverticula in the colon. Symptomatic diverticulosis is called diverticular disease, and the most common symptom is pain. Diverticula are characterized by herniation of the colonic mucosa and submucosa through the colonic wall. Diverticula are classified as true or false depending upon the layers involved. True diverticula involve all layers of the colon, including muscular layer and peritoneum. False diverticula (also known as "pseudodiverticula") do not involve muscular layer or peritoneum. Left-sided colonic diverticula and right-sided colonic diverticula are usually regarded as two units with different etiology and pathology. Similarly, acute left colonic diverticulitis and acute right colonic diverticulitis are different forms of this disease, and they will be described separately.

11.2 Acute Left Colonic Diverticulitis

11.2.1 Epidemiology

The incidence of diverticulosis has increased dramatically throughout the world over the last period. Recent data show that 50% of individuals older than 60 years of age and approximately 70% of people aged at least 80 years have colonic

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diverticula in the United States [1]. The same trend including an increase in the incidence of diverticulosis is observed in Europe. Diverticular disease has been believed to be a disease affecting the elderly people; however, more recent data have reported a dramatic increase in the incidence of left-sided colonic diverticulosis among younger persons in Western countries [2]. Diverticula in Western population are seen predominantly (90–99%) in the sigmoid colon and the distal descending colon. Golder et al. [3] reported 447 patients with barium enema verified diverticulosis including 72% of patients who had solely left-sided diverticulosis and about 22% of patients who had pan-diverticulosis or both-sided diverticula. On the other hand, left-sided colonic diverticulosis is uncommon in Asia and Africa, only 10.9% of all diverticulosis in China [4]. Nevertheless, an increase of the left colon diverticulosis is reported in Asian elderly population caused by the shift to a westernized lifestyle [5].

Acute left colonic diverticulitis (ALCD) is an inflammatory complication of diverticular disease in descending or sigmoid colon. The lifetime risk of developing acute left colonic diverticulitis is traditionally cited 10–25% in those patients harboring diverticulosis. Recent evidence suggests that real lifetime risk of developing ALCD is only about 4% among patients with diverticulosis. Patients who are diagnosed with diverticulosis at younger age may incur more risk of developing acute diverticulitis [6]. In line with the increase in the incidence of diverticulosis, incidence rates of ALCD as well as emergency department visits for acute diverticulitis have increased significantly. More than a half of all patients presenting to the emergency department with a primary diagnosis of acute diverticulitis were admitted to inpatient care in the United States [7]. However, new trends in hospital admission and surgery rate for ALCD have been observed. Decrease in the rates of hospital admission and surgery for ALCD, despite increasing emergency department visits, is associated with safe outpatient management of uncomplicated acute diverticulitis and changes to the surgical guidelines. The surgical rate ranges from 4.7% to 6.0% of emergency department visit patients [7, 8].

11.2.2 Classification

Acute left colonic diverticulitis encompasses a variety of conditions ranging from localized inflammation of the diverticula without colon wall perforation to severe diffuse fecal peritonitis caused by diverticula perforation and inflammation affecting the extensive colon segment. For the last period, the Hinchey classification has been the most commonly used classification especially among surgeons [9]. This classification is based on the surgical intraoperative findings of abdominal abscess or diffuse peritonitis. Nowadays, many patients are treated by antimicrobial therapy or percutaneous drainage only, and surgery is not necessary. Common nonsurgical treatment enforced new classification of ALCD. Several modified classifications were introduced within the last two decades, principally proposed according to the computed tomography (CT) findings [10–13] or combination of clinical, radiologic, and physiologic parameters [14]. Finally, a proposal for a CT-guided classification

Table 11.1 WSES classification of acute diverticulitis [16]

Classification (stage)	CT findings
Uncomplicated acute diverticulitis	
• Stage 0	Diverticula, thickening of the colonic wall or increased density of the pericolic fat
Complicated acute diverticulitis	
• Stage 1A	Pericolic air bubbles or little pericolic fluid without abscess (within 5 cm from inflamed bowel segment)
• Stage 1B	Abscess ≤ 4 cm
• Stage 2A	Abscess > 4 cm
• Stage 2B	Distant air (>5 cm from inflamed bowel segment)
• Stage 3	Diffuse fluid without distant free air (no hole in the colon)
• Stage 4	Diffuse fluid with distant free air (persistent hole in the colon)

of acute left colonic diverticulitis was published by the World Society of Emergency Surgery (WSES) working group in 2015 [15]. It is a simple classification system of ALCD based on CT scan findings. The WSES classification divides ALCD into two groups: uncomplicated and complicated acute diverticulitis. In the event of uncomplicated acute diverticulitis, the inflammation does not extend to the peritoneum. In the event of complicated acute diverticulitis, the inflammatory process proceeds beyond the colon throughout the peritoneal cavity. Complicated acute diverticulitis is divided into four stages based on the extension of the inflammatory process (Table 11.1). The WSES classification may guide clinicians in the management of acute diverticulitis and may be universally accepted for day-to-day practice.

11.2.3 Pathogenesis

It has been suggested that the development of inflammation in the diverticula may be caused by fecal material trapped in the diverticula. Inflammation develops due to abrasion of the mucosa allowing access of fecal bacteria to the deeper layer of the mucosa and submucosa. This can be associated with an acute inflammation of the mesenteric and pericolic fat with formation of an abscess. Another postulated mechanism for the development of acute diverticulitis is a micro-perforation at the fundus of the diverticulum leading to inflammation. However, the mechanism by which asymptomatic diverticula become inflamed and perforate is still under investigation and is probably associated with altered gut motility and increased pressure combined with a deranged colonic microenvironment [17]. The microbial load in the colon is high, with 10^{10}–10^{11} bacteria present per gram of stool. The major pathogens involved in ALCD are likely to be due to a patient's own flora. Therefore, they are predictable and include *Enterobacteriaceae* (predominantly *E. coli* and *Klebsiella* species), viridans group *streptococci*, *enterococci*, and anaerobes (especially *B. fragilis*). The main resistance threat in ALCD is posed by extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* which are becoming increasingly common in community-acquired intra-abdominal

infections worldwide. The most significant risk factors for ESBL-producing infection include prior exposure to antibiotics and comorbidities requiring concurrent antibiotic therapy.

11.2.4 Clinical Manifestation

History and physical examination are the cornerstones of ALCD diagnosis. The clinical presentation of acute diverticulitis depends on the severity and localization of the underlying inflammatory process. Patients often present with acute constant abdominal pain in the left lower quadrant due to involvement of the sigmoid colon. Sometimes patients may complain about suprapubic pain due to the presence of a redundant inflamed sigmoid colon. ALCD may be associated with nausea and vomiting or change in bowel habits (constipation and diarrhea). Patients may have localized peritoneal signs with localized tenderness, rigidity, and rebound tenderness, or they may have signs of diffuse peritonitis. Extensive perforated ALCD with diffuse peritonitis may result in hemodynamic instability and septic shock. However, the majority of patients are misdiagnosed on the basis of clinical decision-making alone. Clinical diagnosis of ALCD is not sufficiently accurate, and misdiagnosis rates vary between 32% and 57% [18]. In addition, the interpreting of clinical findings and diagnostic accuracy depends on the surgeon's previous experience. To improve diagnostic reliability, a clinical decision rule and a clinical scoring system for diagnosing ALCD using logistic regression have been published [18, 19]. For example, Lameris et al. [19] developed a clinical decision rule for the diagnosis of acute diverticulitis, based on three criteria: (1) direct tenderness in the left lower quadrant, (2) CRP > 50 mg/l, and (3) absence of vomiting. If all three criteria were met, 97% of the patients had ALCD.

11.2.5 Laboratory Tests

Serological inflammatory markers are used to support the clinical diagnosis of acute diverticulitis. White blood cell (WBC) count and C-reactive protein (CRP) are commonly determined when acute diverticulitis is suspected. The primary role of inflammatory markers is to verify the inflammatory complication of diverticulosis. However, the diagnostic value of serological inflammatory markers in discriminating complicated from uncomplicated acute diverticulitis was studied. WBC count may show leukocytosis and a left shift, nevertheless, may be normal in immunocompromised persons or elderly patients. Unfortunately, WBC count is of no value in discriminating complicated from uncomplicated acute diverticulitis. CRP has been identified as a useful biomarker of inflammation, and CRP may be helpful in the prediction of the clinical severity of acute diverticulitis. A CRP cutoff value of 150–175 mg/l significantly discriminates complicated from uncomplicated acute diverticulitis [20–22]. CRP may be used as diagnostic tool for identifying patients with increased risk of complicated acute diverticulitis who should always undergo a CT examination.

11.2.6 Imaging

Radiological imaging techniques that are used for ALCD diagnosis in the emergency department are computed tomography and ultrasound (US). CT imaging is the gold standard in the diagnosis of ALCD. The sensitivity and specificity of abdominal CT for the diagnosis of ALCD are 94% and 99%, respectively [23]. CT scan may be also used to determine the grade of severity and may drive treatment planning of patients. According to WSES guidelines, abdominal CT scan is indicated for all patients with suspected ALCD [16]. Ultrasound may be a useful alternative in the initial evaluation of patients with suspected ALCD, since US has wide availability and easy accessibility. In addition, US avoids radiation exposure. However, ultrasound limitations include operator dependency, poor assessment in obese patients, and difficulty in the detection of free air or deeply located abscesses. A step-up approach with CT performed after an inconclusive or negative US may be a safe approach for patients suspected of having ALCD.

11.2.7 Diagnosis and Differential Diagnosis

The diagnosis of ALCD should be suspected in a patient with left lower abdominal pain, abdominal tenderness on physical examination, and laboratory findings of increased inflammatory markers. Imaging, preferably CT scan, is required to establish the diagnosis of ALCD. The differential diagnosis of ALCD includes other etiologies of left lower abdominal pain — colorectal cancer, inflammatory bowel disease, infectious colitis, ischemic colitis, urological disease, gynecological disease, etc.

11.2.8 Treatment

11.2.8.1 Principles of Acute Left Colonic Diverticulitis Treatment

Treatment of ALCD is determined by severity of acute diverticulitis and patient's clinical condition. Patients with ALCD may be treated in outpatient setting or inpatient setting. Outpatient management should be considered in patients with uncomplicated ALCD without significant comorbidities, immunosuppression, and signs of sepsis. Patient's compliance with recommended therapy and reliability for return visits are obvious conditions for outpatient management. Patients should be reassessed clinically two or three days after the initiation of antibiotic therapy. If antimicrobial therapy is necessary, oral administration of antibiotics is acceptable. Clear liquid diet is usually recommended; however, no studies have examined the value of dietary restriction or bed rest [21, 22]. Repeat imaging study is not indicated unless the patient fails to improve clinically. Patients who have persistent abdominal pain and fever and who relapse after initial improvement should be admitted for inpatient treatment. Inpatient management is established for risk patients with uncomplicated ALCD (comorbidities, immunosuppression, advanced age, uncompliance) or patients with complicated ALCD. Patients with complicated diverticulitis must undergo treatment specific to

Table 11.2 Recommendations for antimicrobial therapy for ALCD [24]

Patient	Antibiotics
Stable (non-critically ill) patients	
• No risk factors for ESBL	Amoxicillin/clavulanic acid or ciprofloxacin + metronidazole
• ESBL-associated risk factors	Ertapenem or tigecycline
Critically ill patients	
• No risk factors for ESBL	Piperacillin/tazobactam
• ESBL-associated risk factors	Meropenem or imipenem + echinocandin

their complications. However, in inpatient setting, all patients are treated with intravenous antibiotics, fluids, and pain medications. Antimicrobial therapy plays an important role in the management of complicated ALCD. Antibiotics should be administered as soon as possible. Initial antimicrobial therapy for patients with ALCD is empiric in nature as these patients need immediate treatment and microbiological data (culture and susceptibility results) usually require ≥48 h for the identification of pathogens and antibiotic susceptibility pattern. Most of the complicated ALCD is community-acquired infection with predictable bacterial pathogens. Considering intestinal microbiota of the large bowel, ALCD requires antimicrobial coverage for gram-positive and gram-negative bacteria, as well as for anaerobes. Knowledge of local epidemiological data and regional resistance profiles is essential for antibiotic selection. For stable (non-critically ill) patients with ALCD, antibiotics with a narrower spectrum of activity are preferred. Anti-ESBL-producer coverage should be warranted for patients with prior exposure to antibiotics and comorbidities requiring concurrent antibiotic therapy. By contrast, for critically ill patients with ALCD, antimicrobial regimens with broad spectrum of activity are recommended (Table 11.2). Although discontinuation of antimicrobial treatment should be based on clinical and laboratory criteria, a 4–6-day period of postoperative antimicrobial therapy in complicated ALCD is suggested if source control has been adequate [16]. Disease progression should be suspected in patients with clinical deterioration and those who fail to improve after two to three days of intravenous antibiotic therapy. Repeat imaging is required in such patients. The purpose of repeat imaging is to look for new complications that may require further intervention (percutaneous drainage or surgery). Surgery for ALCD is indicated for patients who present with sepsis and diffuse peritonitis and for patients whose condition did not improve with medical therapy, percutaneous drainage, or both. Surgical options include simple colostomy formation, traditional sigmoid resection with colostomy (Hartmann procedure), and sigmoid resection with a primary colocolonic or colorectal anastomosis with or without a diverting loop ileostomy. Traditionally, surgery for acute diverticulitis encompasses one-stage procedures and two-stage procedures. Colon resection can be performed open or laparoscopically.

11.2.8.2 Treatment of Uncomplicated ALCD

The current consensus is that uncomplicated diverticulitis is a self-limiting condition in which local host defense can manage the bacterial inflammation without antibiotics in immunocompetent patients. Antimicrobial therapy can be avoided in

immunocompetent patients with uncomplicated diverticulitis without systemic manifestations of infection. This recommendation is supported by results of multicenter randomized trial that recruited 623 patients with acute uncomplicated left-sided diverticulitis. This trial reported no difference in recovery, complication, and recurrence in patients with (314 patients) or without (309 patients) antibiotics [25]. However, antimicrobial therapy is recommended in patients with uncomplicated acute diverticulitis associated with systemic manifestations of infection. Oral administration of antibiotics may be equally effective as intravenous administration [26]. Oral antibiotics are prescribed for 7–10 days. Outpatient management is suggested for patients with uncomplicated acute diverticulitis with no comorbidities, whereas patients with significant comorbidities and unable to take fluids orally should be treated in the hospital with intravenous fluid and intravenous antibiotics. In patients with CT-proven uncomplicated acute diverticulitis treated conservatively, a routine colonoscopy is not required. The risk of malignancy is really low. A systematic review investigating the rate of colorectal cancer found by colonoscopy after an episode of uncomplicated diverticulitis was published in 2014. Of the total number of 1468 patients with uncomplicated diverticulitis who underwent colonoscopy, 17 patients were diagnosed with colorectal cancer. The prevalence of colorectal cancer detected by colonoscopy was 1.16% [27]. However, patients aged 50 years or older should participate in colorectal cancer screening program including fecal occult blood test or colonoscopy.

11.2.8.3 Treatment of Complicated ALCD

Localized complicated ALCD encompasses acute diverticulitis with CT findings of pericolic air bubbles or little pericolic fluid and diverticular abscess. CT finding of pericolic air or little pericolic fluid without abscess (stage 1A—WSES classification) is associated with diverticulum perforation, and antimicrobial therapy should be always recommended. Surgery is not usually necessary in these cases. Therapy of diverticular abscess is based on the size of the abscess and patient clinical condition. Patients with small diverticular abscesses (<4–5 cm, stage 1B) may be treated by antibiotics alone, whereas patients with large abscesses (>4–5 cm, stage 2A) should be treated by percutaneous drainage combined with antibiotic treatment [16]. If the percutaneous drainage is not feasible in patients with large abscesses, the initial antibiotic therapy alone is justified; however, patient clinical condition monitoring is mandatory. Drainage catheter can be removed when the output has ceased. Routine fistulogram via the percutaneous drainage is not recommended; it should be performed in doubtful cases only. In patients with diverticular abscesses treated conservatively, early colonoscopy should be planned. In a retrospective study of 633 patients with acute diverticulitis including 145 patients with diverticular abscesses, 11.4% of the patients with abscess had colorectal cancer [28, 29]. Colonoscopy is generally performed 4–6 weeks after an attack of acute diverticulitis.

Generalized complicated ALCD encompasses acute diverticulitis with CT findings of solely distant free air (stage 2B), diffuse fluid without distant free air (stage 3), and diffuse fluid with distant free air (stage 4). These patients with diffuse peritonitis are typically critically ill and require prompt fluid resuscitation, immediate

intravenous antibiotic therapy (Table 11.2), and surgery without delay. Although the absolute prevalence of perforated acute diverticulitis complicated by diffuse peritonitis is low and most patients hospitalized for acute diverticulitis can be managed by nonoperative treatment, approximately 10–25% of all admitted patients may require an urgent operative intervention [30, 31]. Distant pneumoperitoneum is pathognomonic for sigmoid perforation in patients with diffuse peritonitis; nevertheless, a successful nonoperative management in patients with ALCD and a pneumoperitoneum was described [32]. Sallinen et al. reported results of conservative treatment in patients with distant air without diffuse intraperitoneal fluid. Nonoperative treatment was a feasible therapy for hemodynamic stable patients with pericolic extraluminal air or with small amount of distant intraperitoneal air in the absence of clinical diffuse peritonitis or fluid in the pouch of Douglas. Occurrence of large amount of distant intraperitoneal air or distant retroperitoneal air even in the absence of clinical diffuse peritonitis was associated with high failure rate (57–60%) of nonoperative management [28, 29]. It was suggested that only highly selected group of patients with distant pneumoperitoneum without intraperitoneal fluid may be treated by conservative treatment [16]. However, generally recommended treatment for patients at this stage should be surgical resection. Open surgery with colon resection is a commonly accepted treatment for patients with diffuse peritonitis due to ALCD. The principle of surgical treatment of ALCD with diffuse peritonitis is surgical source control and treatment of diffuse peritonitis. Surgical source control encompasses the elimination of the infection source by colon resection and correction of anatomic derangements as well as restoration of normal physiologic function. The aim of surgical treatment of diffuse peritonitis is the elimination of bacterial contamination and inflammatory substances. Hartmann resection (sigmoid resection with primary colostomy) has been considered the procedure of choice in patients with diffuse purulent or fecal peritonitis due to ALCD and remains a safe technique for emergency surgery. Hartmann procedure is still the most commonly performed emergency operation accounting for 64–72% of surgery for ALCD [31, 33]. However, restoration of bowel continuity after a Hartmann procedure has been associated with significant morbidity. Many patients (31–46%) cannot undergo reversal surgery due to comorbidities; therefore, they remain with a permanent stoma [34, 35]. In recent years, some authors have reported the role of colon resection and primary anastomosis with or without diverting stoma in the treatment of acute diverticulitis with diffuse peritonitis. Favorable rates of mortality and morbidity were observed in patients with diffuse peritonitis who undergo colon resection with primary anastomosis [36]. Moreover, greater stoma reversal rates in the primary anastomosis group with diverting stoma compared to Hartmann procedure were proved [37]. However, future randomized controlled trials are needed to evaluate different surgical treatments (Hartmann procedure versus colon resection with primary anastomosis). Hartmann resection is still advised for managing diffuse peritonitis in critically ill patients and in patients with multiple comorbidities. However, in clinically stable patients with no comorbidities, primary resection with anastomosis with or without a diverting stoma may be performed [16]. Emergency laparoscopic sigmoidectomy for the treatment of ALCD with diffuse peritonitis is feasible in selected patients and may be performed

only by a dedicated laparoscopic team. Furthermore, laparoscopic peritoneal lavage and drainage has been debated in recent years as an alternative to colonic resection in patients with diffuse peritonitis. It consists of the laparoscopic aspiration of pus followed by abdominal lavage and the placement of abdominal drains, which remain for many days after the procedure. Based on the disappointing results of the latest prospective trials such as SCANDIV, Ladies, and DILALA trials [38–40], laparoscopic peritoneal lavage and drainage should not be considered the treatment of choice in patients with diffuse peritonitis.

Damage control surgery with lavage, limited bowel resection, laparostomy, and scheduled second-look operation is feasible in critically ill unstable patients with diffuse peritonitis and septic shock.

11.2.9 Prognosis and Elective Surgery

Recurrence of ALCD is lower than previously thought. Recurrence after an uncomplicated ALCD has recently been shown to be less than 5% [41]. The indication for elective colon resection based on the age at onset younger than 50 years and two or more episodes of acute diverticulitis is no longer accepted. After a conservatively treated episode of ALCD, an elective sigmoid resection should be planned only in high-risk patients, such as immunocompromised patients [16]. Recommendations for elective sigmoid colectomy following recovery from ALCD should be made on a case-by-case basis. Elective surgery is recommended for patients with large abscesses treated by percutaneous drainage as well.

11.3 Acute Right Colonic Diverticulitis

11.3.1 Epidemiology

The incidence of right-sided diverticulosis is estimated approximately 1–2% of colonic diverticular disease in the Western world. However, recent results suggest that right colonic diverticular disease is more common and has higher density scores in the West population than previously reported [3, 42]. Diverticular disease of the cecum and the ascending colon is more common than the left-sided form of diverticulosis in Asian population [43]. Wide range in incidence of diverticulosis is reported throughout the Asian countries. Observed incidence of diverticular disease is 1.97% in China [4], 12.1% in Korea [44], and 23.9% in Japan [45]. This difference may be attributed to different race, genetic predisposition, dietary habits, and lifestyle. Diverse trends in the prevalence of diverticulosis were also reported throughout Asia. The prevalence of diverticulosis has been increasing up to about 24% in Japan [45]; in contrast, overall prevalence does not change significantly in China over the time [4]. The diverticula are predominantly (78–85%) located in the right side of the colon in Asian population [4, 45]. Asian patients with right-sided diverticular disease are younger compared to those ones with left-sided localization.

The prevalence of right-sided diverticulosis reaches a peak in patients at 51–60 years of age in Asian population [4, 45]. Considering gender right-sided diverticular disease is found more frequently in males.

The incidence of acute right colonic diverticulitis is increasing, and this diagnosis should be particularly considered in Asian and African population. Acute right colonic diverticulitis (ARCD) typically arises in younger people. Jun-Ho et al. reported that 84.8% of the patients with ARCD were from 20 to 40 years old. It was found that for those patients between 20 and 40 years of age, the incidence of ARCD expressed as a percentage of appendicitis was 8.9% [46].

11.3.2 Pathogenesis

Right-sided diverticula may be solitary or numerous and can be found in the appendix, cecum, or ascending colon. When right-sided diverticula are solitary, they are usually congenital and true diverticula. Most of the congenital diverticula are found between 1 cm proximal to and 2 cm distal from the ileocecal junction. When diverticula are multiple, they are typically acquired and false diverticula. For acquired diverticula, increased intraluminal pressure and abnormal ascending colon motility play an important role in disease pathogenesis. Solitary cecal diverticulum is rare. In Thai adults, the occurrence of solitary cecal diverticulum was only 1.5%, whereas right-sided diverticulosis was reported in 22.3% of individuals [47]. The mechanism by which asymptomatic diverticula become inflamed and perforated is probably the same as in the event of acute left colonic diverticulitis.

11.3.3 Clinical Manifestation

It is difficult to distinguish acute right colonic diverticulitis from acute appendicitis according to symptoms and clinical characteristics. However, the clinical manifestation of ARCD seems to be a little different from those of acute appendicitis. Relatively long-lasting right lower abdominal pain, lateralized right abdominal pain, less nausea and vomiting, and ache starting from the right lower abdomen have been reported to be more specific for ARCD [48]. Also pain migration from the upper abdomen to the right lower abdomen is more characteristic for acute appendicitis than for ARCD. Clinical diagnostic criteria and scoring model for better preoperative diagnosis of ARCD were proposed. Patients are scored upon clinical presentation based on major diagnostic criteria (two points for each symptom) and minor diagnostic criteria (one point for each symptom). Major diagnostic criteria include no pain migration to the right lower abdomen, a leukocyte count of $<10{,}000\ mm^{-3}$, lateralized abdominal pain, and a history of right colonic diverticulum. Minor diagnostic criteria include a history of right lower abdominal pain, no symptoms of nausea or vomiting, symptoms of constipation or diarrhea, and abdominal pain for at least seven days. Score ≥ 3 points is associated with high sensitivity

(85%) but low positive predictive value (28%) [49]. These clinical criteria and scoring model should help to distinguish patients with right lower abdominal pain and high suspicion for ARCD. CT scan should be considered in the event of high clinical suspicion for diverticulitis.

11.3.4 Laboratory Test

WBC count and CRP are generally used for diagnosis of inflammatory complication of the diverticula. In the event of right lower abdominal pain, WBC count has been identified as a useful biomarker discriminating ARCD and acute appendicitis. It was reported that leukocytosis with a left shift is associated more frequently with acute appendicitis than ARCD [46]. It was mentioned above that a leukocyte count of <10,000 mm^{-3} is used as major diagnostic criterion.

11.3.5 Imaging

Computed tomography scan, ultrasound, and magnetic resonance imaging have all been described as effective modalities to differentiate acute right colonic diverticulitis from other intra-abdominal pathology. CT scan has a documented diagnostic accuracy rate of 90% to 95% [50]. However, routine computed tomography in all patients with right lower abdominal pain is not cost-effective. CT scan should be recommended in patients with clinical findings of increased risk of ARCD. CT findings of ARCD are similar to those of acute left-sided diverticulitis, which include thickening of fascial planes, pericolic fat stranding, colonic wall thickening, the presence of an extraluminal mass, and the presence of an extraluminal free air and intraperitoneal fluid. Ultrasound is another widely used modality for assessing right lower abdominal pain. US has 91.3% sensitivity and 99.8% specificity for correct diagnosis of ARCD, but ultrasound examination has to be performed by an experienced operator. Similarly, a step-up diagnostic approach may be recommended. CT should be considered in patients with US findings or clinical findings of suspected acute diverticulitis [50].

11.3.6 Diagnosis and Differential Diagnosis

Historically, the preoperative diagnosis rate of ARCD is extremely low, accounting for 4–16% [50], since there are no clinical signs of symptoms that are truly specific for acute diverticulitis. Moreover, the differential diagnosis of acute diverticulitis includes other etiologies of right lower abdominal pain—acute appendicitis, Crohn's disease, perforation by a foreign body, tumors of the appendix, gastroenteritis, urological disease and gynecological disease, etc. ARCD can be accurately diagnosed and distinguished from most other causes of lower abdominal pain by imaging (CT) only.

11.3.7 Treatment

The correct pretreatment diagnosis of ARCD allows clinicians to determine optimal management according to the severity of the diverticulitis. Patient may avoid unnecessary surgery because ARCD without complications can be treated medically. However, in many cases the correct diagnosis is made intraoperatively.

If a preoperative diagnosis of uncomplicated ARCD is made, patient management should consist of bowel rest and intravenous antibiotics. Reported recurrence rate after first attack of uncomplicated acute diverticulitis ranges 9.9–12.6% [51, 52]. Most of the recurrent attacks of ARCD have indolent course and may be successfully managed with medical therapy. Elective surgery should be considered in cases of frequent recurrence that interfere with activities of daily living. Patients who present with abscess, but nevertheless are hemodynamically stable, should be treated with percutaneous drainage, bowel rest, and intravenous antibiotics. Patients with perforation and diffuse peritonitis or who are clinically unstable should be taken for immediate operative intervention.

If the correct diagnosis is made intraoperatively, the surgical management of the disease is controversial. With the exception of isolated cecal diverticulitis, no consensus currently exists on optimal treatment of patients with ARCD found incidentally at time of operation. Less extensive management with prophylactic appendectomy and postoperative antibiotics has been suggested for the uncomplicated ARCD diagnosed intraoperatively. Prophylactic appendectomy is justified to avoid misdiagnosis in case of future episodes of acute diverticulitis. On the other hand, some surgeons advocate surgical therapy ranging from diverticulectomy and ileocecal resection to right hemicolectomy and depending on the extent of inflammation. Resection of all diverticula is usually suggested because surgery prevents the recurrence of acute diverticulitis. However, it is impossible to determine all the locations of the diverticula without inflammation during surgery. Immediate right hemicolectomy should be considered in cases of extensive inflammatory changes, multiple diverticula, and cecal phlegmon. When malignant disease is suspected, the right hemicolectomy is recommended as well. Surgical resection can be safely performed even in an unprepared colon with few postoperative complications. In cases of isolated cecal diverticulitis, resection is strongly recommended.

11.3.8 Prognosis

ARCD has usually an indolent course and low rate of complicated diverticulitis at first attack. Conservative management and surgery treatment are safe and effective in most patients. Therefore, the therapy outcomes are far more favorable compared to ALCD.

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Postoperative Peritonitis: Etiology, Diagnosis, and Treatment

12

Torsten Herzog and Waldemar Uhl

12.1 Introduction

Even in developed countries, postoperative peritonitis is still associated with a mortality of 20–60%, mostly secondary to organ failure from systemic inflammatory response syndrome (SIRS) and septic shock. The incidence of severe sepsis is approximately 19 million cases worldwide per year [1, 2]. While pneumonia is the most common cause for sepsis among all intensive care unit patients, abdominal sepsis is ranked second [3]. Postoperative peritonitis is the most common diagnosis among critically ill surgical patients leading to sepsis syndrome and severe sepsis [4, 5].

The terms severe intraabdominal infection, peritonitis, and abdominal sepsis are often used simultaneously. It is important to remind that these terms deal with complicated intraabdominal infections. Uncomplicated intraabdominal infections usually require only surgical treatment, while an antibiotic treatment is only required as prophylaxis to prevent postoperative surgical site infections. Nevertheless, among the different forms of complicated intraabdominal infections, there is a wide range in the severity of illness, depending on the mode of acquisition, the origin of the infection, the patients' comorbidities, and the microorganisms encountered in peritonitis [6, 7]. The mortality from peritonitis after appendectomy is less than 10%, while the mortality is more than 20% after gastric ulcer perforations and reaches even 50% for some patients with colon perforations or biliary peritonitis [8, 9].

The term peritonitis describes the local reaction of the organ peritoneum as well as the patients' reaction to digestive fluids, microorganisms, and their toxins. The severity of illness among patients with postoperative peritonitis can differ dramatically. In patients with an accidental small bowel injury during laparoscopic

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surgery, a severe host reaction is initiated, if the injury remains undetected. The treatment is often delayed, because the treating physicians do not expect postoperative peritonitis. On the other hand, most patients with local spillage of infectious fluid secondary to acute cholecystitis or appendicitis will not develop septic complications [4, 10, 11].

Peritonitis is defined as an infection of the abdominal cavity with reaction of the "organ" peritoneum. Peritonitis can be divided into three different forms: primary, secondary, and tertiary peritonitis. Primary or spontaneous bacterial peritonitis is rare among surgical patients and occurs without a disruption of the intestinal integrity, mostly in patients with liver cirrhosis [12].

Secondary peritonitis (SP) is the most common form of peritonitis among surgical patients [13]. SP occurs after disruption of the barrier of the intestinal tract secondary to perforation, anastomotic dehiscence, ischemic necrosis, or other forms of damages of the integrity of the gastrointestinal wall. SP can be community acquired, hospital acquired, or healthcare associated [14]. Patients with community-acquired SP have a low mortality. Community-acquired SP is characterized by microorganisms that are susceptible to narrow spectrum antibiotics. Patients with hospital-acquired SP or healthcare-associated SP have a higher mortality, because hospitalized patients often suffer from severe comorbidities [4, 5, 11]. Most importantly, there is a higher risk for multidrug-resistant microorganisms among patients with hospital-acquired or healthcare-associated SP [6, 15].

Tertiary peritonitis (TP) is rare. TP is defined as a severe recurrent or persistent peritoneal infection after an adequate surgical treatment of SP. TP is associated with a high mortality and frequently caused by multidrug-resistant microorganism. Usually TP only occurs in intensive care patients [16, 17].

12.2 Definition of Postoperative Peritonitis (PP)

Postoperative peritonitis (PP) is subsumed as a form of SP. After abdominal surgery, PP occurs after an anastomotic failure, but PP can also develop secondary to an undetected injury of the small or large bowel wall in patients who underwent abdominal surgery. While SP can be community acquired, healthcare associated, or hospital acquired, PP is always a hospital-acquired form of peritonitis, with a high risk for multidrug-resistant microorganisms [13, 15, 18]. PP may also develop into TP, but compared to the other forms of SP, this is rather rare [16].

12.3 Diagnosis of PP

PP is suspected in patients with abdominal pain, new or sudden clinical impairment, and systemic inflammatory response syndrome (SIRS). On physical examination, tenderness with abdominal distention, abdominal rigidity, and rebound tenderness are suspicious for peritonitis. Local inflammation as well as diffuse peritonitis may result in paralytic ileus with vomiting. Many clinical findings can be altered or even

absent, especially in the critically ill patient or among patients with immune suppression or under chemotherapy. Hypotension, oliguria, organ dysfunction, and altered mental status are indicators for septic shock, requiring further investigation and immediate workup [5, 11].

Laboratory results usually show an increased C-reactive protein (CRP), while leukocytosis only occurs in 61% of patients with a postoperative anastomotic leakage [19, 20]. According to the severity of inflammation, laboratory parameters can be altered, because an ongoing organ dysfunction can influence all laboratory parameters. Procalcitonin is a good indicator for the severity of postoperative peritonitis and for mortality, although it is not suitable to predict postoperative complications or guidance of antibiotic treatment [21, 22]. Several peritoneal cytokines increase among patients with postoperative complications, including TNF-alpha, interleukin-1 (IL), IL-6, and IL-10 [23]. Especially IL-6 has been shown to be an early predictor for postoperative complications, but a routine cytokine measurement is not established, yet [24].

After recent abdominal surgery, changes of the content and the amount and the quality of intraabdominal drainage fluids may be another indicator for PP, although a normal drainage fluid does not exclude the presence of PP. The amount of bile or amylase and lipase in the intraabdominal drainages is helpful, especially if amylase, lipase, and bilirubin are distinctly elevated. Oral application of methylene blue can show an anastomotic leakage, if intraoperative drainages are still in place, but an evaluation of the local perfusion situation is not possible. Endoscopy is excellent to evaluate the local perfusion of the anastomosis, especially after esophageal resection or gastrectomy. Furthermore, endoscopy offers the possibility for local application of stents or endoluminal vacuum therapy [25, 26]. However, endoscopy is also associated with risks especially in the lower gastrointestinal tract. After rectal resections with an extraperitoneal anastomosis, endoscopy with vacuum therapy is an option, if a diverting ileostomy is in place, while the treatment of an intraperitoneal anastomotic leak after colon resections usually requires surgical revision [27–30]. Therefore, a critical evaluation of the treatment consequences is mandatory, before endoscopy is initiated.

Abdominal ultrasound can localize intraabdominal fluid collections. A percutaneous diagnostic puncture shows the quality of the fluid and microbial culture is able to guide antibiotic therapy. Percutaneous drainage can even be sufficient to evacuate infectious fluids. However, not all patients with postoperative peritonitis have high quantity of ascites, and abdominal ultrasound is challenging in obese patients or in patients with meteorism [31, 32]. Oral water-soluble contrast medium application or enema is also able to show an anastomotic leakage, but the quickest and most informative diagnostic investigation is abdominal CT scan with oral, rectal, and intravenous contrast medium [33].

Especially for the differential diagnoses of PP, a CT scan can provide detailed information about the anatomical situation and other organ systems that may be responsible for the clinical impairment after surgery, e.g., in the presence of *Clostridium difficile* colitis [34]. Another advantage of an abdominal CT scan is that an immediate percutaneous drainage of an intraabdominal abscess can often

avoid surgical drainage, especially in pancreatic and hepatobiliary surgery [32, 35].

12.4 General Consideration for the Risk of PP

There are three basic requirements for the healing of an anastomosis. The anastomosis must be tight and tension free with a regular perfusion. Therefore, meticulous suturing or stapling, sufficient mobilization, and careful preparation with special attention to the vascular supply are mandatory to avoid a breakdown of intestinal anastomoses. Nonetheless, a postoperative anastomotic leak depends on several other risk factors, especially patient-associated characteristics that surgeons cannot always control. Therefore, an anastomotic leakage can always occur.

The risk for a postoperative peritonitis from an anastomotic leak depends on the surgical procedure performed, but as mentioned before a few analysis also evaluated the risk for a postoperative anastomotic leak after different abdominal procedures. These risk factors include anastomotic tension, hypoxia, intraoperative or postoperative red blood cell transfusion, iron deficiency, ischemia, malnutrition, preoperative radiation therapy, prolonged duration of the operation, renal failure, shock, steroid therapy, cigarette smoking, zinc deficiency, vasopressor application, previous abdominal surgery, and male gender [11, 36–39]. The specific risk factors for postoperative leaks according to the operative procedure performed are discussed in the section PP after standardized operative procedures.

12.5 Treatment of PP

Theoretically the treatment of PP is simply based on three principles: focus elimination, antibiotic therapy, and intensive care treatment (Fig. 12.1) [40].

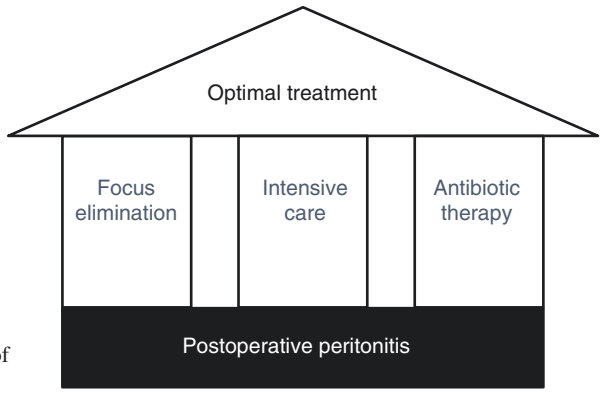

Fig. 12.1 Optimal treatment of postoperative peritonitis

12.5.1 Focus Elimination

Immediate focus elimination is the goal, but there are different approaches to achieve local control. Resection of the infectious focus or the intraabdominal organ that is responsible for PP with restoration of intestinal integrity is the safest way of focus elimination [11]. Surgical revision is often associated with an adverse outcome, but the patients' morbidity is mostly due to the ongoing sepsis and not the operative procedure. Nevertheless, depending on the location and the extent of peritoneal contamination, restoration of intestinal integrity cannot always be achieved, and temporary intestinal deviation may be required. Indeed percutaneous drainage can also be sufficient for anastomosis leaks after selected abdominal operations [5].

12.6 General Consideration for the Treatment of PP

An early postoperative anastomotic leak is usually the result of an error in surgical technique or difficulties during anastomosis. If the patient's condition is good, surgical revision with reanastomosis should be anticipated. The outcome after early surgical revision is usually good, while the outcome for patients with reoperations in the late postoperative period is worse [11, 41–43].

There are many definitions of postoperative anastomosis failure, and some surgical groups published well-accepted classification systems for postoperative anastomosis failure, especially after pancreatic and hepatobiliary surgery [44, 45]. Briefly, postoperative anastomosis failure is classified into three different grades, according to the severity of patients' illness and the treatment that is performed. The general condition of patients with postoperative grade A leaks is not influenced. These patients do not require special intervention and the outcome is not affected. Grade B leaks affect the patients' general condition and require an interventional therapy with drainages and an antibiotic therapy, but no surgical revision. Patients with grade C leaks show septic complications and require surgical revision [44, 45]. Although such classifications have been established in pancreatic and hepatobiliary surgery, they are not suitable for patients after esophageal, gastric, and colorectal surgery. Anyway, grading into different degrees of severity of postoperative anastomosis leaks after upper and lower GI surgery has been performed, although routine clinical application is not established, yet [46, 47].

After pancreatic, hepatobiliary, esophageal, and rectal surgery, minor leaks without severe clinical impairment or sepsis can often be treated with local drainage of infectious fluid and antibiotic therapy. Endo-sponge-assisted devices that are placed into extra anatomical wound cavities secondary to anastomosis leaks help to evacuate infectious fluids and improve faster wound healing. Endo-sponge vacuum treatment is established after esophageal and rectal resections and is suitable for some patients after gastric surgery [28, 48–50]. According to the clinical situation of patients with PP secondary to anastomotic leaks, the "conservative" approach to reach local control is often favored, but for patients with severe sepsis or without improvement during conservative management, surgical revision is inevitable [51, 52].

A necrosis of one part of the anastomosis is the worst postoperative scenario that requires surgical revision with resection of the necrotic part of the anastomosis. In selected patients, a reanastomosis can be performed. The safest operative procedure is a resection of the necrotic organ. An ileostomy, a colostomy, or even a blind closure of the proximal esophagus can be required with a reconstruction after complete recovery [53, 54].

PP can occur after many different operative procedures. Therefore, the following pages will illustrate the different risks for PP after the most common abdominal operations and outline the most effective treatment principles.

12.7 PP After Standardized Operative Procedures

12.7.1 PP After Esophageal Resections

A postoperative leak after esophageal resections with a cervical anastomosis results in a local phlegmon, and an intrathoracic anastomosis causes a pleural empyema or mediastinitis, but not peritonitis [55, 56]. However, esophageal resections belong to the repertoire of major abdominal surgery. Postoperative leaks after esophageal resections are associated with a high mortality, and patients with anastomotic leakage after esophageal resections have a reduced long-term survival [57, 58]. The frequency of postoperative leaks from the esophagogastrostomy is between 0% and 26% without differences between stapled or hand-sewn anastomoses with a higher risk for cervical anastomoses [58, 59]. The risk for an anastomotic leak decreases with hospital volume [60]. The most important steps for prevention of an anastomotic leak include a sufficient mobilization of the duodenum to achieve a tension-free anastomosis and meticulous preparation of the gastric tube without injury of the gastroepiploic artery and the gastroepiploic vein. A residual tumor at the anastomosis increases the risk for an anastomotic leak. Therefore, from an oncological point of view and to avoid postoperative anastomotic failure, tumor infiltration should be excluded by intraoperative frozen section [61].

Treatment of postoperative leaks after esophageal resections depends on location of the anastomosis (cervical vs. intrathoracic), the postoperative period (early vs. late), and the perfusion situation of the gastric tube. Endoscopy and CT are the diagnostic of choice. In patients with cervical leaks, local wound drainage by opening of the cervical wound and a salivary fistula is often sufficient [55, 62]. Early postoperative leaks are mostly caused by technical problems during resection and reconstruction. These “early” postoperative leaks often require surgical revision, because the leak is not covered by adherent tissue. Late postoperative leaks are often covered by adherent tissue and respond to conservative management [63]. A small leak requires an endoluminal vacuum therapy, while a larger leak can also require the placement of a covered stent, or even a combination of both devices [26, 64–66]. An intrathoracic abscess requires thoracic drainage or interventional percutaneous drainage. Most patients will recover after conservative management, but if patients develop severe sepsis with necrosis of the gastric conduit, salvage operation with blind closure of the esophageal remnant and salivary fistula is indicated [67, 68].

12.7.2 PP After Gastric Resections

After total gastrectomy with an intrathoracic anastomosis, a postoperative leak causes a mediastinitis or pleural empyema, while an intraabdominal anastomosis failure after gastric resections results in PP. The best diagnostic evaluation of leaks from the esophagojejunostomy is similar to the diagnostic of leaks after esophageal resections, including abdominal and thoracic CT scan and endoscopy [33, 66]. Similarly, to esophageal resections, patients with postoperative anastomotic leak after gastrectomy have a reduced long-term survival [58, 69]. The risk for an anastomotic leak from the esophagojejunostomy after total gastrectomy is approximately 5–8% [69–71]. The risk for an anastomotic failure after gastroduodenostomy is 2%, the risk for duodenal stump insufficiency is lower than 2%, and a leak of the gastrojejunostomy is rare [72–76]. After gastric resection with transection of the left gastric artery, the arteriae gastricae breves should be preserved to ensure a sufficient blood supply of the gastric remnant. If a splenectomy is required, total gastrectomy should be performed. Risk factors for an anastomotic leak after total gastrectomy are smoking and alcohol abuse, male gender, cardiovascular disease, perioperative transfusion, and tumor location in the upper part of the stomach [77, 78].

The treatment of postoperative leaks with intrathoracic anastomosis is comparable to the treatment of postoperative leaks with an intrathoracic anastomosis after esophageal resection and includes conservative management with endoluminal vacuum therapy, the application of covered stents and surgical revision [51, 66, 79]. A leak that occurs within the first three postoperative days is usually the result of technical problems during surgery. With early surgical revision, the outcome is usually good [43]. Nonetheless, small leaks that occur in the early postoperative period can also effectively undergo conservative management with endoluminal vacuum therapy or covered stents [26, 79]. However, most leaks are caused by local ischemia or tension and occur in the late postoperative period. For approximately 70% of patients, conservative management with placement of a naso-jejunal feeding tube and percutaneous drainage of intraabdominal abscesses is successful [70]. An intrathoracic abscess is usually treated with an additional interventional percutaneous drainage [51]. Leaks from the gastrojejunostomy or the gastroduodenostomy usually require surgical revision. Duodenal stump leak requires local drainage, either through drainages that have been placed during resection or with an additional percutaneous drainage. Gentle suction can be applied to the drainage. A conservative approach is the treatment of choice, while surgical revision should be reserved for severe cases or for patients with failure of conservative management [73, 80].

12.7.3 PP After Small Intestine Surgery

Anastomoses of the small intestine are an integral part of many abdominal operations, including the ileostomy reversal after rectal resection, small intestine resections secondary to ileus, Roux-en-Y reconstruction after gastrectomy, hepaticojejunostomy, ileocolostomy, and pancreatic resections. The risk for an anastomotic leak in elective

operations is below 3% [81]. After ileostomy reversal, there is no significant difference between hand sutured and stapled anastomoses [82]. An anastomosis failure after reconstruction of the small intestine causes a peritonitis, while the leakage of a hepaticojejunostomy or pancreaticojejunostomy does not necessarily cause peritonitis. The risk for an anastomotic leak also depends on the preexisting disease, e.g., in patients with Crohn's disease, where the risk for an anastomosis failure seems to be reduced if a side-to-side anastomosis is performed [83, 84]. The best diagnostic evaluation for patients with a suspicion of an anastomosis leakage after small intestine reconstruction is clinical examination with critical analysis of the content of the intraoperative drainages, optionally with the oral application of methylene blue. An abdominal CT scan does not accurately detect a postoperative anastomotic insufficiency from the jejunojejunostomy, but a percutaneous drainage or a diagnostic puncture may demonstrate the presence of small intestine secretion [75].

After elective operations and in early postoperative leaks, surgical revision with restoration of the intestinal integrity should always be anticipated. An alternative is intestinal deviation, especially for patients with a high risk for an anastomosis failure. In patients who underwent multiple abdominal operations or leaks that occur in the late postoperative period, where the small intestine secretion does not cause a generalized peritonitis, because of abdominal compartimentation, conservative management can be effective. For this purpose, intestinal fluids must be evacuated as an enterocutaneous fistula with the possibility of restorative surgery after several months.

Comparable to leaks after gastric or esophageal resections, surgical revision is required for patients with severe peritonitis, with persisting sepsis or after failure of conservative treatment approaches.

12.7.4 PP After Colorectal Surgery

An intraperitoneal anastomotic leakage after colorectal resections causes a peritonitis, while an extraperitoneal anastomosis after rectal resections does not necessarily cause a PP, especially if a diverting ileostomy is present [30]. In the literature, there is a plethora of definitions of anastomotic failure after colorectal anastomoses. Recently a grading of postoperative anastomotic leakage for rectal resections has been proposed, although clinical application is not established, yet [46]. The classification distinguishes three different grades of severity of anastomotic leaks. Patients without clinical impairment are classified as grade A leaks and do not require further interventions or treatment. Patients with clinical impairment who require active therapeutic intervention, but no surgical revision, are classified grade B leaks, while patients with severe clinical impairment or sepsis who require revisional surgery are classified as grade C leaks [46].

The risk for anastomotic failure after colorectal resections is between 0.5% and 21% with a clear association with postoperative morbidity and mortality [85–88]. The risk for an anastomotic disruption is higher after rectal resections and after operations that included a colorectal anastomosis during major abdominal, gynecological, or

urological procedures [87]. The risk for an anastomotic leak after colon resections is lower than 3%, while the risk for an anastomotic leak after rectal resections reaches more than 20% in some series but should be below 5% in experienced centers [38, 89–91].

Risk factors for an anastomotic leak after rectal resections include alcohol abuse, cigarette smoking, male gender, obesity, severe comorbidities, a large tumor size of more than 5 cm, preoperative chemotherapy, intraoperative blood loss of more than 100 ml, longer operative time, more than three stapler firings, and an anastomosis within 5 cm from the anal verge [92, 93].

The diagnostic of choice is an abdominal CT scan with enema with water-soluble contrast medium or endoscopy [94]. Rectal digital examination is only appropriate for low rectal anastomoses, but this examination may fail to detect small leaks. Endoscopy is suitable for patients with an anastomosis after rectal resection, sigmoid resection, or left-sided hemicolectomy. The treatment of postoperative leaks after colorectal resections depends on the distance from the anal verge. An intraabdominal anastomosis rather requires surgical revision, while a leak with an extraperitoneal anastomosis after rectal resections may effectively be treated by conservative management, if a diverting ileostomy is present [29, 30]. Depending on the clinical situation, the time point when the postoperative leak occurs and the dimension of the defect determine the treatment of postoperative leaks after colon resections. The treatment includes interventional or surgical drainage; surgical revision, if necessary with diversion ileostomy; re-suturing of an anastomosis; or even blind closure of the rectal remnant with ileo- or colostomy [19, 29].

After introduction of devices for endoluminal vacuum therapy, postoperative leaks after rectal resections with diverting ileostomy are mostly managed conservatively, although patients with severe sepsis or failed conservative management may require surgical revision [28].

12.7.5 PP After Hepatobiliary Surgery

Without appropriate intraoperatively placed abdominal drainages, a postoperative bile leak after hepatobiliary surgery or liver transplantation causes biliary peritonitis, although several earlier reports suggested that postoperative bile leaks are not associated with major postoperative morbidity [95, 96]. Per definition, a postoperative bile leak is present if the bilirubin concentration in the intraabdominal drainages is three times higher than the serum bilirubin concentration on or after the third postoperative day or if patients require interventional radiological drainage or surgical intervention from biliary collections or biliary peritonitis [45]. According to the ISGLS criteria, postoperative bile leaks should be classified into grades A, B, and C [45]. Patients without clinical impairment without the need for interventional treatment are classified grade A bile leaks. Patients with clinical impairment, fever, or signs of sepsis who require antibiotic therapy and interventional drainage of biliary collections are classified grade B bile leaks, while patients who require surgical revision secondary to biliary peritonitis or delayed visceral hemorrhage are classified grade C bile leaks

[97]. The diagnosis of a postoperative bile leak in the early postoperative period is usually done by clinical examination, analysis of intraoperatively placed drainages, and abdominal ultrasound with diagnostic or therapeutic puncture of biloma, while an abdominal CT is more accurate, especially in the late postoperative period [35].

The risk for a postoperative bile leak varies according to the operative procedure performed from 2% to 8% after simple hepaticojejunostomy to approximately 50% for some patients after liver transplantation [42, 95, 96]. Risk factors for a postoperative bile leak include obesity, an anastomosis of segmental bile ducts, former chemoradiation, preoperative biliary drainage, low cholinesterase level, biliary complications necessitating a hepaticojejunostomy, and simultaneous liver resections [95, 96]. The most important risk factor for an anastomotic failure after hepaticojejunostomy is a small bile duct diameter with a thin bile duct wall [98]. A t-tube drainage at the site of the anastomosis is not able to reduce the risk for a postoperative bile leak, but reoperations are less often required if a t-tube is placed into the anastomosis [99].

After liver transplantation, endoscopic treatment of bile leaks from the bile duct anastomosis can effectively be treated by ERC with placement of endoscopic bile duct stent [100]. Treatment of hepaticojejunostomy leaks is challenging, because endoscopy is usually not able to reach the anastomosis. Therefore, PTCD, percutaneous drainage of biloma via CT scan or abdominal ultrasound are often required. Early postoperative bile leaks are usually the result of a technical error during resection and reconstruction. Although some authors argue that all bile leaks will close after conservative management, especially bile leaks that occur in the late postoperative period often require surgical revision and are associated with a high postoperative mortality [42, 101].

12.7.6 PP After Pancreatic Surgery

A postoperative pancreatic leak from the pancreatic anastomosis usually causes secondary complications, but no peritonitis. Delayed gastric emptying, intraabdominal abscesses, surgical site infections, pancreatitis of the pancreatic remnant, sepsis, and delayed visceral hemorrhage are the most common postoperative complications, but perforations of hollow viscous can also occur [102–106]. All of these complications are associated with an adverse outcome. A postoperative pancreatic leak is defined as an amylase level in the intraabdominal drainages, three times above the serum amylase concentration on or after the third postoperative day [44]. According to ISGPF criteria, patients without clinical symptoms and without therapeutic interventions are classified grade A pancreatic leak, and patients with mild clinical impairment who require interventional therapy or antibiotic treatment, but no surgical revisions, are classified grade B leaks, while all patients with severe clinical impairment and signs of sepsis who require revisional surgery are classified grade C leaks [44].

The most important risk factors for a postoperative pancreatic leak are a small pancreatic duct diameter, obesity, soft pancreatic tissue, and tumor location in the bile duct without pancreatic duct obstruction [107–112]. The only way to prevent a

postoperative pancreatic fistula is a meticulous anastomosis technique and the use of Sandostatin, while a total pancreatectomy is a radical solution with severe side effects for the patient, suffering from a difficult to treat diabetes [108, 113–115]. The diagnosis of a postoperative pancreatic leak is usually done by measuring the amount and the concentration of drainage fluids, while an abdominal CT scan with a percutaneous drainage is the treatment of choice in the late postoperative period, when drainages have been removed [35]. Conservative management is the treatment of choice, while surgical revision with resection of the pancreatic remnant is a salvage procedure that is usually only performed when all other treatment options failed [116–118].

12.7.7 Intensive Care Management

Without treatment, PP leads to SIRS, sepsis with septic shock, and death secondary to multiple organ failure. The continuum of SIRS results in capillary leak with volume depletion, peripheral vasodilation, myocardial depression, and increased metabolism [1]. The consequence is an imbalance between oxygen delivery and oxygen supply with global tissue ischemia and organ dysfunction. The goal of intensive care management is to support organ dysfunction and to avoid multiple organ failure [4, 119]. There is no master plan for the patient with postoperative peritonitis, and the discussion among intensive care physicians about the best treatment modalities for septic patients is still going on [120].

The best summary that describes the way to prevent organ dysfunction is “early goal-directed therapy.” The goal of this treatment principle is to balance oxygen delivery with oxygen demand. This treatment principle significantly reduces mortality from septic shock [121]. Basically, the initial resuscitation in patients with septic shock secondary to postoperative peritonitis is monitoring of cardiac output, fluid status, fluid responsiveness, and organ perfusion. Sufficient fluid resuscitation and application of appropriate inotropic agents is the cornerstone of the initial intensive care management [122]. Central venous pressure, pulmonary occlusion pressure, and mean arterial pressure are used to guide fluid therapy, but in recent years, it became clear that these parameters should be interpreted individually. Pulse pressure variation and stroke volume variation may be better parameters to guide fluid therapy [123].

Urine output cannot be recommended as an end point of successful sepsis therapy but is still a good indicator for fluid resuscitation in situations with limited monitoring. A mixed central venous oxygen saturation of at least 70% is recommended, although this parameter should be regarded in relation to preexisting comorbidities and lactate level. An excessive fluid balance leads to an increasing extravascular lung water accumulation and should be avoided [120]. A differentiated discussion about the options, how to achieve the abovementioned parameters, and how organ function is preserved best is beyond the scope of this work. Nonetheless, the most important mechanism to prevent multiple organ failure in patients with postoperative peritonitis is early recognition of postoperative complications with immediate treatment initiation.

12.7.8 Antibiotic Treatment

Early administration of broad-spectrum antibiotics is the basis of an effective antibiotic treatment in PP, because every delay of an appropriate antimicrobial treatment dramatically increases mortality [124]. For an adequate antibiotic treatment, surgeons and intensive care physicians must anticipate the most common microorganisms according to the operative field (Table 12.1, modified by Herzog et al. [6]).

By definition, all patients with PP have HA peritonitis. The microorganisms encountered in PP are the same microorganisms that can be found in patients with CA peritonitis, but there is a higher probability of opportunistic microorganisms. These microorganisms include all kinds of *Enterobacteriaceae* with extended spectrum ß-lactamase (ESBL), carbapenemase-resistant *Enterobacteriaceae*, vancomycin-resistant *Enterococcus* spp. (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, *Acinetobacter* spp., and *Candida* spp. [125–128]. Postoperative infections with these resistant microorganisms are associated with a higher postoperative morbidity and mortality, reaching a mortality of 50% for candida infections [7, 129]. Therefore, the antibiotic treatment should be selected according to patients' risk factors for resistant microorganisms. The most commonly used antibiotic regimes for the treatment of patients with postoperative peritonitis are listed in Table 12.2 (modified by Herzog et al. [6]).

Table 12.1 Microorganisms according to the operative field

	Esophagus	Gastroduodenal	Biliary tract	Pancreas	Small bowel	Large bowel
Common aerobes						
Gram-positive						
Streptococcus spp.	+	++	–	––	––	––
Enterococcus spp.	–	––	++	––	––	++
Staphylococcus spp.	–	––	–	––	––	––
Gram-negative						
E. coli	–	++	++	++	++	++
Enterobacter spp.	–	––	–	––	––	––
Pseudomonas spp.	+	––	–	––	++	––
Klebsiella spp.	+	––	++	++	––	+
Proteus spp.	–	––	––	++	––	–
Other	–	––	––	––	––	––
Common anaerobes		––				
Bacteroides spp.	–	––	––	++	++	++
Clostridium spp.	–	––	––	–	––	++
Anaerobe Cocci	–	––	––	–	––	+
Candida	+	+	–	–	–	–

++ most frequent species, + occasionally present, – usually not present, –– rarely present

Table 12.2 Antibiotic treatment options for suspected resistant microorganisms

	MRSA	VRE	ESBL	*Acinetobacter*	*Pseudomonas aeruginosa*
Piperacillin/sulbactam	–	–	+	(+)	+
New ß-lactams	+	–	(+)	+	–
Quinolones	–	–	(+)	(+)	(+)
Glycopeptides (vancomycin)	(+)	–	–	–	–
Lipopeptides (daptomycin)	+	+	–	–	–
Oxazolidinones (linezolid)	+	+	–	–	–
Carbapenemes	–	–	+	(+)	+
Glycylcycline (tigecycline)	+	+	+	(+)	–

+ effective, – not effective, (+) partial activity

12.8 Treatment Strategy for Patients with Postoperative Peritonitis

Antibiotic therapy can be used according to the national guidelines for the treatment of complicated intraabdominal infections, but treatment according to guidelines should not prevent antibiotic cycling out of the large amount of differently acting antibiotic agents available. Antibiotic stewardship is extremely important for patients with postoperative peritonitis, because surgeons need a specific strategy to deal with patients, who have a high risk for infections with resistant microorganisms [130].

The best description for a modern treatment of patients with PP is a modified application of the Tarragona strategy that was published in 2003 by Sandiumenge et al. [131]. Five simple principles for the antibiotic therapy should be remembered:

12.8.1 Hit Hard and Early

The initial treatment should be broad enough to cover all kinds of possible resistant microorganisms. The treatment should be initiated as soon as possible, because every delay of an appropriate antibiotic therapy increases the risk for mortality.

12.8.2 Listen to Your Hospital

Antibiotics should be selected according to the local surveillance data. Antibiotic prescription and antibiotic consumption may change the local resistance pattern. Therefore, regular evaluation of the microorganisms encountered in patients with postoperative peritonitis should guide the antibiotic therapy.

12.8.3 Lock at Your Patient

Patients with PP have a risk for infections with multidrug-resistant microorganisms. The risk is even higher if patients already had a prior broad-spectrum antibiotic therapy, if patients suffer from severe comorbidities, or if patients already had a long postoperative in hospital stay.

12.8.4 Get to the Point

The initial doses should be high enough to reach a sufficient concentration at the focus. For patients with postoperative peritonitis, antibiotics should be selected according to pharmacokinetics and pharmacodynamics characteristics that enable a good tissue penetration to reach a high concentration at the focus peritoneum.

12.8.5 Focus, Focus, Focus

Surgeons and intensive care physicians should avoid a long-term ineffective broad-spectrum antibiotic exposure. After effective focus elimination, a critical evaluation of the results of the microbiology should be performed. In stable patients, de-escalation of the antibiotic therapy is essential to prevent the development of even more resistant microorganism.

Summary and Conclusion

Postoperative peritonitis mostly occurs secondary to an anastomotic failure after different abdominal operations and is associated with an inverse oncological outcome and increased mortality. Although the prognosis of patients with postoperative peritonitis depends on the general state of health, the most important issues to prevent septic shock are early diagnosis and immediate and effective treatment. Focus elimination is the basis of an effective treatment. Patients with early postoperative anastomosis leak should undergo surgical revision, because usually early postoperative leaks are the result of an error in surgical technique. Local ischemia is the reason for late postoperative leaks and will respond rather to conservative treatment. Anyway, for patients with severe sepsis and uncertain focus, a re-laparotomy is often inevitable. The successful treatment of postoperative peritonitis requires modern intensive care management and antibiotic therapy with special focus on resistant microorganisms. However, effective therapy of postoperative peritonitis remains a challenge with further options to improve patients' outcome.

Conflict of Interest Both authors certify that they do not have any conflict of interest or financial association conflicting with the presented manuscript.

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Damage Control Surgery in Managing Abdominal Sepsis (Fausto Catena, Italy)

13

Fausto Catena and Gennaro Perrone

13.1 Introduction

Sepsis, a syndrome of physiologic, pathologic, and biochemical abnormalities induced by infection, is a major public health concern [1]. The reported incidence of sepsis is increasing [2, 3], likely reflecting aging populations with more comorbidities, greater recognition [4], and, in some countries, reimbursement-favorable coding [5]. Although the true incidence is unknown, conservative estimates indicate that sepsis is a leading cause of mortality and critical illness worldwide [6, 7]. Furthermore, there is an increasing awareness that patients who survive sepsis often have long-term physical, psychological, and cognitive disabilities with significant healthcare and social implications [8].

A 1991 consensus conference [9] developed initial definitions that focused on the then-prevailing view that sepsis resulted from a host's systemic inflammatory response syndrome (SIRS) to infection. SIRS is primarily characterized by the presence of at least two of the following: temperature >38.6 °C or <36 °C, heart rate > 90 beats/min, respiratory rate > 30 breaths/min, and leukocyte count >12,000 cells/mm^3 or <4000 cells/mm^3.

Sepsis complicated by organ dysfunction was termed severe sepsis, which could progress to septic shock, defined as "sepsis-induced hypotension persisting despite adequate fluid resuscitation." A 2001 task force, recognizing limitations with these definitions, expanded the list of diagnostic criteria but did not offer alternatives because of the lack of supporting evidence [10]. The current use of two or more SIRS criteria to identify sepsis was unanimously considered by a new task force [11], convened by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine, to be unhelpful. Changes in white blood cell count, temperature, and heart rate reflect inflammation, the host response to "danger" in

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the form of infection or other insults. The SIRS criteria do not necessarily indicate a dysregulated, life-threatening response. They are present in many hospitalized patients, including those who never develop infection and never incur adverse outcomes (poor discriminant validity) [12].

While there are many different components to damage control (DC), abdominal packing has historically been the foundation principle of damage control and was first reported in the early twentieth century by Pringle [13]. His technique was modified by Halstead [14], who in 1913 recommended placing nonadhesive rubber sheets between the packs and the liver. This technique was used until the Second World War but then fell out of favor; perhaps it was used only when nothing else worked [15].

In 1955, Madding [16] wrote that temporary packs may be effective for checking bleeding, and 20 years later, Lucas and Ledgerwood reported on three of their patients with major liver injuries, who were packed and survived as a part of a large series of evaluation of over 600 patients with liver injuries [17]. These good results from liver packing were supported by Feliciano [18] in 1981, while in 1983, Stone et al. [19] described a stepwise operative management including initial abandonment of laparotomy, intra-abdominal packing, correction of coagulopathy, and reoperation for definitive surgical repair. In 1993, Rotondo et al. [20] introduced the term "damage control" and detailed a standardized three-phase approach. DC is well recognized as a surgical strategy that sacrifices the completeness of the immediate repair in order adequately to address the combined physiological impact of trauma and surgery. This term is derived from the US Navy and describes the capacity of a ship to absorb damage and maintain mission integrity.

13.2 Damage Control Surgery

Damage control surgery (DCS) can be defined as a series of operations which are performed in order to accomplish definitive repair of abdominal injuries in accordance with the patient's physiologic tolerance. Trauma surgeons focus more on the physiological reserve of patient rather than the anatomy of the lesions. Surgical techniques are focused on hemorrhage and contamination control to stop bleeding and control intestinal, biliary, or urinary leak into the abdominal cavity. Obviously, patient selection is crucial as patients with relatively simple abdominal injuries should not undergo unnecessary procedures. Optimal results are also achieved by the early identification of patients who require damage control. The clinical manifestations of hemodynamic instability, hypotension, tachycardia, tachypnea, and altered mental status are indications for the potential need of DC.

Currently, DC is one of the most topical areas in trauma management. Principles of DC can be applied not only to the abdomen but for many other body regions.

The abbreviated laparotomy [21] for trauma patients is defined as the initial control of surgical bleeding by simple operative techniques such as hemostasis, drainage, packing, etc. for life-saving techniques. The patient is taken to the intensive care unit (ICU) where subsequent resuscitation corrected hypothermia,

acidosis, and coagulopathy. It can be defined as the initial source control of intra-abdominal infection by simple operative techniques (life-saving techniques/abdominal compartment syndrome prevention).

The open abdomen (OA) concept is closely linked to damage control surgery (DCS) and may be easily adapted to patients with advanced sepsis and can incorporate the principles of the Surviving Sepsis Campaign, a performance improvement initiative targeted changing clinical behavior (process improvement) via bundles based on key SSC guideline recommendations on process improvement and patient outcomes [22]. DCS is employed in a wide range of abdominal emergencies and is an increasingly recognized life-saving tactic in emergency surgery performed on physiologically deranged patients. Correct patient selection is crucial for the benefit from a DCS to be maximized; not applying the strategy to critically ill patients will increase their risk of death, although its overuse will expose patients to the risks of multiple operations, OA management, and prolonged intensive care stay, negating the potential benefits of the concept. Fewer than 30% of civilian trauma laparotomies typically benefit from a damage control strategy in modern trauma surgery, although this number varies greatly depending on the mechanism of injury and population affected. The authors estimate that an even lower number, perhaps not more than a few percent, of all non-traumatic abdominal emergencies would benefit from this strategy. This prediction reflects the fact that most of these abdominal emergencies will not reach the critical level of physiological compromise at which a damage control strategy is indicated. Insufficient data exist to define the precise incidence accurately. The practical aspects of easy abdominal reentry required in staged operations serve further to make this practice attractive. However, damage control surgery does not equate to, or mandate, an OA. The frequent association exists owing to the positive correlation between this surgical strategy and the presence or risk of abdominal compartment syndrome. To decide which patients will benefit from an OA requires the same clinical judgment as that used to identify patients who may benefit from the damage control strategy in the first place. The strategy should be applied to the patients at highest risk of abdominal compartment syndrome. Unfortunately, there is little other direct evidence to guide this decision. Individual patient factors, the degree of tissue injury from the hemorrhagic and/or septic shock, the nature of the pathology (such as severe acute pancreatitis or visceral obstruction), the severity of the physiological effects, and the quality of the resuscitation and treatment, are all critical determinants of the overall risk. DC is applied to a small extent in the abdominal hemorrhagic shock like bleeding duodenal/gastric ulcer when endoscopy fails to be effective.

Also during an accidental injury to the portal or retroperitoneal venous structures during elective pancreaticoduodenectomy if it is difficult to control surgically, OA is a viable alternative to the reconstruction and direct closure of the wall, in order to prevent such adverse events such as tissue edema.

If the gastrointestinal perforation does not allow the treatment defined, in the most severe instances, when generalized peritonitis and septic shock dominate the clinical phenotype, the patient's compromised physiology may preclude a safe primary definitive surgical strategy. An anastomosis or large anatomical reconstruction performed in this clinical situation would probably fail owing to the severe

physiological compromise. Furthermore, it is unlikely that this failure would be tolerated in this already critical situation. In these extreme situations, the patient may benefit from a damage control strategy.

DCS has found broad indication for acute mesenteric ischemia, one of the abdominal surgical catastrophes. The possible delays in diagnosis compound the already severe physiological insult associated with the primary pathology. The treatment involves resection of infarcted bowel and revascularization. Because of the deranged physiology, a long procedure with vascular repair and immediate bowel resection is not advisable; a staged procedure adhering to damage control principles is recommended.

In situations such as toxic megacolon and acute cholecystitis, the use of the DC leads to a physiological stabilization of the patient in the first instance. Gallbladder drainage under spinal anesthesia and partial cholecystectomies are performed in two times to stabilize the inflammatory situation.

Application of DC principles are based on the clinical recognition of a trauma patient who is physiologically decompensated as defined by the lethal triad seen with hemorrhagic shock: acidosis, coagulopathy, and hypothermia. Decompensated trauma patients must be rescued to avoid progression to irreversible physiologic exhaustion and death; abbreviated operations allow stabilization, correction, and reevaluation of physiologic derangements in an intensive care unit setting.

This approach has taken hold in the operative management of emergency general surgery (EGS) [23] where the staged laparotomy is an extension of trauma surgeons operating on this population. In the trauma patient population, severe physiologic derangements, particularly the lethal triad (hypothermia, acidosis, and coagulopathy), guide management decisions. Research into these postinjury systemic inflammatory states has established the importance, for example, of the damage control laparotomy for early definitive source control and more recently the concept of DC resuscitation. In critically ill patients, the substantial benefits of blunting the proinflammatory immune response has led to such key practices as early goal-directed therapy and standardized treatment protocols for sepsis. In EGS patients, upregulation of the systemic inflammatory response leads to a cascade of physiologic insults and is a prime contributor to death, with mortality rates for severe sepsis/septic shock of over 40%. However, unlike in trauma and critically ill patients, where physiologic derangements are aggressively acted on with specific corrective interventions, in EGS patients similar preoperative derangements are often recognized but may not be targeted with explicit restorative management techniques. One solution to mitigating the negative downstream effects of physiologic insults seen preoperatively in EGS patients has been the application of DC techniques. Akin to the DC concept in trauma, it has been theorized that EGS patients needing operative intervention may benefit from an abbreviated laparotomy (i.e., rapid source control laparotomy, RSCL) with planned take-back. Such an operation is one of the first stages on a continuum of care that prioritizes the restoration of physiologic normality and homeostasis and deemphasizes the importance of immediate organ repair and definitive anatomic reconstruction. When correctly applied, the staged RSCL may help to improve survival in decompensated EGS patients. The best candidates

for staged RSCL are those patients with severe sepsis/septic shock, who are also male, over age 70 years old, with multiple comorbidities, and have an elevated lactate with acidosis. Use of the staged RSCL can also avoid unplanned reexplorations, which occurred in nearly 50% patients with severe sepsis/septic shock who underwent primary fascial closure at the initial operation. To overcome this lack of high level of evidence data about the OA indications, management, definitive closure, and follow-up, the World Society of Emergency Surgery (WSES) promoted the International Register of Open Abdomen (IROA). The register will be held on a web platform (Clinical Registers®) through a dedicated web site: www.clinicalregisters.org. This will allow to all surgeons and physicians to participate from all around the world only by having a computer and a web connection. The IROA protocol has been approved by the coordinating center Ethical Committee (Papa Giovanni XXIII hospital, Bergamo, Italy) [24].

Over the years, many comparative studies have tried to encode the DC procedures, for example, regarding the closure of OA. In a retrospective review of Bleszynski et al. [25], OA with vacuum-assisted closure (VAC) is associated with significantly improved survival compared with primary abdominal closure (PAC) in abdominal sepsis requiring laparotomy.

In recent years, many studies have been carried out in favor of OA but none of randomized type. In 2007, the Robledo [26] group, in a randomized study, has shown that postoperatively there were no differences in the likelihood of acute renal failure (25% vs. 40%), duration of mechanical ventilatory support (10 vs. 12 days), need for total parenteral nutrition (80% vs. 75%), or rate of residual infection or need for reoperation because of the latter (15% vs. 10%) between open and closed management of the abdomen in the surgical treatment of severe secondary peritonitis. Although the difference in the mortality rate (55% vs. 30%) did not reach statistical significance, the relative risk and odds ratio for death were 1.83 and 2.85 times higher in group OA. This clinical finding, as evidenced by the clear tendency toward a more favorable outcome for patients in group CA, led to termination of the study at the first interim analysis. Polyglactin mesh (MESH) and vacuum-assisted closure (VAC) are both useful methods for abdominal coverage and are equally likely to produce delayed primary closure. The options vary by institution, surgeon preference, and type of patient. Some advocate MESH, while others favor VAC. The fistula rate for VAC is most likely due to continued bowel manipulation with VAC changes with a feeding tube in place-enteral feeds should be administered via naso-jejunal tube. Neither method precludes secondary abdominal wall reconstruction. The search identified 74 studies describing 78 patient series, comprising 4358 patients, of which 3461 (79%) had peritonitis. The best results in terms of achieving delayed fascial closure and reducing the risk of enteroatmospheric fistula were shown for negative-pressure wound therapy (NPWT) with continuous fascial traction [27]. There are described several temporary closure techniques, among the most common are NPWT that is the most frequently described temporary abdominal closure (TAC) technique, NPWT with fascial closure, mesh, Bogotà bag, zippers, dynamic retention sutures, loose packing, and Whitman patches. In its presence VAC had the highest delayed primary closure and the lowest mortality rates [27, 28].

In these works, the parameters compared between the different techniques used were delayed primary fascial closure, enteroatmospheric fistula, mortality, and onset of abscesses. Limited prospective comparative data suggests that NPWT versus alternate TAC techniques may be linked with improved outcomes. However, the clinical heterogeneity and quality of available studies preclude definitive conclusions regarding the preferential use of NPWT over alternate TAC techniques [29].

Negative-pressure wound therapy (NPWT) is a technology that is used in wound care on complex wounds. NPWT involves the application of a wound dressing through which a negative pressure (or vacuum) is applied, often with any wound and tissue fluid that is drawn away from the area being collected in a canister. The intervention was developed in the 1990s, and the uptake of NPWT in the healthcare systems of developed countries has been dramatic. In the USA, a US Department of Health report estimated that between 2001 and 2007, Medicare payments for NPWT pumps and associated equipment increased from USD 24 million to USD 164 million (an increase of almost 600%, Department of Health and Human Services 2009). Initially only one NPWT manufacturer supplied NPWT machines (the VAC system, KCI, San Antonio, Texas); however, as the NPWT market has grown, a number of different commercial NPWT systems have been developed, with machines becoming smaller and more portable. Indeed, the most recent introduction to the market is a single-use, or "disposable," negative-pressure product. Ad hoc, noncommercial negative-pressure devices are also used, especially in resource-poor settings. These devices tend to use simple wound dressings, such as gauze, or transparent occlusive (non-permeable) dressings, with negative pressure generated in hospital by vacuum suction pumps [30].

There are many devices for vacuum therapy; the most popular on the market are vacuum-assisted closure (VAC, KCL), ABThera™ (KCL), Renasys (Smith & Nephew), Suprasorb devices (Lohmann & Rauscher), and VivanoMed (Hartmann). In a 2015 Kirkpatrick's study [31], the ABThera technique and Barker's vacuum technique were compared. This trial highlighted a survival difference between patients randomized to the ABThera and Barker's vacuum pack that did not seem to be mediated by improved peritoneal fluid drainage, fascial closure rates, or increased clearance of well-known mediators of systemic inflammation.

There are three most common wound closure methods: (1) primary (primary fascial closure), (2) temporizing (skin only, spit thickness skin graft and/or absorbable mesh), and (3) prosthetic (fascial repair using nonabsorbable prosthetic mesh). One of the most debated topic is the fascial closure; it was demonstrated that the maximum peak of complications after fascial closure is about the tenth day after closure [32], regardless of the technique initially used. As temporary abdominal closure, negative-pressure therapy (VAC with continuous fascial traction when abdominal sepsis is controlled) should be used aiming to close the abdomen as soon as possible within 1 week. Ioannis Pliakos et al. [33] demonstrated the superiority of the retentions sutured sequential fascial closure RSSFC compared with the single use of the VAC device. It occurred fewer incisional hernia in RSSFC group and a lower OA duration. This study shows that sequential fascial closure can immediately begin when abdominal sepsis is controlled.

Antimicrobial management of severe intra-abdominal infections (IAIs) involves a delicate balance of optimizing empirical therapy, which has been shown to improve clinical outcomes, while simultaneously reducing unnecessary antimicrobial use. Two sets of guidelines for the management of intra-abdominal infections were recently published. In 2010, the Surgical Infection Society and the Infectious Diseases Society of America (SIS-IDSA) created guidelines for the diagnosis and management of complicated IAIs. The new SIS-IDSA guidelines replace those previously published in 2002 and 2003. The World Society of Emergency Surgery (WSES) [34] guidelines represent additional contributions, made by specialists worldwide, to the debate regarding proper antimicrobial drug methodology. These guidelines represent the conclusions of the consensus conference held in Bologna, Italy, in July 2010 during the first congress of the WSES. Antimicrobial therapy plays an integral role in the management of IAIs, especially in critically ill patients who require immediate empiric antibiotic therapy. An insufficient or otherwise inadequate antimicrobial regimen is one of the variables most strongly associated with unfavorable outcomes. [35, 36]

Conclusions

In conclusion, damage control surgery should be employed in an increasingly recognized life-saving tactic in emergency surgery, performed on physiologically deranged patients with severe sepsis or septic shock in order to control any persistent source of infection, to prevent abdominal compartment syndrome (ACS), or to defer definitive intervention and anastomosis. Once severe sepsis has been controlled, definitive surgical reconstruction should be performed within 48 h. Rapid closure by negative pressure and dynamic retention sutures of the fascia should be the primary objective in the management of these patients, in order to prevent severe morbidity such as fistulae, loss of domain, and massive incisional hernias. The open abdomen strategy presents a clinical challenge that is associated with significant morbidity and OA should be used in the right patients at the right time. Even with the lack of strong evidence in international literature, OA may be an important option in the surgeon's strategy for the treatment of severe abdominal sepsis. Well-designed prospective and randomized studies are required to adequately define the role of OA and negative pressure in managing patients with abdominal sepsis [37].

Surgeons should be aware of physiopathology of sepsis and always keep in mind the rationale of open abdomen to be able to use it in the right patient at the correct time. A correct management is crucial to avoid severe complications.

Despite the lack of high-quality data, OA may be an important option in the surgeon's armamentarium for the treatment of severe peritonitis.

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Ongoing Peritonitis

14

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14.1 Introduction

Rapid initial source control and an adequate antimicrobial and supportive intensive care therapy are the key elements to treat secondary peritonitis successfully [1, 2]. Nevertheless some patients develop a complex clinical state, which is characterized by:

- A persistent abdominal infection
- An altered microbial flora
- A progressive or resistant organ dysfunction

These patients are a challenge for nowadays' emergency surgeons and require two essential approaches:

1. An everyday reassessment of the intensive care patient
2. An interdisciplinary everyday round and discussion of the critical state

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In literature the term "tertiary peritonitis" is often used to describe the above-mentioned situation.

According to the ICU Consensus Conference from 2005, tertiary peritonitis is defined as a severe recurrent or persistent intra-abdominal infection >48 h after apparently successful and adequate surgical source control in secondary peritonitis [3, 4]. Mortality rate is inacceptably high and ranges between 30 and 65% [3]!

In everyday routine, the term "ongoing peritonitis" as a "smoldering fire" within the peritoneal cavity is used more often and will be used in the following.

Review of the literature reveals that certain premorbid factors result in an increased risk for impaired control of an intra-abdominal focus: patients with increased age [5], with chronic renal insufficiency, diabetes mellitus, and HIV infection, or under corticosteroid [6] and other immunosuppressives should be monitored carefully concerning development of ongoing peritonitis. Despite these risk factors, the identification of the "typical patient" with ongoing peritonitis failed in the literature [7].

Despite preexisting morbidity, an unsuccessful source control and an inadequate antimicrobial therapy of a secondary peritonitis should be seen as main reasons for persistent peritonitis. As published recently, severe intra-abdominal infection, inadequate source control, and fungal isolates were independent risk factors for an ongoing peritonitis [8].

14.2 Diagnosis of Ongoing Peritonitis

After initial surgical source control, in particular, signs and symptoms of sepsis or an ongoing peritonitis are unspecific and often missed by clinicians and nurses. Early signs of an abdominal reinfection or persistence of an intra-abdominal inflammation require an expert view on the patient. Literature reveals that especially non-intensivists have a dramatic lack of knowledge on the signs of (intra-abdominal) sepsis and peritonitis [9–11]. Even experienced surgeons misdiagnose a recurrence or persistence of an intra-abdominal infection after initial source control, because peritonitis can be masked by and attributed to "normal" postoperative problems like intestinal paralysis, under-resuscitation, postoperative mental deterioration, etc. [12]. In ongoing peritonitis after initial surgery abdominal pain, rebound tenderness and fever occurred less often than in secondary peritonitis after intestinal perforation [13].

Signs and symptoms of an ongoing or recurrent peritonitis are often masked and misinterpreted.

Besides clinical examination of the abdomen, an elevated respiratory frequency is a clinical parameter to detect patients with an ongoing intra-abdominal sepsis. It thus became part of many established ICU scores like quickSOFA, CURB-65 score, or APACHE II.

Due to the masked clinical signs and symptoms, a slight suspicion of a recurrence/persistence of peritonitis should lead to a radiographic imaging like CT, ultrasound, or X-ray. During everyday rounds, the patient should be reevaluated concerning

persistence/occurrence of organ dysfunctions (urinary output, ventilation parameters, cardiovascular support), inflammatory parameters, quality of drainage secretion, etc.. In an interdisciplinary approach, the decision to perform radiographic imaging has to be reevaluated everyday. Although CT shows highest sensitivity (97.2%) in cases of secondary peritonitis, it is significantly lower in ongoing peritonitis. Thus, a negative CT scan in a critically ill patient with an ongoing peritonitis should lead to the critical discussion, if a relaparotomy/relaparoscopy is indicated [14]. As a bedside technique, ultrasound allows an immediate examination of the peritoneal cavity, which includes the possibility to drain intra-abdominal fluid collections. CT- or ultrasound-guided drainages are of diagnostic value on the one hand (pus? clear fluid? hematoma? etc.). On the other hand, drainage of intra-abdominal abscesses or bilioma can be one kind of source control with minor morbidity compared to surgery in ongoing peritonitis.

CT-/ultrasound-guided drainage of intra-abdominal fluid collections is one important element for diagnosis and therapy of ongoing peritonitis.

Routine parameters of intra-abdominal infections are white blood cell count (WBC) and C-reactive protein (CRP). While specificity of CRP is low [15], it is a routine parameter to monitor septic patients on intensive care units. During sepsis therapy, a secondary increase of CRP can indicate an infectious complication. The same is true for a CRP persistence. A landmark study from Heidelberg showed that an elevated CRP (>140 mg/dl) on the fourth day after elective surgery is a predictor for inflammatory complications [16]. During ongoing peritonitis, procalcitonin (PCT) has been shown to be a sensitive and rapid parameter for a bacterial (re-) infection. While systemic infections go in line with an up to 5000-time increase within 4 h, located sources of infection can be PCT negative. So far it remains nebulous, if PCT can distinguish between ("sterile") SIRS and sepsis [17–19]. In contrast PCT is a helpful tool to monitor a patient with an intra-abdominal infection [20]. It furthermore can indicate when to finish antimicrobial therapy [20, 21]. As published recently, PCT guidance stimulates reduction of duration of treatment and by this reduces mortality [22].

Immunological research on biomarkers indicating sepsis mainly focusses on rapid detection of the septic patients. Modern research could identify markers like interleukin (IL)-6, IL-1α, TNFα, HMGB-1, MMP-9 VEGF, ICAM-1 MPO, methylglyoxal, and caspase 3 as sensitive indicators of sepsis development [23]. *Whether these markers could also help to detect the patient with a complicated, recurrent, and refractive peritonitis remains unclear up to date.*

On intensive care units, the regular collection of specimen, e.g., from urinary catheters, drainages, and bronchial secretion, is necessary to detect hospital-acquired (re-)infections. The examination of blood cultures plays a central role in the diagnosis of persistent peritonitis: two to three pairs (aerobic and anaerobic) of blood culture bottles should be collected regularly from both peripheral blood and also from central venous catheters [24]. Especially in cases of ongoing peritonitis, the preexisting antibiotic therapy reduces the detection rate of blood culture technique, which furthermore cannot differentiate between infection and colonization [25].

The latter is an important risk factor for the development of ongoing peritonitis. These patients are threatened by hospital-acquired infections. The colonization with multidrug-resistant pathogens like methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and multidrug-resistant gram-negative bacteria (MRGN) is often diagnosed in surgical patients and leads to isolation of the patient. The simple colonization of our patients with multidrug-resistant germs nevertheless is not treated routinely nowadays. Results of the REDUCE (Randomized Evaluation of Decolonization versus Universal Clearance to Eliminate) MRSA trial could change our view on antimicrobial therapy of the colonized patient: results reveal that intensive care patients clearly profit from a universal decolonization compared to screening and isolation methods [26]. If patients with ongoing peritonitis, who are colonized with MDR germs, should be decolonized, has to be shown in future studies.

In contrast to blood culture, PCR-based techniques like IRIDICA System (Abbott) or the next-generation sequencing (NGS) could provide a more rapid detection of bacteria and certain resistant phenotypes [27]. So far prospective studies are still missing. As published recently, these new techniques could play a crucial role to monitor therapy of a septic patient with an ongoing peritonitis in the future [28, 29].

14.3 Therapy

14.3.1 Surgery

Surgical source control is the only causal and life-saving treatment option for patients with secondary peritonitis. It is based on the four crucial elements: debridement, removal of infected devices, drainage of purulent cavities, and decompression of the abdominal cavity. To avoid a prolonged primary emergency operation, the reconstruction of anatomy and function could be performed in a second intervention 24–48 h after emergency. This goes in line with modern concepts of damage control surgery, which were established for trauma patients first [12, 14]. Indication for damage control surgery is the lethal triad of coagulopathy, inflammation, and cardiovascular instability. This easy rule is not only true for the emergency room situation but can also be established for the critically ill patient with a persistent or recurrent peritonitis, who dynamically develops this critical health state after initial source control (Fig. 14.1).

As mentioned above, the mortality of ongoing peritonitis is incredibly high and reaches up to 65% in literature! The most important independent risk factor is an insufficient source control during initial surgery. A bundle of trials could prove that non-successful source control leads to a dramatically increase in mortality (Table 14.1).

Besides adequacy of initial source control, the importance of the timing of surgery gets into the focus of research. Several trials analyzed the importance of the “time to intervention” for the outcome of patients with secondary peritonitis [30–34].

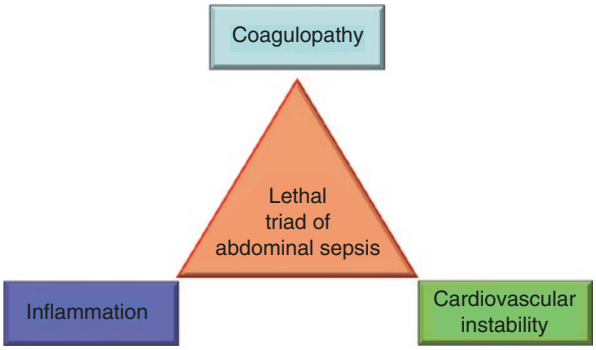

Fig. 14.1 The lethal triad of abdominal sepsis consists of coagulopathy, inflammation, and cardiovascular instability. These clinical conditions are indicators for immediate surgery. In ongoing peritonitis, patients have to be monitored both technically and clinically and carefully be reevaluated during everyday rounds [14] (Reproduced with permission from Springer)

Table 14.1 Impact of surgical source control on the mortality of patients with secondary peritonitis [14]

Reference	Kind of inflammation	Number of patients (*n*)	Initial source control not successful	Mortality
Seiler et al.	*Diffuse peritonitis*	258	11%	27% (vs. 13%)
Büchler et al.	*Diffuse peritonitis*	186	11%	25% (vs. 10%)
Barie et al.	*Intra-abdominal infection*	465	?	+22.6%
Wacha et al.	*Diffuse peritonitis*	355	30% (8.4%)	47% (vs. 14%)
Anderson et al.	*Severe intra-abdominal sepsis*	125	48%	90.2% (vs. 19.2%)

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In cases of ongoing peritonitis, there are three different surgical strategies for patients in general:

1. Relaparotomy on demand
2. Planned relaparotomy within 36–48 h
3. Open abdomen technique

The concept of planned relaparotomy is based on the a priori decision to reexplore the peritoneal cavity independent from its necessity. This is in contrast to the relaparotomy on demand, which is performed, if there are hints of clinical deterioration of the critically ill patient. Of course, the critical everyday reevaluation of the patient during interdisciplinary rounds is necessary to perform this concept (Fig. 14.2). In a landmark study from Ruler et al., there was no difference between "on-demand" (n = 116) and "planned" (n = 116) laparotomy concerning patients' mortality (29% on demand, 36% planned), but intervention rates and hospital costs were significantly lower in the "on-demand" study group [35].

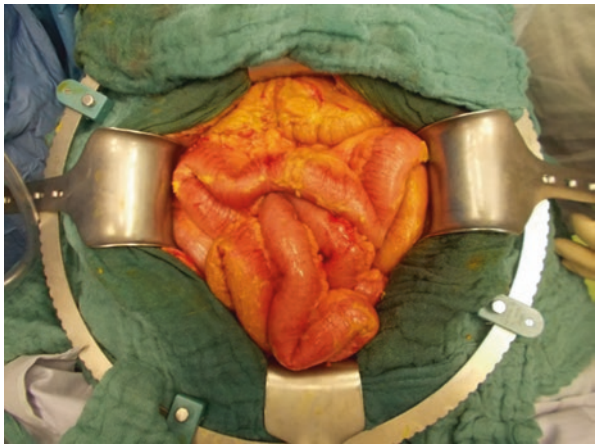

Fig. 14.2 Second look 48 h after initial emergency operation. In cases of persisting or new organ failure, a relaparotomy should be evaluated. If so, surgery should be performed within 48 h after the first operation

The decision to perform a "relook" on demand is difficult and requires much surgical experience. Besides the abovementioned lethal triad of sepsis, there are no clinical selection criteria for patients with an ongoing peritonitis [3, 36]. Van Ruler et al. analyzed 219 patients with secondary peritonitis and emergency laparotomy concerning the indication for surgical reintervention. Neither the initial origin of the intra-abdominal focus nor the findings of the surgeon during primary emergency surgery could indicate the need for a "second look." In contrast the persistence and occurrence of organ failure after emergency surgery were indicators for ongoing peritonitis and independent risk factors for an early surgical reexploration [37].

If the decision for surgical relaparotomy (on demand) is made, it should be performed rapidly. Koperna et al. analyzed 523 patients, who had undergone initial emergency surgery in cases of secondary peritonitis. In 105 patients, therapy failed, and a relaparotomy was indicated. In these cases mortality was significantly lower, if surgical relook was performed within 48 h after initial emergency surgery [38]. In contrast to open abdomen surgery, both concepts of relaparotomy "on demand" and of planned relaparotomy bear the risk to develop an acute abdominal compartment syndrome (ACS) in ongoing peritonitis. Thereby, the patient with ongoing peritonitis can develop a combination of a primary ACS, caused by the peritonitis itself, and a secondary ACS, which is caused by a capillary leakage, volume resuscitation, etc. [39]. Surveys revealed that, despite its hazardousness, ACS is often misdiagnosed or diagnosed too late. Only 47% of the physicians interviewed could define ACS [39]. As the diagnostic of choice, intra-abdominal pressure is typically measured indirectly through the bladder. ACS is defined as a sustained intra-abdominal pressure >20 mmHg associated with a new organ dysfunction. Due to its importance for the survival of patients with ongoing peritonitis, the guidelines recommend the monitoring of the intra-abdominal pressure by measurement through the bladder every 6 h in these patients [40].

Despite the preferred concept of an on-demand laparotomy, there are still clearly defined indications for a staged laparotomy like reevaluation of the intestinal viability in cases of mesenteric ischemia with secondary peritonitis [14].

Current clinical guidelines do not recommend the routine use of open abdomen surgery for abdominal sepsis [3]. Although, of course, a regular second look is easy to perform, open abdomen treatment bears the risk of enteroatmospheric

fistulas and fascial deviation [41]. This increased surgical morbidity in the critically ill patient with ongoing peritonitis can result in higher mortality rates, which was published recently [42]. Although not standard, open abdomen surgery nevertheless is one important tool for trauma surgeons: open abdomen surgery is the gold standard surgical approach for patients with ongoing peritonitis, who bear the risk of abdominal compartment syndrome (ACS) development. As published recently, it is also a safe and effective technique for patients, in whom a second look is expected to be performed [3]. This is the case for severe cases of secondary (and ongoing) peritonitis [3]. The World Society of Emergency Surgeons (WSES) published a landmark position paper on the open abdomen procedure in this emergency setting [3].

14.3.2 Intensive Care

As for the secondary peritonitis, supportive intensive care medicine is essential for patients with ongoing peritonitis. In contrast to patients with secondary peritonitis, the intensivists could be confronted with open abdomen surgery. Patients with ongoing peritonitis are typically threatened by increased fluid loss, muscle proteolysis, heat loss (especially in open abdomen surgery), and an impaired immune function. For patients with an open abdomen, intensive care furthermore has to focus on:

- Restrictive fluid management
- Monitoring of the body weight
- Tailored ventilatory support (low tidal volume)
- Rewarming
- Sedation and pain control
- Monitoring of pH (>7.2) and serum lactate

In ongoing peritonitis especially the surgical "on-demand" concept requires a vigilant observation of the patient in the ICU. According to the guidelines of the Surviving Sepsis Campaign [43], patients with a persisting peritonitis should be treated in concordance with certain target criteria:

1. Prophylaxis of ulcers (e.g., proton pump inhibitor)
2. Lung-protective ventilation (ARDS network protocol)
3. Hemodynamic stabilization
   - Mean arterial pressure >65 mmHg
   - Volume according to clinical examination
   - Inotropics in cases of myocardial dysfunction
   - Invasive hemodynamic monitoring, echocardiography
   - Glomerular filtration rate >0.5 ml/kg body weight
   - Repetitive measurement of serum lactate
4. Blood glucose 110–180 mg/dl
5. Prophylaxis of thrombosis
6. Enteral nutrition, if possible

While these core values could be a valuable guideline for everyday rounds, the exact doses, the amount of monitoring, etc. are—at least in part—a controversial topic of debate in modern literature.

As one example for one ongoing debate, recent literature reveals that a conservative/restrictive way of ventilation (paO_2 70–100 mmHg, SpO_2 94–98%) is advantageous for critically ill (long-term) ventilated patients in contrast to a conventional ventilation regimen (paO_2 up to 150 mmHg, SpO_2 97–100%) [44].

While hydrocortisone is one adjunctive tool to treat patients with septic shock, its use in patients with severe sepsis does not reduce the risk to develop cardiovascular instability/septic shock (HYPRESS trial) [45]. An update of recent literature furthermore reveals that calcium-sensitizing drugs like levosimendan are not associated with a decreased mortality or an improved organ function [46].

During everyday rounds, intensivists should monitor key aspects of modern intensive care medicine, according to the "FAST-HUG" (*f*eeding, *a*nalgesia, *s*edation, *t*hromboembolic prophylaxis, *h*ead-of-bed elevation, stress *u*lcer prevention, and *g*lucose control) principle published by Vincent et al. [47] before. As shown in Fig. 14.3, any lack of clinical improvement or deterioration after initial source control should lead to an interdisciplinary discussion, if a relaparotomy (on demand), a second look (into the opened abdominal cavity), or any radiographic imaging should be performed.

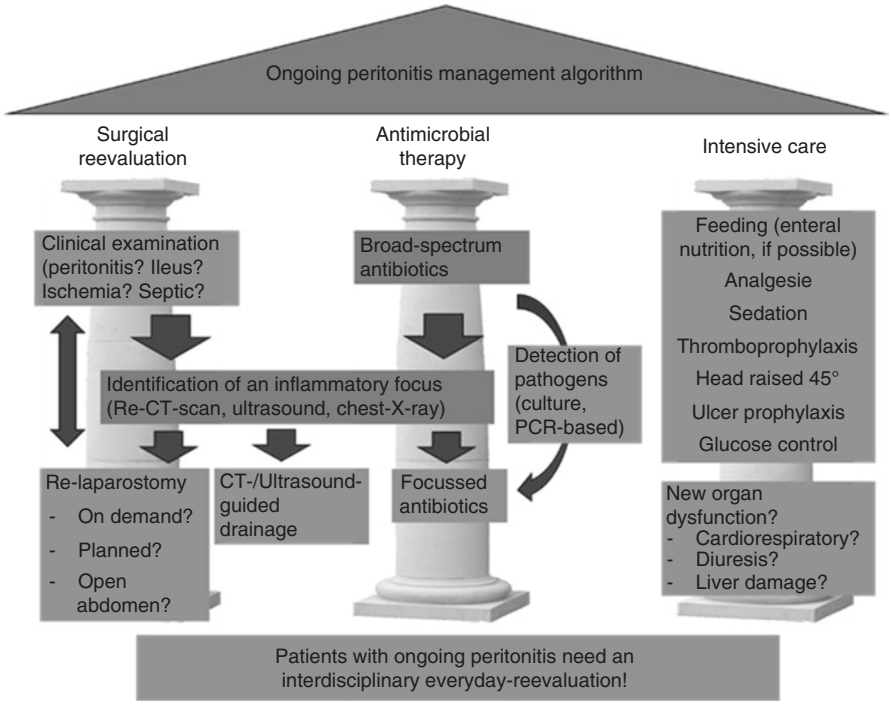

Fig. 14.3 Schematic drawing of the three columns of modern therapy of ongoing peritonitis. Essential is the interdisciplinary everyday reevaluation of the patients [14]. (Reproduced with permission from Springer)

14.3.3 Antimicrobial Therapy

Broad-spectrum antibiotics (Tarragona strategy) are the third therapeutic column in sepsis therapy. While in secondary peritonitis the broad-spectrum antimicrobial therapy often can be de-escalated and focused according to resistograms from blood culture or other specimen, ongoing peritonitis often requires an escalation and modification of antibiotics. In ongoing peritonitis, the antimicrobial state of a patient has to be reevaluated during daily rounds on intensive care units. In contrast to secondary peritonitis, patients with a persistent or recurrent peritonitis are more often confronted with multiresistant germs or fungi [7, 14]. Furthermore the hospital-specific individual microbial flora has to be considered, when choosing the appropriate antimicrobial therapy. There are hints from recent literature that a permanent intravenous infusion of β-lactam antibiotics could be more effective than the standard intermittent infusion in severe sepsis [48]. Whether this is also true for patients with ongoing peritonitis remains nebulous.

If the intra-abdominal infection is not under control, the antibiotic therapy has to be critically reevaluated after 48 h.

Depending on the suspected location of the infectious source (ongoing/recurrent infection of the peritoneal cavity, pulmonary infection, catheter-associated infection, etc.), intensivists have an impression on the bacterial flora and can treat the patient accordingly. Figure 14.4 gives an overview on the microbial flora of intra-abdominal infections and the corresponding "standard schemes" of antimicrobial therapy.

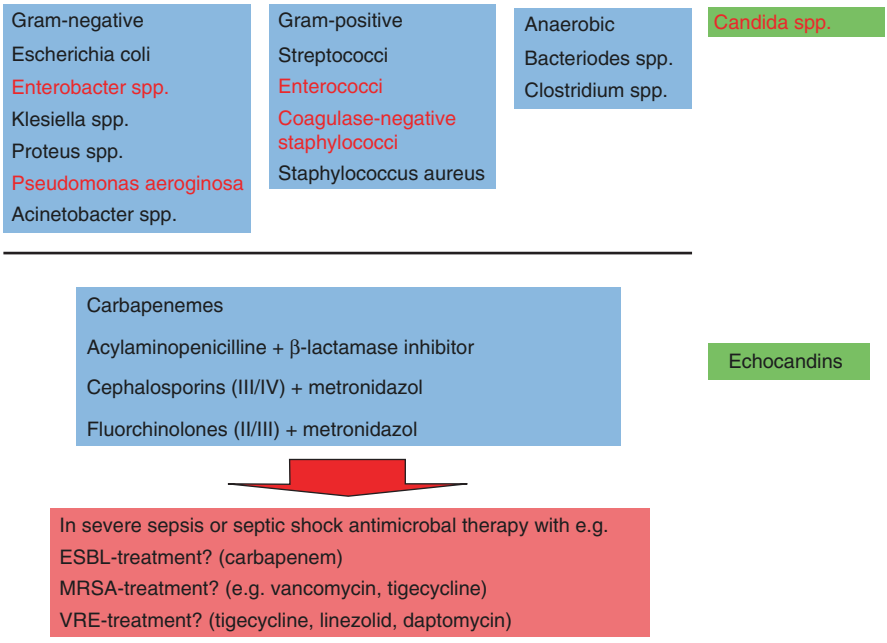

Fig. 14.4 Typical microbial flora in intra-abdominal sepsis. In cases of ongoing peritonitis, the spectrum shifts to nosocomial flora with typical pathogens (in *red*) [14] (Reproduced with permission from Springer)

As stated above, the antimicrobial therapy can be adapted to certain results of bacterial cultures or PCR-based methods from specimen collected at different sources of infection.

Antibiotic stewardship is gaining importance on nowadays' ICUs. The surveillance on the use of antimicrobials is essential both for the patient and to avoid antibiotic resistance.

Ongoing peritonitis could be seen as a nosocomial infection of the peritoneal cavity. The spectrum of MDR microorganisms includes enterococci, *Enterobacteriaceae*, *Pseudomonas*, and candida. Additionally ongoing peritonitis is often accompanied by pulmonary (30%) or urinary (8%) infections. Inadequate use of antibiotics threatens especially patients with ongoing peritonitis. As published by Hackel et al., none of the ten most frequently isolated bacteria from intra-abdominal infections was sensitive to ampicillin/sulbactam [1, 49] in the USA. New antibiotics and combinations were designed also for intra-abdominal infections and could be life-saving for patients with ongoing peritonitis. Table 14.2 provides an overview on "new-generation" antibiotics, which could be used as second-/third-line therapy in cases of ongoing peritonitis.

In patients with ongoing peritonitis, germs like *Staphylococcus epidermidis*, *Enterococcus*, and *Enterobacter* are selected out by initial broad-spectrum antibiotics. The same is true for candida species. If a patient has a neutropenia, immunosuppression, or a prolonged peritonitis, an antimycotic drug should be integrated into the antimicrobial therapy. Fungal isolates have been identified as independent risk factors for the development of a persistent peritonitis/ongoing peritonitis [1]. Bassetti et al. underlined the relevance of intra-abdominal candidiasis for intensive care patients. While mortality of ICU patients with intra-abdominal candidiasis was 50% (!), it was only half for non-ICU patients [60]. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommends echinocandins as first-choice medication for intensive care patients with candida infection [61]. In cases of *Candida parapsilosis*,

Table 14.2 New-generation antibiotics and their potential indications

Antibiotic	Class	Indication	Reference
Ceftobiprol	β-Lactam antibiotic	Pneumonia	[50]
Ceftaroline	β-Lactam antibiotic	SSI, pneumonia	[51, 52]
Ceftolozane/tazobactam	Fifth-generation cephalosporin + β-lactamase inhibitor	*3.3.1.1.1. Pseudomonas aeruginosa*	[53]
Cefolozane/tazobactam and Ceftazidime/avibactam	Cephalosporin + β-lactamase inhibitor	Intra-abdominal infections Urinary infections	[54–56]
Tedizolid	Oxazolidinone	SSI	[57]
Dalbavancin and oritavancin	Lipoglycopeptides	SSI, catheter-associated infection	[58, 59]

The corresponding literature is provided in the right column

fluconazole could be a rational alternative. The antimycotic should be applied until 14 days after the patient is candida negative in culture. Inadequate therapy of intra-abdominal candidiasis has been proven to be one important negative prognostic parameter for the survival of ICU patients [1, 60]. In contrast, the use of micafungin as a routine empirical treatment in critically ill patients with suspected fungal infection did not improve fungal infection-free survival at 28 days, as published recently [62].

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Evolving Treatment Strategies for Severe *Clostridium difficile* Colitis: Defining the Therapeutic Window

15

Peter K. Kim, Peng Zhao, and Sheldon Teperman

15.1 Introduction

Clostridium difficile is the leading cause of hospital-acquired infections in the United States [1]. The disease began as a nosocomial annoyance at the end of the last century and has evolved into a hypervirulent strain [2]. The risk factors for acquiring *C. difficile* colitis are merely hospitalization, exposure to antibiotics, immunosuppression, advanced age, and malnutrition—all characteristics of the frail patient that populate nursing homes [3]. What is important for clinicians is to recognize the signs and hallmarks of the disease process early. Timely recognition of severe *Clostridium difficile* infection (CDI) can avoid emergency surgery to extirpate the colon and prevent the ravages of septic shock and ultimately death.

In this chapter, we will define new criteria for the clinical recognition of severe disease and the "therapeutic window" when the failure of medical management begins and a point where even surgical intervention becomes futile. We will examine options for colon-preserving techniques in treating *C. difficile* colitis in comparison to traditional surgical interventions for source control. Important clinical keys to optimize success with intracolonic vancomycin (ICV) will be included. Finally, in cases where *C. difficile* colitis has been successfully overcome, we will discuss areas of microbiome manipulation that can be used as prevention strategies necessary to evade recurrent *C. difficile* colitis.

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15.2 Clinical Recognition of *C. difficile*-Associated Diarrhea and Colitis

C. difficile-associated diarrhea (CDAD) is a terrible healthcare-associated disease that has afflicted hospitalized patients only since the end of the last century and was first described in 1978 [4]. We recommend reading *Missing Microbes* by Martin Blaser from NYU to get a cross section of the scope of problems caused by antibiotics in humans [5]. Half of antibiotic use in the United States is in the livestock industry, which efficiently fattens the calves and chickens. Only now are people catching on that antibiotics in domesticated animals and agriculture are problematic.

The overuse of antibiotics and the rise of *C. difficile* colitis make the prospects of receiving healthcare very dangerous in America, Europe, and the rest of the developed world [6]. Let's say it again—hospitals are dangerous places [7]. So if you are old and frail with a hint of an infection, someone will prescribe antibiotics for a patient who may then develop unremitting diarrhea and abdominal pain that requires an emergency surgery with an ileostomy to save his or her life.

There is hope, but also confusion, as to the right things to do for the sickest patients. As we tell the residents we train, much of your care depends on who is on call, the time of day, and the phase of the moon. With luck and education for "Surviving Sepsis," someone will identify your severe infection early and start empiric antibiotic therapy with broad bacterial coverage. However, finding the correct source of sepsis can be difficult, and *C. difficile* colitis in particular can elude even the best clinicians. Moreover, the microbiome-altering effects of empiric gram-negative coverage will exacerbate the problems fueled by *C. difficile*. Once *C. difficile*-associated diarrhea is identified, stopping the broad-spectrum antibiotics becomes a hard sell, as there is often a concern for other sources of infection in the lungs, blood, or urine. Nevertheless, the absolute desistance of unnecessary antibiotics is critical to the management of *C. difficile* in the early stages to prevent the escalation of infection to life-threatening colitis.

Currently in our hospital, we have a culture that believes in early surgical consultations and intracolonic vancomycin enemas for severe *C. difficile* colitis. Due to the "ick" factor of transanal therapies in America, when the medical students are polled, one-third say they would go for surgery, a third say colonoscopic fecal transplant, and half would agree to the rectal tube with antibiotics delivered directly into their colon in order to obtain source control of a raging infection caused by *C. difficile*.

15.3 Mechanisms and Pathogenicity of a New Strain

C. difficile has abruptly replaced methicillin-resistant *Staphylococcus aureus* as the most common "healthcare-associated infection" [8]. The "ground zero" of a deadly epidemic was Quebec Canada in 2002 [9]. Fortunately, our Canadian colleagues recognized that they were dealing with an organism that had lethally transformed

itself and sounded the claxon loudly [10]. The mutation would later be defined in careful detail by researchers at the CDC and dubbed "B1/NAP1/027 toxinotype III" [11]. This classification of a highly virulent strain of *C. difficile* relates to various biochemical and genetic signatures of the strain.

A report appeared in the Lancet in September 2005 that chronicled a cross-Atlantic collaboration to characterize the virulence of the new organism [2]. *C. difficile* produces three kinds of exotoxins—A, B, and a binary toxin. Toxin B seems to be the most virulent toxin compared to toxin A, but it is becoming clearer that the binary toxins have a role in pathogenesis [12]. The toxins seem to function through Rho GTPases to change actin polymerization and alter the gap junctions of colonocytes making the colon leaky and permeable for the rest of the microbiome to rush into the body [13, 14]. Remember the gastrointestinal tract is a tube and what is inside the colon is actually external to the body. Perhaps sepsis is induced by a break in the colonic mucosal wall, the host barrier, where microbiomic predators can invade the house.

With NAP1, the Lancet investigators found the organism elaborated between 16 and 23 times more toxin than any form of *C. difficile* theretofore [2]. So the mystery of how this organism was causing such a severe and deadly presentation had been solved. The public health investigators in Quebec then fell on their swords in an effort to explain: "What is going on in Canada?" They cited the rampant use of fluoroquinolones (the new strain is resistant to them and undoubtedly encouraged by them), aging infrastructure (crowded hospital rooms), and poor infection control practices (the spores of *C. difficile* can only be eradicated by handwashing with soap and water and not alcohol-based solutions). But, in truth, the same factors exist across a broad spectrum of the healthcare continuum, and the United States certainly has its share of these problems.

15.4 Treatment Strategies of Mild, Moderate, and Severe (Stage 1), Complicated (Stage 2), and Fulminant (Stage 3) Colitis

The standard diagnosis and therapy of *C. difficile*-associated disease has been reviewed in detail and extensively by Sartelli et al. in the 2015 World Society of Emergency Surgery (WSES) review and guidelines [15]. However, the management of severe, complicated, and fulminant colitis by *C. difficile* is still controversial, and new strategic methods of therapy are still in development to combat the rise of this deadly hospital-acquired infection. In our review of the literature for CDI, the classification of severe disease has been confounding to clinicians due to the different standards and terminology, and the timing of surgery remains controversial. We wish to present a simple classification system for CDI (Table 15.1). In particular, we draw attention to three stages of severe CDI and associate each stage with an appropriate therapeutic modality to achieve better outcomes and endorse colon-preserving therapies whenever possible.

Table 15.1 Severity scoring system for *Clostridium difficile* infection (CDI) and antibiotic treatment recommendations to include intracolonic vancomycin for severe disease stages 1, 2, and 3

Severity	Diagnosis	Treatment
Mild CDI	• Diarrhea	• Metronidazole 500 mg PO or IV q8h × 10d • Stop unnecessary antibiotics
Moderate CDI	• Diarrhea and abdominal pain	• Vancomycin 125 mg PO q6h × 10d
Severe CDI Stage 1	• Serum albumin <3 g/dL • WBC >15,000 cells/mm^3 • Abdominal tenderness • Creatinine >1.5 times normal	• Metronidazole 500 mg IV q8h • Vancomycin 250 mg PO q6h • Intracolonic vancomycin 1 g in 500 cc LR per rectum q6h as retention enema • Surgery consultation
Severe CDI Stage 2 (complicated)	• ICU admission • Fever >38.5 °C • Hypotension • Mental status changes • WBC >35 or <2 cells/mm^3 • Serum lactate >2.2 mmol/L • End-organ failure (respiratory, renal)	• Metronidazole 500 mg IV q8h • Vancomycin 500 mg PO q6h • Diverting loop ileostomy with colonic washout • Antegrade intracolonic vancomycin 1 g in 500 cc LR via ileostomy tube q6h × 10d
Severe CDI Stage 3 (fulminant)	• Increasing pressors • Worsening renal failure • WBC > 50 cells/mm^3 • Peritonitis • Abdominal compartment syndrome	• Subtotal colectomy with ileostomy • Rectal vancomycin via stump 500 mg PR q6h • Consider futility if end-stage chronic illness

15.4.1 Mild and Moderate Disease

The treatment of CDAD has evolved over the past several years from the routine use of oral metronidazole to routine oral vancomycin and intravenous metronidazole for severe disease [16]. The 2013 American College of Gastroenterology (ACG) guidelines endorsed a severity scoring system for CDI [17]. We propose that "mild" disease presents with diarrhea only and can be treated with oral metronidazole alone. Moderate disease presents with both diarrhea and abdominal pain. Oral antibiotics are the treatment of choice for patients belonging to the first two classes of severity, but intravenous metronidazole can be used for hospitalized patients. Unfortunately, metronidazole has been associated with an increasing failure rate for CDAD [18]. Oral vancomycin should be considered especially if there is no improvement after 5–7 days of metronidazole alone. Intravenous vancomycin is never used for CDI because, unlike metronidazole, vancomycin is not secreted into the gastrointestinal tract.

Importantly, CDI recurs in 15–35% of patients with one previous episode and 33–65% of patients with more than two episodes [19]. A new macrolide antibiotic fidaxomicin was approved for mild to moderate *C. difficile*-associated diarrhea [20].

Fidaxomicin has a narrow focus of activity against gram-positive anaerobes. Initial trials show it to be at least as effective as existing therapy, but with fewer recurrent episodes. The mechanism for this is thought to be less perturbation of the microbiome [21]. Because of its cost, fidaxomicin is largely held in reserve until there is recurrent disease since it is three times more expensive than the equivalent vancomycin orally.

15.4.1.1 Fecal Microbiota Transplantation for Recurrent CDI

The increasing understanding of the colonic microbial environment and mucosal immunity has led to the emergence of fecal microbiota transplantation (FMT) [13, 22–25]. FMT is the only treatment modality that gives a high cure rate for recurrent disease and alters the colonic flora deficiency and dysbiosis. Although the usefulness of FMT in situations other than recurrent disease has not been well studied, there is increasing evidence that stool transplantation could benefit patient with mild, moderate, and even severe disease. Increasing evidence suggests that some form of microbiome manipulation may be the future standard of care for *C. difficile* and other diseases.

15.4.2 Severe Stage 1: *Clostridium difficile* Colitis

The SHEA/IDSA guidelines from 2010 defines "severe" as WBC > 15,000 cells per μL or a serum creatinine level >1.5 times the premorbid level [17]. "Severe" CDI Stage 1 is defined by WBC > 15,000 cells/mm^3, low serum albumin <3 g/dL, serum creatinine level >1.5 times the premorbid level, or abdominal tenderness (Table 15.1). We prefer to include patients early who are frail with any signs of sepsis or renal failure.

For managing Severe Stage 1 disease, the SHEA/IDSA guidelines endorse a combination regimen of intravenous metronidazole and a higher dose of oral vancomycin. In 2007, we did come across one "trick," to outsmart a very clever foe. There were just a few whispers of the idea of instilling vancomycin directly in to the colon, as an adjunctive therapy [26–28]. There was one case study with just a handful of patients [29]. If NAP1 was causing an ileus and preventing the most effective antibiotics from reaching it, why not outsmart it and short-circuit it? We started employing it on every patient that would be classified as severe disease. During the NAP1 epidemic, we did show a 70% complete response rate with the early application of intracolonic vancomycin (ICV) in 47 patients [30]. The other 30% required lifesaving colectomies to save another 70% making a salvage rate of 79%. Importantly, all patients who failed vancomycin enemas died without surgery. Our statistical analysis showed that older patients with low albumin levels, a common nursing home denizen, tended to fail intracolonic vancomycin. Indeed, we strongly believe that ICV should certainly be in every surgeon's toolbox for Severe Stage 1 disease. Nevertheless, the response to therapy and need for early surgery needs to be monitored carefully, especially in the old and frail patients. We have a large experience with the technique of intracolonic vancomycin enemas, and we wanted to share our insights into the keys to success with the technique in Table 15.2.

Table 15.2 Know your local armamentarium: keys to success for vancomycin enemas for severe *C. difficile* colitis

1. Start ICV early with surgical consultation
2. Stop all unnecessary antibiotics!
3. Use a large rectal tube, 32 French Mallekodt, or Foley catheter. Use as a retention enema. Clamp as tolerated for 15 min, and then drain for 5 h
4. If you use a large Foley catheter as your rectal tube, don't leave the rectal tube balloon inflated on the Foley catheter due to ischemic pressure on the rectum causing lower gastrointestinal bleeding that will stop ICV therapy
5. DO NOT USE the irrigation port of the Flexi-Seal® rectal tube and fecal collection or management systems as some have suggested [70]. We have experienced several failures due to the use of the fecal management tubes. These systems are designed for collection, not for instillation. The key to success is delivery of the vancomycin to the right side of the colon. Tape or fasten the tube to the leg so it doesn't fall out
6. Use higher doses, 1 g; it doesn't get absorbed systemically by the colon
7. Use larger volumes, 500 cc, or even 1 L; the risk of perforation is so low there are no reported cases. The IDSA/SHEA recommendation of 100 cc volumes is just too little, and this likely contributes to failure. We agree that 500 mg in 100 cc every 8 h is a good dose and volume for the rectal stump with pouchitis for 7 days after colectomy [71]
8. Use lactated ringer's instead of normal saline due to metabolic acidosis of normal saline [72]
9. To save money, tell the pharmacy to use intravenous vancomycin to make the rectal vancomycin enemas. The PO vancomycin is much more expensive and hard to crush

Another case-cohort retrospective study with 26 patients treated with ICV also suggests that retrograde ICV has some protective effects, but their numbers were also low and the correlation was not a strong one [31]. The American Society of Gastroenterologists and the World Society of Emergency Surgery both endorse the use of retrograde ICV for severe disease, and we include this modality as an important adjunct medical therapy for Severe Stage 1 disease. We and others strongly suggest early surgical consultation for Severe Stage 1 disease to monitor response to therapy and need for emergent surgery if the disease progresses [32].

15.4.3 Severe Stage 2: Complicated *C. difficile* Colitis

So once we have determined that maximal medical therapy has failed, we are left with the good old general surgeon on call in the emergency room or medical intensive care unit (MICU) in the middle of the night [33, 34]. Hopefully, the MICU team has consulted surgery early, hours before the patient gets intubated or pressors are started. Consultations before any signs of organ failure are the best time for these decisions. With proper resources, the patient gets transferred to the surgical ICU for care because this approach may improve outcomes [35]. And hopefully there is a surgeon who can recognize the deceptive animal called abdominal compartment syndrome that would require decompressive laparotomy [36].

The decision to perform surgery still remains a difficult one, but the indications are summarized in Table 15.1. We propose the name for complicated *C. difficile* colitis be classified broadly as Severe Stage 2 disease that includes any patients in

the intensive care unit with illness attributable to CDI, patients with hypotension with or without the requirement for vasopressors, patients with ileus or significant abdominal distention, and especially patients with signs of end-organ damage or dysfunction such as renal failure, mental status changes, and need for mechanical ventilation [15, 17, 37]. Any signs of organ failure should herald the need for surgery, and the lowest mortalities are associated with the diverting loop ileostomy with colonic washout [38]. In Pittsburgh, Zuckerbraun et al. developed a protocol to operate early and by a minimally invasive approach of laparoscopic ileostomy; intraoperatively, they would lavage the colon with 8 L of GoLYTELY® and deliver the vancomycin intracolonically into the right colon via a tube passed through the distal limb of the loop ileostomy. Compared with abdominal colectomy, diverting loop ileostomy with colonic lavage is a less invasive and colon-sparing procedure [39]. The procedure was used in the treatment of severe, complicated CDI in 42 consecutive patients with historical controls. Loop ileostomy was created laparoscopically in 35 (83%) patients in the study cohort. The colon was preserved in 39 (93%) patients in the study cohort. Mortality was significantly lower in the study cohort than in historical controls that received colectomy (19% vs. 50%; odds ratio, 0.24; $p = 0.006$).

Of note, the Pittsburgh group continued antegrade intracolonic vancomycin for ten days, and they too had a 70% survival rate in a patient population that was quite similar to our own experience with ICV per rectum [30]. The ileostomy technique is far less surgery for the patient than a subtotal colectomy. For the surgeon and the patients, this procedure is a less daunting minimally invasive surgery to contemplate [40]. This minimally invasive procedure represents a step-up from the rectally delivered intracolonic vancomycin given in Severe Stage 1 disease, but remains far less invasive and traumatic than a laparotomy with subtotal colectomy. All patients received antegrade vancomycin enemas via the ileostomy postoperatively, and they also showed a 70% success rate. As such, it leaves the door open to intestinal continuity at a remote time. In fact, 79% of the long-term survivors had their ileostomies reversed [38].

Was the surgery necessary? For many of the patients, we would argue yes. The combination of lavage, antibiotic, and oxygen delivered to the right colon to kill and wash out the anaerobic *C. difficile* bacteria was lifesaving and necessary. These patients avoided colectomy, but could these patients have avoided surgery and an ileostomy altogether if ICV had been administered early via rectal tube? The answer to this question we will never know until a future randomized trial is established. The art of nonoperative, colon-preserving emergency surgery for CDI has yet to be mastered.

We recommend continuous evaluation and communication by critical care, infectious disease, and surgical services to determine the initiation and termination of ICV therapy and particularly, the need for further surgical intervention. Unfortunately, there are case reports showing death after loop ileostomy, and the technique does not always succeed in saving the patients [41]. Some patients go on to needing a subtotal colectomy, and some will die [38]. Early recognition of signs of worsening disease is crucial because these patients can still progress to fulminant colitis (Severe Stage 3) and life-threatening CDI.

15.4.4 Severe Stage 3: Fulminant *C. difficile* Colitis

Although there is no one clear-cut definition for fulminant CDI, it is believed to be the most serious disease manifestation of CDI. One study casts a wide net and defined fulminant disease as the need for colectomy or the need for intensive care unit admission [42]. The caveat is that surgical treatment of CDI by colectomy has high mortality rates when the disease reaches the fulminant stage [43]. With multisystem organ failure in play, the options look like surgery or death; unfortunately, we tell the families of the patients in septic shock on pressors that they have the same risk of mortality with or without total abdominal colectomy. Most studies agree that improved survival might be achieved with earlier operation prior to the development of fulminant disease [35, 44].

Current literature have not been able to confidently describe which patients might fail medical management or who will likely progress to fulminant disease with multisystem organ failure [19]. However, in patients with fulminant colitis, those who received emergency colectomy were more likely to survive than patient treated only medically [41]. The improved mortality with surgery is an important reason for advocating early input from a surgical team.

The major camp of surgeons believes in subtotal colectomy with ileostomy. These surgeons value definitive source control in these desperate situations of fulminant *C. difficile* colitis that requires removal of the entire colon leaving a rectal stump. This procedure is highly morbid, time-consuming, and if the patient lives, she will need an ileorectal anastomosis to restore continuity with the prospect of a lifetime of diarrhea and even life-threatening recurrence of *C. difficile* colitis [45]. Those patients may never get reversed, and the poor survivors suffer the ravages of dehydration and electrolyte imbalances due to their ileostomies starting on postoperative day 1 [46]. Elderly patients with ileostomies in nursing homes do not do well.

Our algorithm for Stage 3 disease might delay subtotal colectomy if the pressor requirement was a small one with dramatic improvement within 24 h with intracolonic vancomycin via rectal tube. Nevertheless, the Eastern Association for the Surgery of Trauma (EAST) Guidelines tried to address this very question of timing of surgery for CDI [47]. These *C. difficile* guidelines were the first to use the new GRADE methodology. EAST strongly recommends patients with severe *C. difficile* "undergo surgery early, before the development of shock or the need for vasopressors." They take pains to point out the quality of evidence underpinning this recommendation is "very low." The flip side of their argument is that it is clear that waiting just a bit too long can yield a mortality, so early surgery, though radical (they favor subtotal colectomy), is preferred. We also liberally employ abdominal CT looking for that characteristic diffuse colonic thickening. That practice of CT imaging is a habit we got into before the advent of rapid *C. difficile* testing (stool GDH and real-time PCR). We also wait, just a bit, for the per rectum vancomycin (ICV) to have infused the mucosa of the colon. Nevertheless, Dr. Ferrada and her committee probably got this right: Early surgery will save lives.

One thing is abundantly clear—subtotal colectomy rids the body of the disease with the stroke of the knife [32]. The response, if the surgeon is not too late, is immediate and dramatic. The WBC drops, the lactate clears, and the pressors are

usually weaned. But very often, the residual of all that sepsis is too much for the patient. And though they don't die, per se, their life is shortened. In particular, we have found that renal failure commonly intervenes.

Currently, many centers would remove your entire colon if you were sick with CDI. Indeed, the 2013 EAST guidelines were aware of the less invasive technique but chose to espouse subtotal colectomy with ileostomy as the standard of care; however, this conclusion was based on some shaky retrospective data [48]. More recently, Dr. Ferrada has organized a ten-center retrospective review of surgical therapy for *C. difficile* colitis that shows lower mortality for patients receiving the loop ileostomy therapy as opposed to subtotal colectomy [49]. Could the improved results for loop ileostomy have been attributable to patient selection? Maybe. There was an effort at the Mass General to lead a prospective trial on this important question. It is aptly titled: "Diverting Loop Ileostomy and Colonic Lavage: An Alternative To Total Abdominal Colectomy For The Treatment Of Fulminant *Clostridium difficile* Colitis. A Randomized Controlled Trial." Randomized trials are hard to come by, and the trial attempted at the Massachusetts General Hospital had trouble recruiting enough centers and patients. Unfortunately, these recruitment and randomizations are hard to pull off in the middle of the night, and the ethics of such experiments get fuzzy.

15.4.4.1 Predictors of Mortality for Severe *C. difficile* Colitis: When Surgery to Remove the Colon Is Necessary to Save a Life, It May Be Too Late

Although patients who undergo emergency colectomy are more likely to survive than patients who are treated only medically, the mortality rates after colectomy are still very high [50]. For individuals ≥65 years of age, the mortality rate in this geriatric population was 55.1 deaths per 100,000. As with other diseases requiring emergency surgery, mortality is associated with age, white blood cell count, serum albumin, and serum creatinine [51]. Importantly, CDI was the 17th leading cause of death in this age group. However, it is important to realize that this data was generated before the use of intracolonic vancomycin [11].

In the most severe cases, fulminant colitis (Severe Stage 3) that requires surgical intervention occurs in up to 8% of patients infected with *C. difficile* [52]. Subtotal colectomy with ileostomy is necessary in up to 3.5% of patients with *C. difficile*-associated diarrhea [53]. Surgery to remove the colon remains a highly morbid therapy for patients with fulminant colitis. Historical controls report a mortality rate of 35–57% for patients who require colectomy, and severe cases may be associated with strains of *Clostridium difficile* that produce high toxin levels [54]. Even if patients survived colectomy in the short term, their five-year survival rate is only 38% [55]. For this reason alone, it is imperative that surgical consultation be obtained for patients who are in the Severe Stage 1 and 2 disease categories before fulminant Stage 3 disease sets in and the "therapeutic window" has closed shut.

Interestingly, mortality rates are higher for patients who received partial colectomy than for those who received subtotal colectomy [56–58]. This discrepancy may have resulted from persistent disease in the remnant colonic segment, high

frequency of pancolonic disease, and inadequate intraoperative assessment of the colon, which is often based on the visualization of the serosal surface [51, 59]. More recently, we have seen partial colectomies work with the use of postoperative ICV via the ostomy, with partial colectomies performed more often in children [60].

15.4.5 Futility/Cost

More and more often, we come across several patients with CDI who are old and sick with end-stage cancer or fulminant AIDS. To these poor souls, we offered surgery without hope for survival, and some of the patients and families refused. These people may have died of *C. difficile* colitis, but their underlying end-stage diseases are not going to be changed by taking out their colons. From a palliative perspective, surgery would be heroic, and some would argue "futile." We know that 65% of all the people who have ever made it to the age of 65 years old are alive today, thanks to the magic of modern medicine. As emergency surgeons in this rapidly aging population, we have to show some forbearance when we offer surgery as therapy for the very old, frail, and ill. We can no longer frame the decision as "Do everything to save your loved one's life, or do nothing." We now have less invasive alternatives—loop ileostomy with washout or vancomycin enemas or stool transplant or immunotherapy. We just don't always know what is the best therapeutic strategy, and we often tell the families of the sickest patient who are contemplating emergency surgery that there is no right or wrong decision in these situations. Unfortunately, for Severe Stage 3 disease, the patients may die with or without surgery.

15.4.5.1 New Horizons

If hope in science prevails, there will be a future where no colons will need to be removed for *C. difficile* colitis. New science has discovered that nature may have an answer to our problem if we can harness the weapons developed by viruses to attack bacteria in their epic battle to control the mammalian microbiome. Amazingly, there are viruses called phages that not only target bacteria for lysis, but also specific phages exist that can hone in on receptors of *Clostridium difficile* [61]. The future for phage therapy has been used effectively in Russia for years, and the United States could benefit from learning from other countries' homeopathic remedies.

Closer to home, the recent data on vaccines for *C. difficile* have shown promise [62, 63]. The elderly are relatively immunosuppressed, and boosting their response to *C. difficile* antigens seems like a noble process [64], much like giving Pneumovax to prevent pneumonia. Targeted therapy for the binary toxins has been studied [65]. The role of modulating the immune system in severe disease is yet to be trialed, but prevention of recurrence may give fecal transplants and fidaxomicin a run for their money.

Fecal microbial transplantation for severe disease has shown some promising results in elderly patients. We are hopeful that standardized therapies that reconstitute the depleted microbiome will prove more efficacious than the use of antibiotics and surgery [66]. Finally, scientists are looking at the pathophysiology of

C. difficile, and we are starting to understand that spores, although contagious, are not directly harmful [67]. The molecular mechanisms of sporulation and germination are just starting to be understood in *C. difficile*, and these molecular targets form an array of potential mechanisms for pharmacotherapy to prevent germination and induce or maintain sporulation [13]. The role of secondary bile acids in this process is confirmed, and modulation of innate bile production may also aid in preventing or even treating *C. difficile* colitis [68, 69].

Conclusion

Complications of *Clostridium difficile* infection have created an enormous burden on healthcare systems throughout the world. We propose a new classification system of CDI that includes three stages that emphasize the early recognition of severe disease. We emphasize the beginning of a therapeutic window for Severe Stage 1 with the liberal use of retrograde intracolonic vancomycin per rectal tube. We endorse stepping up to early and minimally invasive surgery in Severe Stage 2 (complicated *C. difficile* colitis) with diverting loop ileostomy, colonic washout, and antegrade intracolonic vancomycin as a legitimate and effective colon-sparing technique for the old and frail patients who develop severe CDI. The key is to get early source control by delivery of the ICV therapy to the entire colon. Severe Stage 3 disease, or fulminant *C. difficile* colitis, marks the closing of the therapeutic window when subtotal colectomy may be the only option to save a life with the highest risk for mortality, and in some cases, even surgery cannot save the patient. Our current goal in using adjunct ICV either retrograde or antegrade for severe CDI Stages 1 and 2 is to limit the morbidity and mortality of this important and common healthcare-associated infection until techniques to modulate the human microbiome can be used reliably to eradicate this disease.

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Complicated Intra-abdominal Infections: Principles of Antimicrobial Therapy

16

Matteo Bassetti, Elda Righi, and Massimo Sartelli

16.1 Introduction

Intraabdominal infections (IAI) represent a significant problem worldwide, showing high morbidity rates especially among elderly and critically ill patients [1].

IAI occur in a wide variety of pathological conditions, ranging from uncomplicated appendicitis to faecal peritonitis. IAIs are usually classified as either uncomplicated or complicated (cIAI) [2].

In uncomplicated IAIs, the infection only involves a single organ and does not extend to the whole peritoneal cavity [2]. Patients with such infections can be treated with either surgical resection or antibiotics. When the infection is effectively resolved by surgical excision, post-operative therapy may be not necessary, as demonstrated in acute uncomplicated appendicitis or cholecystitis [3–5].

In cIAI, the infectious process spreads beyond the organ, causing either localized or diffuse peritonitis. The treatment of patients with IAIs involves both source control and antibiotic therapy.

Routine cultures to detect the etiology of cIAI are important to monitor epidemiological trends in pathogens' resistance patterns, and to direct step-down therapies (e.g., switch to oral treatment). Cultures should be always obtained in patients who previously received broad-spectrum antimicrobials and in areas where

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Table 16.1 Main principles of antimicrobial therapy in cIAI

Obtainment of microbiology cultures to monitor resistance levels to antimicrobials and to allow targeted step-down therapy to oral treatment
Association of adequate antimicrobial therapy with adequate source control (drainage, removal of necrotic tissue, etc.)
Evaluation of risk factors for disease severity and resistance acquisition
Knowledge of local data for susceptibility rates of pathogens that are commonly involved in cIAI
Allowing step-down therapy (e.g., switch to narrower spectrum antibiotics or oral treatment) as soon as possible
Limitation of overall treatment duration

significant resistance rates (e.g., 10–20% of isolates) is detected among pathogens that are commonly involved in cIAI [6].

Although the types and characteristics of cIAI are diverse, common management principles need to be applied in order to reduce infection incidence and complications, including the timely administration of an appropriate antimicrobial therapy as well as an effective source control, such as adequate debridement or control of drainage (Table 16.1).

Guidelines providing recommendations for the choice of an appropriate antimicrobial regimen based on high-quality evidence are currently available and should be taken into account when managing cIAI [6].

Overall, the empiric therapy of intra-abdominal infection should include molecules that are active against enteric gram-negative aerobic bacilli and streptococci. Coverage of anaerobic bacilli should be considered for specific interventions including distal colon-derived, small bowel, and appendiceal infections. The choice of the correct molecule depends on various factors, including the severity of the infection (low-to-moderate or severe), the setting of acquisition (community-acquired or hospital-acquired infections), and the reduced susceptibility to antimicrobials shown by various pathogens, especially among Enterobacteriaceae and *Pseudomonas aeruginosa* [6, 7].

Table 16.2 summarizes the main antimicrobial regimens recommended for the treatment of cIAI.

The indiscriminate and excessive use of antimicrobial drugs appears to be the most significant factor in the emergence of resistant microorganisms in recent years [8]. Although a decrease in antimicrobial susceptibility, especially among third generation cephalosporins and fluoroquinolones, has been registered among Gram-negative bacteria worldwide, resistance profiles still widely vary in different countries and even among different hospitals in the same area. For these reasons, the knowledge of local resistance patterns is paramount for the correct management of patients with cIAI.

Specifically, the knowledge of local rates of resistance is always an essential component of the clinical decision-making process when chosing the optimal antibiotic regimen to use for empirical treatment of infection. Predicting the pathogens and potential resistance patterns of a given infection begins by establishing whether the infection is community-acquired (CA) or hospital acquired (HA).

For patients with CA-cIAI, antibiotics with a narrow spectrum of activity encompassing all likely organisms should be administered. The major pathogens

Table 16.2 Antimicrobial regimens suggested for the treatment of community acquired and hospital acquired cIAI

Community-acquired cIAI		Hospital-acquired cIAI	
Low-to moderate severity	High severity	Overall	Selected populations[a]
Amoxicillin/clavulanate, ampicillin/sulbatcam, cefoxitin, tigecycline or Cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin (+ metronidazole)	Carbapenems (e.g., meropenem, imipenem-cilastatin, doripenem), piperacillin-tazobactam, tigecycline or Ceftolozane/tazobactam and ceftazidime/avibactam (+ metronidazole)	Carbapenems (e.g., meropenem, imipenem-cilastatin, doripenem), piperacillin-tazobactam, tigecycline + carbapenems or piperacillin/tazobactam or ceftolozane/tazobactam or ceftazidime/avibactam (+ metronidazole) ± Aminoglycoside	Anti-fungal therapy Anti-MRSA therapy Coverage of *E. faecium* Coverage of ESBL- or carbapenemase-producing bacteria

[a]According to risk factors (e.g., previous colonization or infection with resistant strains, use of broad spectrum antimicrobials, etc.)

involved in CA-IAIs are likely to be due to a patient's own flora. Therefore, they are usually predictable and include *Enterobacteriaceae* (predominantly *Escherichia coli* and *Klebsiella* species), streptococci, and anaerobes (especially *Bacteroides fragilis*) [6].

However, if patients with CA-IAI have risk factors for infections due to extended-spectrum-β-lactamases-producing (ESBL) *Enterobacteriaceae*, including recent exposure to antibiotics (particularly beta-lactams or fluoroquinolones) within 90 days, or known colonization with ESBL-producing strains, antimicrobial agents that are effective against ESBLs may be warranted [8, 9].

By contrast, the spectrum of microorganisms involved in HA infections is significantly broader. In the past 20 years, the incidence of HA caused by drug-resistant microorganisms has risen dramatically, probably in correlation with escalating levels of antibiotic exposure and increasing frequency of patients with one or more predisposing conditions [10].

For patients with HA-cIAI, antimicrobial regimens with broader spectra of activity are preferable, as those patients have a higher risk of infections due to resistant bacteria [11]. Microbiological cultures from peritoneal fluid should be always performed in these patients.

16.2 Community-Acquired and Hospital-Acquired c-IAI

For mild-to-moderate CA-cIAI, drugs with substantial anti-*Pseudomonal* or *Enterococcal* activity, aminoglycosides, and antifungal agents may not be necessary and other regimens are usually preferred [6]. Molecules such as moxifloxacin, cefoxitin, ertapenem, or tigecycline can be considered. Alternatives are represented by combinations of cefazolin, cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin with metronidazole (Table 16.2). Due to an increase in resistance to

ampicillin/sulbactam, clindamycin, and cefotetan, the use of these molecules should be carefully evaluated for use in cIAI, especially in areas in which Enterobacteriaceae and *Bacteroides fragilis* show increased resistance levels to these antimicrobials [6].

CA-cIAI are considered severe when they occur in patients with high APACHE II score, advanced age, multiple comorbidities, malignancies, low albumin level and poor nutritional status, diffuse peritonitis, and inability to achieve and adequate source control [6]. These infections usually require the use of broad-spectrum antimicrobials that are active against Gram-negative bacteria, including carbapenems (e.g., meropenem, imipenem-cilastatin, doripenem), piperacillin-tazobactam, tigecycline or other molecules in combination with metronidazole (e.g., ceftazidime, cefepime, ceftolozane/tazobactam). Although the use of ciprofloxacin or levofloxacin in association with metronidazole is frequently used, the presence of high resistance rates to fluoroquinolones should be considered and their use appears limited when resistance rates above 10% are documented. In these infections, the empiric coverage of Gram-positive bacteria, such as streptococci or enterococci, is usually recommended [6].

In severe cIAI, a prompt adjustment of the regimen based on the results of microbiological culture is key to ensure a correct targeted therapy and to avoid the overuse of antimicrobials.

An ineffective or otherwise inadequate antimicrobial regimen is one of the variables more strongly associated with unfavourable outcomes, especially in critical ill patients [12]. Empiric antimicrobial therapy should be therefore started as soon as possible in patients with organ dysfunction and septic shock [13, 14]. Surviving Sepsis Campaign guidelines recommend intravenous antibiotics within the first hour, use of broad-spectrum agents with good penetration into the presumed site of infection, and reassessment of the antimicrobial regimen daily to optimize efficacy, prevent resistance and avoid toxicity [15].

As previously mentioned, empiric antimicrobial therapy for HA-cIAI should be based on local microbiologic resistance trends. Overall, combination regimens including an aminoglycoside (e.g. gentamicin, amikacin) or antimicrobials with extended spectrum of activity against Gram-negative bacteria (e.g., carbapenems, piperacillin-tazobactam, ceftazidime, ceftazidime/avibactam, cefepime or ceftolozane/tazobactam in combination with metronidazole) may be needed. In areas where infections due to extended spectrum beta-lactamases (ESBL)- or carbapenemase-producing bacteria are common, combination treatment and molecules such as tigecycline, ceftolozane-tazobactam, ceftazidime-avibactam, or colistin may be required [6].

Antifungal therapy for patients with severe infection is recommended if *Candida* is grown from intra-abdominal cultures or for patients with repeated surgical interventions [6].

Fluconazole is preferred for the treatment of susceptible *Candida albicans* infections, while echinocandins (e.g., anidulafungin, caspofungin, micafungin) are recommended for fluconazole-resistant *Candida* species and critically ill patients [16].

Empiric anti-enterococcal therapy (e.g., ampicillin, piperacillin- tazobactam, and vancomycin) is used in patients with postoperative infection and those who were previously treated with cephalosporins that may select for *Enterococcus* species, immunocompromised patients, and patients with valvular heart disease or

prosthetic intravascular materials [6]. *Enterococcus faecium* infections should be suspected among high-risk patients for these infections, including liver transplant recipient, biliary infections, or colonized patients. Patients colonized with methicillin-resistant *Staphylococcus aureus*, should receive appropriate antimicrobial therapy directed against MRSA, including vancomycin, tigecycline, daptomicin, or linezolid [6].

16.3 Dosage, Step-Down, and Therapy Duration

A correct antimicrobial dosing regimen should be established depending on host factors and properties of antimicrobial agents. The achievement of appropriate target site concentrations of antimicrobials is essential to eradicate the pathogen. Suboptimal target site concentrations may have important clinical implications, and may explain therapeutic failures [8].

Knowledge of the pharmacokinetics (PK) and pharmacodynamics (PD) antimicrobial properties of each antibiotic including (inhibition of growth, rate and extent of bactericidal action, and post-antibiotic effect) may provide a more rational determination of optimal dosing regimens in terms of the dose and the dosing interval. Optimal use of the PK/PD relationship of anti-infective agents is important for obtaining good clinical outcomes and reduction of resistance especially in critically ill patients [8].

Antimicrobial therapy should be always adjusted in presence of microbiological susceptibility tests. Step-down therapy, in particular, includes the targeted use of molecules and the switch to oral therapy, and should always be considered in cIAI in order to optimize the treatment and avoid the unnecessary use of antibiotics. Oral antimicrobials can substitute IV agents as soon as the patient is tolerating an oral diet [6, 8].

Therapy duration for cIAI, however, remains debated. Traditionally, patients are treated until sign, symptoms, and laboratory alterations indicating an infection resolve (usually between 7 and 14 days of treatment). A shorter course of antimicrobials, between 4 and 7 days, has been recently suggested and is recommended once that adequate source control is reached and depending on the clinical response [17].

A randomized study encompassing 517 patients comparing two strategies to guide the duration of antimicrobial therapy, fixed-duration of 4 days after source control and administration of antibiotics until 2 days after the resolution of fever, leukocytosis, and ileus (with a maximum of 10 days of therapy) showed no significant differences in outcomes between groups [18].

Duration of therapy should therefore be shortened as much as possible unless there are circumstances that require prolonging antimicrobial therapy such as ongoing infections.

Patients who have signs of sepsis beyond 5–7 days of treatment warrant aggressive diagnostic investigation to determine if an ongoing uncontrolled source of infection or antimicrobial treatment failure is present [6, 8].

Conclusions

Rational use of antimicrobials is an integral part of good clinical practice. It can maximize the utility and therapeutic efficacy of treatment, and minimize the risks associated with emerging infections and the selection of resistant pathogens. The problem of antimicrobial resistance is widespread; clinicians should be aware of their role and responsibility for maintaining the effectiveness of current and future antimicrobials. It is very important that clinicians prescribe antimicrobials when they are truly needed, and that the right antimicrobial is chosen to treat the illness [8]. Despite strenuous efforts to control antimicrobial drug use and promote optimal prescribing, clinicians continue to prescribe excessively [19]. The main objectives of antibiotics in the treatment of cIAI are to prevent local and haematogenous spread. Initial antibiotic therapy for patients with cIAI is usually empiric in nature because, especially in critically ill patients, microbiological data (culture and susceptibility results) usually requires ≥24 h to be completed. Obtaining microbiological cultures from peritoneal fluid allows both to expand antimicrobial regimen if the initial choice is too narrow or to perform a de-escalation is the empirical regimen is too broad [8]. The algorithm for the empirical antibiotic management of cIAI depends on the presumed pathogens involved, the risk factors for reduced antimicrobial susceptibility, and patients' clinical condition. The timing, regimen, dosage, route of administration and duration of antimicrobial therapy should be always optimized to avoid treatment failures and resistance selection.

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Antimicrobial Armamentarium

17

Sean M. Stainton and David P. Nicolau

17.1 Introduction

Peritonitis comprises a varied group of infections sharing a common anatomical location between the diaphragm and the pelvis. Infections of this type are, in fact, most often the cause of severe sepsis in the ICU and thus present a unique challenge to clinicians to provide targeted therapies as expediently as possible [1, 2].

When discussing the etiology of peritonitis, it is important to distinguish between primary, secondary, and tertiary infection. Primary peritonitis is defined by its lack of anatomical derangement and is often referred to as spontaneous bacterial peritonitis. Secondary peritonitis is an infection most often the result of perforation or penetrative injury, ischemic necrosis, and abscess formation [2, 3]. Tertiary infection is defined to be the result of a secondary infection that persists or reoccurs within 48 h of adequate treatment and source control by surgical means [3]. These are considered complicated intra-abdominal infections (cIAI) by definition [4].

Treatment of these infections reflects their heterogeneous nature and is driven by factors such as location and degree of localization, microbiological profile, and the presence of pathology due to structural abnormalities [2]. Particularly in the case of tertiary peritonitis, lack of clinical response dictates that treatment will require the tailoring of therapy to bacteria likely seen in resistant nosocomial infections (e.g., *Pseudomonas* or *Enterococcus*), as well as local resistance patterns. Additionally,

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effective source control in concert with optimal antibiotic selection is paramount to good clinical outcomes [5]. Multidrug resistance has been observed in the context of tertiary peritonitis thus highlighting the need for an ever-widening antibiotic armament [3].

17.2 Resistance

The landscape of bacterial resistance is ever changing. With the ease of international travel, the presence of bacterial mobile genetic resistance units, and positive evolutionary pressure attributed to overprescription, the speed of evolution and propagation only increases. In fact, the prevalence of multidrug-resistant (MDR) Enterobacteriaceae has nearly doubled in hospitals in the USA from 2006 to 2012 [6]. Coupling these factors with the reality that a number of treatment options are presently losing efficacy in the clinical setting, practitioners are faced with new and difficult challenges when treating IAIs [7–9].

The Study for Monitoring Antimicrobial Resistance Trends (SMART) is an ongoing surveillance program to monitor resistance patterns. In a study conducted from 2012 to 2013, 1285 isolates were obtained and characterized from hospital-acquired intra-abdominal infections (HA-IAI). Isolates were collected from 21 geographically diverse locations (12 different states) throughout the United States [10].

Enterobacteriaceae isolates comprised 80.8% of the overall samples ($n = 1038$). Of those, 83 were found to be multidrug resistant. ESBL-producing *E. coli* found to be 97.4% susceptible to ertapenem and imipenem and 99.8% to amikacin. Piperacillin/tazobactam showed 94.9% susceptibility. Resistance was observed to fluoroquinolones (82.1% of isolates were susceptible to ciprofloxacin and levofloxacin). Cephalosporin susceptibility for ESBL-producing *E. coli* ranged from 66.7 to 84.6%.

ESBL *K. pneumoniae* were less susceptible compared to ESBL *E. coli* (carbapenems (60–65%), amikacin (62.5%), and fluoroquinolones (10–12.5%), cephalosporins (12.5–35%), and piperacillin/tazobactam (22.5%)). This trend is thought be explained by the prevalence of SHV, CTX-M, or AmpC β-lactamases. Additionally, the increasing incidence of *K. pneumoniae* carbapenemases also may play a role [11, 12].

New Delhi metallo-β-lactamases (NDM) also pose a significant threat to global health and only further highlight the need for increased fortification of the current antimicrobial armament. This pernicious enzyme, capable of hydrolyzing nearly all β-lactam drugs, continues to spread globally, and treatment options are limited. NDMs are typically found to possess co-resistance to fluoroquinolones, tetracycline derivatives, and aminoglycosides. Twelve NDM enzyme variants often found on mobile genetic elements have been identified worldwide to date [13, 14].

The SMART study conducted surveillance of metallo-β-lactamases from 2008 to 2012. Of the 8604 isolates collected globally, 135 were identified as NDM (134 Enterobacteriaceae and 1 *Acinetobacter*). Eighty-nine of the NDM isolates originated from IAIs (the others from urinary tract infections). Countries of origin were India, Serbia, Vietnam, the Philippines, Saudi Arabia, Egypt, Georgia, Guatemala, and the USA [15].

Moreover, a high degree of resistance to nearly all available agents was observed. MIC_{90} values were found to be 4 and 8 mg/L for ertapenem and imipenem, respectively. The NDMs exhibited resistance to all β-lactam/β-lactamase inhibitor combinations in addition to resistance to amikacin (79.9%) and levofloxacin (82.8%). Many also encoded for AmpC resistance genes and ESBLs as well.

Indeed, all of these findings underscore the need for judicious use of currently available treatment options and a continued push toward the discovery of new agents. In this era of ever-increasing resistance, the effect on global health and safety may be catastrophic if optimization of treatment cannot be achieved. An ever-renewed commitment to stewardship in addition to developmental innovation is vital in combating this trend.

17.3 Treatment

Treatment algorithms provided by the Infectious Diseases Society of America (IDSA) for IAI are guided by source acquisition (i.e., hospital vs. community-acquired) and the severity of infection. IDSA recommends treatment with a single agent for community-acquired infection with either ticarcillin/clavulanic acid, cefoxitin, ertapenem, moxifloxacin, or tigecycline. These agents are chosen for their broad coverage of those species most commonly associated with community-acquired infections, i.e., enteric gram-negative aerobic, facultative bacilli, and enteric gram-positive streptococci. Combination therapy may include metronidazole plus either ceftazidime, cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin [4].

Healthcare-associated infections carry with them inherently greater risk of morbidity and mortality due to the increased prevalence of resistant organisms. Empiric treatment should be guided by local resistance trends and the presence of risk factors which predispose patients to infection with more virulent bacterial strains. For example, providers may consider empiric anti-enterococcal therapy especially in cases of postoperative infection, immunocompromised patients, those who have previously received cephalosporins, valvular heart disease, or the presence of a prosthetic valve [4].

Those patients deemed high risk according to IDSA meet the following criteria: advanced age, comorbidity and degree of organ dysfunction, delay in initial intervention >24 h, inability to achieve adequate debridement or control of drainage, APACHE score ≥15, low albumin, poor nutritional status, malignancy, degree of peritoneal involvement, or diffuse peritonitis. In these cases, meropenem, imipenem-cilastatin, doripenem, or piperacillin/tazobactam is recommended. Combination therapy for high-risk patients includes metronidazole and ciprofloxacin, levofloxacin, ceftazidime, or cefepime [4].

Within the context of high-risk infection, optimization of antibiotic selection is critical for both survival as well as minimization of creation and spread of resistance. This is particularly true as increasing rates of carbapenem-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* have been observed with the overuse of carbapenems [16, 17].

A recent meta-analysis and systematic review conducted by Mikamo, Yuasa, Wada, and colleagues compared the efficacy and safety of combination therapy metronidazole vs. carbapenems in IAI [18]. The analysis identified eight randomized control clinical trials whose primary endpoints were clinical success, drug-related adverse events, and all-cause mortality.

Combination therapy was found to be statistically equivalent to monotherapy with carbapenem. Odds ratios for endpoints were reported as follows: clinical success ([OR] 1.31; 95% confidence interval [CI] 0.37–1.00), all-cause mortality ([OR] 0.61; 95% confidence interval [CI] 0.37–1.00), drug-related adverse events ([OR] 0.58; 95% confidence interval [CI] 0.18–0.81), and bacterial eradication ([OR] 1.27; 95% confidence interval [CI] 0.84–1.91). These data would therefore suggest that combination therapy with metronidazole is not only equivalent to carbapenem but also offers an alternative which may limit the spread of carbapenem resistance.

Obesity is not specifically addressed in treatment guidelines as an independent risk factor for treatment failure. However, concern exists among clinicians regarding response to treatment within this population, as pharmacokinetic and pharmacodynamic parameters of many antibiotics are known to be altered in obese patients. Unfortunately, there is a dearth of studies designed to address this specific need [19, 20]. In this respect, IAI is not unique. Little is known about clinical response to therapy for obese patients with IAI as compared to a non-obese patient population.

The Study to Optimize Peritoneal Infection Therapy (STOP-IT), conducted by the Surgical Infection Society, was an open label multicenter trial randomized 518 patients stratified by body mass index [21]. Those patients with a BMI $\geq$ 30 were defined to be obese. The trial was designed to identify optimal duration of antimicrobial therapy in patients after source control was achieved in those defined to have complicated intra-abdominal infection (cIAI). Patients were included who met the following criteria: those >16 years of age, fever, peripheral white blood cell count >11,000 ml^{-1}, had undergone percutaneous or surgical intervention, and infection precluding the intake of more than half their normal diet. Those patients with non-infectious peritonitis were excluded. Main endpoints in 4-day treatment with antibiotics and clinical resolution were measured for both groups. Additional endpoints of interest included incidence of recurrent intra-abdominal infection, composite of all complications, and death.

Those with BMI $\geq$ 30 comprised 38.3% ($n = 198$) vs. 61.7% non-obese ($n = 319$). Both endpoints, 4-day treatment and clinical resolution, were found to be similar between obese and non-obese (25% vs. 18.7% ($p = 0.19$)) and 25% vs. 20.7% ($p = 0.42$)), respectively. Rates of recurrent infection, composite of all complications, and death for obese patients vs. non-obese were as follows: 16.2% vs. 13.8% ($p = 0.46$), 25.3% vs. 19.8% ($p = 0.14$), and 1% vs. 0.9% ($p = 1.0$). These data indicate no statistically significant difference between groups. It would seem that despite altered PK and PD parameters, clinically, tailoring therapies using weight-based dosing in obese patients with cIAI are not necessary provided adequate source control is achieved.

With respect to European IAI guidelines, many similarities exist when comparing to IDSA. Algorithms are similarly dictated by source acquisition and degree of organ involvement. The importance of source control is emphasized, and empiric coverage should be tailored to a patient risk profile (presence of risk factors for infection with resistant organisms, infection with fungal species, etc.) [22, 23].

Guidelines provided by the Société Française d'Anesthésie et de Réanimation outline a slightly different treatment regimen for IAI [23]. For example, first-line agents for community-acquired IAI differ from those employed in the USA. These include cefotaxime or ceftriaxone plus metronidazole or amoxicillin/clavulanic acid plus gentamicin. Healthcare-associated infection is treated empirically with piperacillin/tazobactam (amikacin may be added if the infection is considered severe), provided that risk factors for infection with MDR organisms are absent. A patient is considered high risk for infection with a multidrug-resistant organism if any of the following two risk factors are present: isolation of an ESBL-producing Enterobacteriaceae or ceftazidime-resistant *P. aeruginosa*, from any source isolated within the previous 3 months; patient living in a nursing facility or long-term care with an indwelling catheter or gastrostomy; failure of broad-spectrum antibiotic therapy with third-generation cephalosporin, fluoroquinolone, or piperacillin/tazobactam; previous antibiotic therapy (third-generation cephalosporin or fluoroquinolone) within the previous 3 months; hospitalization in a foreign country within the previous 12 months; and early recurrence (<2 weeks for an infection treated by piperacillin/tazobactam for at least 3 days). Notably, only one such risk factor is required for placement in this category if sepsis is present. In such cases, the guidelines recommend treatment with a carbapenem plus amikacin (if severe). Empiric coverage for *Enterococcus* is advocated in cases of liver transplant, hepatobiliary disease, or ongoing antibiotic therapy.

Treatment of cIAI in Asia requires special considerations specific to this region. As outlined in the previous section, bacterial resistance is at its highest in Asia as compared to any other global region. Particularly, resistance among Enterobacteriaceae is of key concern [24]. It is believed that ESBL producers evolved de novo and were first observed in China, South Korea, Japan, and India [25]. Importantly, clinicians should be aware of some tropical infectious diseases which can produce abdominal sepsis which are endemic to this region (e.g., amebiasis, abdominal tuberculosis, ascariasis, and salmonellosis). When determining a differential diagnosis, malaria and dengue hemorrhagic fever may present similarly to cIAI [24].

According to recommendations put forth by the Asian Consensus Taskforce on Complicated Intra-Abdominal Infections, amoxicillin/clavulanic acid is the first choice agent for community-acquired IAI. Combination therapy with a cephalosporin plus metronidazole may also be used. Healthcare-associated infections are to be treated with either a carbapenem or piperacillin/tazobactam. Combination therapy for severe infections includes cefepime/levofloxacin plus metronidazole, meropenem plus vancomycin or, tigecycline plus aztreonam/ciprofloxacin [24]. Unfortunately, lack of access to medication can play a role in the choice of treatment options in this context.

17.4 New Agents

17.4.1 Ceftolozane/Tazobactam

Ceftolozane/tazobactam is a novel cephalosporin combination with the most potent anti-pseudomonal activity of any available cephalosporin. As with all β-lactams, ceftolozane exerts its effect through the binding and inhibition of penicillin-binding proteins, which, in turn, inhibit cell wall synthesis. Tazobactam is a well-known β-lactam inhibitor, most often combined with piperacillin. The combination of ceftolozane/tazobactam shows good effect against ESBL-producing Enterobacteriaceae [26, 27]. Ceftolozane/tazobactam is currently approved for the treatment of urinary tract infections and complicated intra-abdominal infections when combined with metronidazole [28].

In a recent surveillance study conducted by our group, isolates collected from 44 hospitals were used to characterize MIC values for ceftolozane/tazobactam in addition to 11 other agents [29]. A total of 3759 non-duplicate, non-urine Enterobacteriaceae and *Pseudomonas* were collected from following sources (% of isolates): blood 43%/14%, respiratory tract 18%/39%, wound 18%/30%, bodily fluid 11%/5%, and other 10%/12%.

For Enterobacteriaceae and *Pseudomonas*, susceptibilities were reported as follows: colistin (96–98%), meropenem (93–99%), imipenem (92–98%), ertapenem (91–98%), and ceftolozane/tazobactam (89–98%). The majority of MICs for *E. coli* and *Klebsiella* for all tested agents fell 1–2 dilutions below the breakpoint. Among Enterobacteriaceae collected, 442/2511 (18%) were confirmed to be ESBL-producing. Within this subgroup, ranked susceptibilities were reported as follows: ceftolozane/tazobactam 82%, piperacillin/tazobactam 67%, tobramycin 42%, ciprofloxacin 13%, cefepime 9%, aztreonam 7%, and ceftriaxone 2%.

Ceftolozane/tazobactam showed the greatest susceptibility and potency for *Pseudomonas aeruginosa*. Susceptibility and MIC_{90} were 97% and 2 mg/L, respectively. Multidrug-resistant *Pseudomonas* strains comprised 122 (10%) of the population. Within this subgroup susceptibilities and MIC_{90} were as follows: colistin 96% (MIC_{90} = 2 mg/L), ceftolozane/tazobactam 77% (MIC_{90} = 64 mg/L), tobramycin 47% (MIC_{90} = 128 mg/L), aztreonam 17% (MIC_{90} = 128 mg/L), imipenem 14% (MIC_{90} = 32 mg/L), meropenem 14% (MIC_{90} = 64 mg/L), ciprofloxacin 12% (MIC90 = 32 mg/L), cefepime 10 (MIC_{90} = 128 mg/L), ceftazidime 7% (MIC_{90} = 128 mg/L), and piperacillin/tazobactam 5% (MIC_{90} = 512 mg/L). Our study confirms ceftolozane/tazobactam potency and susceptibility remains favorable, particularly in the case of *Pseudomonas* and ESBL producers.

The ASPECT-cIAI trial was a multicenter, prospective, double-blind, randomized, placebo-controlled phase 3 clinical trial conducted by Solomkin et al. investigating clinical outcomes for hospitalized patients with cIAI treated with either ceftolozane/tazobactam plus metronidazole or meropenem [30]. Patients were included if they were >18 years of age and percutaneous or operative drainage was either planned or had been recently performed, thus confirming infection. Patients with creatinine clearance <30 ml/min, those with low likelihood of adequate source

control with surgery, abdominal repair in which fascia was not closed, and those who recieved systemic antibiotic therapy for IAI for >24h prior to first dose of study drug were excluded. Evaluation occurred at end of therapy (within 24 h of therapy), test of cure (TOC) (measured 24–32 days after start of therapy), and late follow-up visit (38–45 days after start of therapy). Primary endpoints were clinical cure and failure. Clinical cure was defined to be the complete resolution of symptoms or significant improvement from the infection in question such that no further interventions were required. Persistent or recurrent infection, death due to cIAI prior to test-of-cure visit, treatment for ongoing symptoms of infection, and surgical intervention all defined clinical failure.

A total of 993 patients were enrolled, and 806 met criteria for the modified-intent-to-treat population and randomized to either ceftolozane/tazobactam or meropenem. Roughly half of this population received treatment for 7 days. The remaining 36.5% received 10 days of therapy. Pathogen distribution and incidence was similar between groups at baseline. Most infections were determined to be polymicrobial; 66.1% (257/389) and 69.1% (288/417) in the ceftolozane/tazobactam and meropenem groups, respectively. The overall incidence of ESBL Enterobacteriaceae was 7.2% (58/806). Multidrug-resistant *Pseudomonas* comprised 5.8% (3/52), while 11.5% (6/52) were non-susceptible to ≥3 anti-pseudomonal drug classes.

Clinical cure rates were 83.0% (323/389) and 87.3% (364/417) for ceftolozane/tazobactam and meropenem, respectively, in the MITT population. The weighted difference between groups met criteria for non-inferiority (−4.2%, 95% confidence interval −8.91% to 0.54%). Within the MITT population for both groups, 8.2% failed treatment according to assessment conducted at TOC. With respect to cases of ESBL Enterobacteriaceae, cure rates were 95.8% (23/24) and 88.5% (23/26) for ceftolozane/tazobactam and meropenem, respectively. Among the 26 patients receiving ceftolozane/tazobactam infected with *Pseudomonas*, all met criteria for clinical cure, while 27/29 (93.1%) were considered cured in the meropenem group. The occurrence of adverse events was similar between groups (44% vs. 47%, ceftolozane/tazobactam and meropenem), and most were mild to moderate in severity. The most frequently occurring events were nausea, diarrhea, and vomiting.

These studies suggest that ceftolozane/tazobactam is a potent agent for resistant infections and particularly in the case of *Pseudomonas* infection. It will undoubtedly play a role in combating gram-negative infections in the hospital setting and play an important role in the treatment of cIAI. While resistance to ceftolozane/tazobactam has been difficult to develop in vitro, the judicious use of this agent must be advocated to preserve its utility [31].

17.4.2 Ceftazidime/Avibactam

Avibactam is a novel diazabicyclooctane β-lactamase inhibitor. This inhibitor differs from other commercially available agents in structural characteristics, spectrum, and mechanism, as it reversibly acetylates the active site of the β-lactamase [32].

In addition to ESBL and AmpC inactivation, KPC and OXA-48 inhibition is also observed with avibactam. It is, however, inactive for those strains which lack an active-site serine residue (i.e., NDM, VIM, or IMP). As a result of its potency, when combined with ceftazidime, avibactam greatly reduces MICs for Enterobacteriaceae possessing a variety of enzyme-mediated resistance profiles when compared to ceftazidime alone [33, 34].

Ceftazidime/avibactam is currently FDA approved for cIAI infections in combination with metronidazole for infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Klebsiella oxytoca*, *Providencia stuartii*, *Proteus mirabilis*, and *Enterobacter cloacae* in patients 18 years or older. It is also approved for the treatment of complicated UTI including pyelonephritis [35].

Mazuski et al. conducted a randomized, controlled, double-blind phase 3 study assessing the efficacy of ceftazidime/avibactam plus metronidazole vs. meropenem for the treatment of complicated intra-abdominal infections [36]. A microbiologically modified intent to treat (mMITT) design was employed. Patients were included if they were between the ages of 18–90 years and required surgical intervention or percutaneous intervention within 24 h before or after randomization with a diagnosis of cIAI. Patients were excluded if they had a traumatic bowel perforation requiring surgical intervention within 12 h, abdominal abscess, bowel obstruction, and gastroduodenal ulcers requiring surgery within 24 h, ischemic bowel without perforation, simple cholecystitis, simple appendicitis, infected necrotizing pancreatitis, suppurative cholangitis, or pancreatic abscess. Ultimately, 1066 patients were randomized. Primary endpoint for this study was clinical test of cure defined to be 28–35 days after randomization assessed by non-inferiority of combination ceftazidime/avibactam as compared to meropenem. Importantly, ESBL-producing organisms comprised approximately 80% of the ceftazidime-resistant isolates while 3% were positive for metallo-β-lactamase production.

Criteria for non-inferiority (margin less than −12.5%) comparing ceftazidime/avibactam vs. meropenem were met across all primary analysis populations. The clinical cure rate for combination therapy against ceftazidime-resistant gram-negative bacteria as compared to meropenem was 83 and 85.9%, respectively. Relative to ceftazidime susceptible isolates, efficacy was seen in 82% of cases as compared to 87.7% in the meropenem group. Between both the modified-intent-to-treat and the microbiologically modified-intent-to-treat groups, a clinical difference was observed among those patients with impaired renal function at baseline favoring meropenem treatment. The between-group difference for the mMITT population was −29.1%; 95% CI −50.05 to −5.36) and for MITT group −25.6%; −44.53 to −4.78). Ceftazidime/avibactam offers an attractive alternative to carbapenems in the context of cIAI, and its use may thus limit the spread of carbapenemase resistance.

In addition to the agents discussed previously, many new β-lactam/β-lactamase inhibitor combinations are currently in various stages of development. A listing of promising agents is provided in Table 17.1 [28, 35–42].

Table 17.1 Selected antimicrobial agents in development for treatment of IAI and cIAI

Drug product	Company	Stage of development
Ceftolozane/tazobactam	Merck	*FDA-approved indications*: Complicated urinary tract infections (cUTI) and pyelonephritis cIAI in combination with metronidazole
Ceftazidime/avibactam	Allergan and Pfizer	*FDA-approved indications*: cUTI and pyelonephritis cIAI in combination with metronidazole VAP and HAP *Ongoing clinical trials*: Safety and tolerability of ceftazidime-avibactam for pediatric patients with suspected or confirmed infections (phase 1)
Aztreonam/avibactam	Allergan/Pfizer	*Ongoing clinical trials*: Determine the PK and safety and tolerability of ATM-AVI for the treatment of cIAIs in hospitalized adults
Imipenem-cilastatin/relebactam	Merck	*Completed trials*: Phase 2, dose-ranging study of relebactam with imipenem/cilastatin in subjects with complicated intra-abdominal infection *Ongoing clinical trials*: Efficacy and safety of imipenem + cilastatin/relebactam (MK-7655A) versus colistimethate sodium + imipenem + cilastatin in imipenem-resistant bacterial infection (MK-7655A-013) (RESTORE-IMI 1)
Meropenem/vaborbactam	The Medicines Company	*Completed trials*: TANGO phase 3 clinical trials completed for cUTI and serious bacterial infections due to confirmed or suspected Carbapenem-resistant Enterobacteriaceae (CRE) *Ongoing clinical trials*: Efficacy, safety, and tolerability of Carbavance compared to best available therapy in serious infections due to carbapenem-resistant *Enterobacteriaceae*, in adults
Cefepime/zidebactam	Wockhardt	*Completed trials*: A randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and pharmacokinetics of multiple escalating doses of intravenous WCK 5222 (Zidebactam and Cefepime) in healthy adult human subjects
S-649266 Cefiderocol (S-649266)	Shionogi	*Ongoing clinical trials*: Study of S-649266 or best available therapy for the treatment of severe infections caused by carbapenem-resistant gram-negative pathogens (phase 3)

(continued)

Table 17.1 (continued)

Drug product	Company	Stage of development
Eravacycline	Tetraphase	*Completed trials*: Phase 2, randomized, double-blind study of the efficacy and safety of two dose regimens of eravacycline versus ertapenem for adult community-acquired complicated intra-abdominal infections *Ongoing clinical trials*: Efficacy and safety study of eravacycline compared with Ertapenem in complicated intra-abdominal infections (IGNITE1) (phase 3)
Plazomicin	Achaogen	Ongoing clinical trials: The CARE (Combating Antibiotic-Resistant *Enterobacteriaceae*) trial (phase 3)

17.4.3 Cefiderocol

Cefiderocol is a siderophore cephalosporin which exerts its activity though chelation with ferric iron and uptake by the bacterial iron uptake system allowing the drug access within the periplasmic space. The so-called "trojan horse effect" is facilitated by the catechol moiety located at position 3 of the side chain. Once taken up, this leads to disruption in the synthesis of the cell wall [43].

Recent *in vitro* studies with S-649266 have shown promising results in the face of resistance to other commonly utilized therapies. The agent was tested against clinical isolates of Enterobacteriaceae collected from seven different regions worldwide inclusive of KPC, NDM, IMP, and VIM producers. In total, 617 different isolates were screened from 2009 to 2011 [44].

S-649266 showed significant activity against β-lactamase-producing strains. MIC values for all KPC-producing strains ranged from ≤0.125 to 4 mg/L. Additionally, among the 69 carbapenem-producing strains, 62 were found to have MIC values ≤4 mg/L including those strains expressing VIM, IMP, and NDM enzymes. MIC values for the 92 ESBL producers were ≤4 mg/L (three of those strains tested were found to have MIC to meropenem ≥16 μg/ml). S-649266 also showed significant activity against OXA-type D class enzymes. Of the 12 isolates identified (other than OXA-48-producing strains), values ranged from ≤0.125 to 2 mg/L. By contrast, cefepime demonstrated MICs to those same isolates ranging from 1 to >16 mg/L. Among those 233 strains found to be resistant, only seven had MIC values for S-649266 which were ≥16 mg/L.

In a study conducted by our group, a neutropenic murine thigh infection model was employed to characterize the exposure-effect profile of S-649266 against eight MDR *P. aeruginosa* isolates [45]. MIC values for S-649266 ranged from 0.063 to 0.5 mg/L. S-649266 was administered at total daily doses of 12.5, 25, 50, 100, 200, 300, 400, and 500 mg/kg given every 8 h.

Results at the 24-h endpoint showed growth of 3.4 log in the untreated controls and a corresponding decrease of 3.1 log in treated animals. A CFU reduction >1 log,

the measure of sufficient in vivo activity, was observed for all isolates at doses ≥100 mg/kg/day. The dose-response curve was sigmoidal, and the effect of increasing dose resulted in increased effect for all isolates tested up to a maximum threshold. Results from this study and others show promise for S-649266 in the treatment of MDR bacterial infections, and it is reasonable to anticipate broader application of this potent agent in the context of cIAI.

17.4.4 Eravacycline

Eravacycline is a novel fluorocycline, representing the first agent in this class. As with previous tetracyclines, the drug works through inhibition of the bacterial ribosome. As a class, tetracyclines have classically been categorized as bacteriostatic, although new evidence suggests eravacycline may be bactericidal [46]. This molecule retains the previous tetracycline structure. Chemical additions of a fluorine atom and pyrrolidinoacetamido group were added at C7 and C9, respectively [47]. These alterations confer protection against the inactivity of the drug by resistance mechanisms, e.g., ribosome hydrolysis and efflux pumps. This leads therefore to increased activity observed against vancomycin-resistant *Enterococcus* (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) [48]. It is also a potent agent against MDR gram-negatives including Enterobacteriaceae expressing various classes of β-lactamases, multidrug-resistant *Acinetobacter baumannii*, and carbapenem resistance mechanisms [49].

A recent study conducted by our group was designed to assess the killing profile of eravacycline on both gram-positive and gram-negative strains in an immunocompetent murine thigh model over a period of 72 h [46]. The study examined the effect of a humanized dose (2.5 mg/kg iv q 12 h) on three Enterobacteriaceae strains *E. coli* 373, *C. freundii* 26, and *E. coli C3–14* (eravacycline MIC's = 0.125–0.25 mg/L). Comparator antibiotic agents included linezolid, tigecycline, meropenem, and vancomycin.

Log reductions in CFU at 72 h were 2.96, 1.81, and 1.31 for *E. coli* 373, *C. freundii*, and *E. coli C3–14*, respectively. Comparators did show antibacterial activity against all three isolates with the exception of meropenem against *E. coli* C3–14. At 48 and 72 h, meropenem and tigecycline showed a greater reduction in log10 CFU than eravacycline ($p < 0.003$ for all). Although these initial data are promising, more studies are needed for further characterization of pharmacodynamic profile of this agent.

Currently a phase 3 multicenter, double-blind clinical trial known as the IGNITE 1 trial is underway and has been designed to evaluate the safety and efficacy of eravacycline as compared to ertapenem for the treatment of cIAI [41]. A total of 541 patients have been enrolled at 66 centers worldwide. Data from the preceding phase II trial among patients with community-acquired cIAI only has shown similar rates of clinical success between ertapenem and eravacycline [42]. As this agent moves further down the pipeline, investigators remain hopeful that it will serve a critical function in future therapy, offering an alternative for the treatment of MDR gram-negative pathogens in cIAI.

17.4.5 Plazomicin

Plazomicin is a novel antibiotic which was developed by means of modifying an existing aminoglycoside, sisomicin. With the addition of an amino group in the gentamicin ring and unsaturated hydroxyethyl tail, the resulting compound provides no substrate for the aminoglycoside-modifying enzymes known to be present in carbapenemase and ESBL producers and thus enhances its activity and potency [50]. *In vitro* data are promising and show plazomicin to be highly effective against a variety of MDR gram-negative and gram-positive organisms [51]. Currently, a phase 3 clinical trial CARE (Combating Antibiotic-Resistant Enterobacteriaceae) designed to treat patients with serious bacterial infections due to carbapenem-resistant Enterobacteriaceae is in progress [40].

Conclusions

Highly resistant bacterial infections pose an ever-present challenge for clinicians. Particularly, in an age of increased mobility on a global scale, the rate of spread of resistance only continues to increase. Multidrug-resistant gram-negative infections in the context of cIAI require potent and targeted therapies designed to combat the multitude of ways in which bacteria evade our attempts to eliminate them. So too, as the landscape of antibiotics continues to shift, and selective pressures drive new bacterial resistance mechanisms, continued emphasis must be placed on the development of novel agents.

In cases of MDR *Pseudomonas* or ESBL-producing Enterobacteriaceae, an agent like ceftolozane/tazobactam offers an alternative to carbapenems and thus limits the potential for the development and spread of carbapenemase-producing organisms. In the face of increasing carbapenemase-producing bacteria possessing KPC and OXA genotypes, ceftazidime/avibactam provides a much needed alternative to the potentially toxic polymyxin class of agents. As a result of this evolution of enzyme-mediated resistance in the cIAI pathogens, more β-lactam/β-lactamase inhibitor combinations are expected to be introduced. In addition to these β-lactam-derived regimens, agents possessing differing mechanisms of action like plazomicin and eravacycline are anticipated to have an important role in the management of resistant gram-negative pathogens. While new agents are under development to combat the increasing resistance to our current armamentarium, early surgical interventions which optimize source control, antimicrobial stewardship, and strong infection control programs will continue to be important components of the successful management strategy for cIAI.

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Antimicrobial Resistance in Intra-abdominal Infections

18

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18.1 Introduction

Optimal management of abdominal sepsis relies upon several factors, the most important being prompt resuscitation, timely and efficient source control, provision of intensive care and administration of appropriate effective antimicrobials [1–3]. Antimicrobial resistance is a globally expanding threat, jeopardizing the therapeutic approach in diverse clinical settings [4–6]. Clinicians face the crucial dilemma between the administration of inadequate antimicrobial therapy entailing the risk of high failure rates and the unjustified use of broad-spectrum antibiotics promoting further selection of resistant pathogens. Understanding the underlying mechanisms of resistance development and the overall toll from antibiotic misuse is essential in order to effectively use antibiotics in intra-abdominal infections while limiting hazardous overprescribing behaviors [1].

The worldwide spread of antimicrobial resistance has been clearly associated with a significant increase of morbidity, mortality, and healthcare expenditures. As a general principle, resistance occurs as a natural microbial evolution phenomenon; antibiotics accelerate this process though selection pressure exerted on intestinal microbiota. Horizontal transfer of individual resistant bacteria to adjacent patients adds a dreadful dissemination potential [7]. Increased AMR prevalence in the community is becoming a major public health issue; community occurring multidrug-resistant (MDR) strains can be transferred across borders by displaced, otherwise healthy populations in their destination countries [8, 9]. Moreover, travels for professional reasons and medical tourism are other potential sources of importation of alarming MDR phenotypes from distant geographic regions; the introduction of

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NDM-1-producing bacteria into the UK has been linked to medical tourism and elective surgery performed in India and Pakistan. Worldwide dissemination of such resistant strains is possible, and prompt coordinated international surveillance is needed [10, 11]. A very recent, more worrisome event is the reports of imported plasmid-mediated resistance to colistin, a last resort drug, frequently used for carbapenemase-producing strains [12].

18.2 Mechanisms of Antibiotic Resistance

Antimicrobial resistance can be intrinsically expressed by a given species via chromosomal genes or acquired through two distinct but not mutually exclusive genetic events; mutations on existing genes (vertical evolution) or horizontal transfer of mobile genetic elements (MGEs) acquired from other species or strains (horizontal gene transfer). Vertical evolution is the increased expression of intrinsic resistance mechanisms resulting in production of antibiotic-inactivating enzymes or efflux pumps, alteration of membrane permeability, or modification of antimicrobial targets. Horizontal gene transfer is mediated through mobile genetic elements such as plasmids or transposons which often carry multiple resistance determinants, enabling the recipient strain to express multidrug resistance phenotypes. Horizontal dissemination of the conjugating plasmids or transposons among different bacterial species is fueled by the selection pressure of antimicrobial overuse [7].

18.2.1 *Enterobacteriaceae*

18.2.1.1 β-Lactam Resistance

β-Lactam resistance in *Enterobacteriaceae* is mainly mediated through the production of β-lactamases, enzymes that hydrolyze β-lactams and therefore prevent penicillin-binding protein inhibition. β-Lactams are classified either according to protein homology (Ambler classification, schematically presented in Fig. 18.1) or functional characteristics (Bush-Jacoby-Medeiros classification) [6, 7, 13]. Some *Enterobacteriaceae* species (e.g., *Enterobacter* spp., *Citrobacter freundii*, *Morganella morganii*, *Serratia marcescens*, and *Providencia* spp.) may exhibit strong induction of chromosome-encoded AmpC cephalosporinases in the presence of amoxicillin, clavulanic acid, cefoxitin, and first-generation cephalosporins (1GC), thereby potentially expressing an AmpC hyperproducing phenotype with intrinsic resistance to penicillins, aztreonam, third-generation cephalosporins (3GC), and ertapenem. Although cefepime is a poor inducer and substrate for AmpC β-lactamases, its effectiveness is questioned in the presence of high bacterial inoculum, and its use should be avoided in critically ill patients with suboptimal source control [14, 15]. Carbapenems are not vulnerable to AmpC-mediated hydrolysis, representing an optimal treatment option for severe cases.

Plasmid-borne extended-spectrum β-lactamases (ESBL) and carbapenemases carry the most important clinical impact on resistance among *Enterobacteriaceae*. Genes

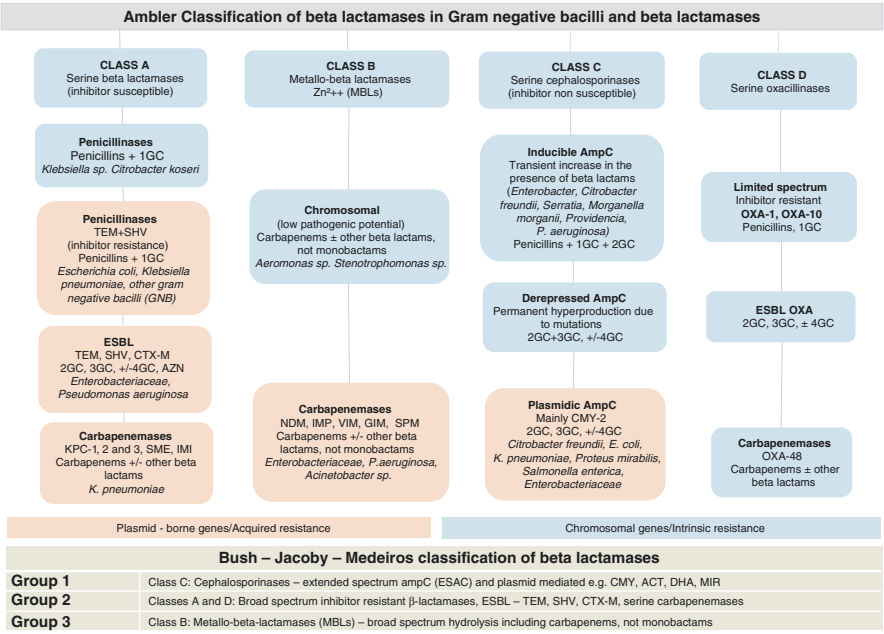

Fig. 18.1 Classification of beta-lactamases in Gram-negative bacilli according to two major systems [6, 7, 13]. *1GC* first-generation cephalosporins, *2GC* second-generation cephalosporins, *3GC* third-generation cephalosporins, *4GC* fourth-generation cephalosporins, *ESBL* extended-spectrum beta-lactamases

encoding for the majority of ESBL enzymes (TEM-, SHV-, and CTX-M) are located on plasmids that usually harbor additional resistance mechanisms to other agents such as aminoglycosides and fluoroquinolones. These enzymes (most frequent being CTX-M) are capable of inactivating most β-lactams including 3GC. Although carbapenems remain active, carbapenems-sparing schemes are narrowed by co-resistance to other agents described above [15, 16]. Recent literature on the use of β-lactam/β-lactam inhibitor combinations (BLBLI) in the treatment of infections caused by ESBL producers has been conflicting, depending on the infectious source, inoculum, and patient's clinical condition [17, 18]. Currently EUCAST has recommended and set a threshold for BLBLI use against ESBL-producing *Enterobacteriaceae*, that is, a MIC ≤ 8 mg/L (or ≤4 mg/L according to most recent publications) [19]. In critically ill septic, bacteremic patients with uncontrolled intra-abdominal septic foci, the inoculum effect should be taken into account; therefore, only patients with less serious infections originating from the urinary tract or well-controlled intra-abdominal foci (i.e., biliary tract) could be administered a high dose of BLBLI [17, 20]. Dissemination of ESBLs, within the community represents a challenging scenario in Southeast Asia and the eastern Mediterranean countries, with rates of intestinal carriage among otherwise healthy individuals reported to be as high as 60%. This community based reservoir provides a continuous inflow of resistant strains within hospital settings, hampering appropriateness of empirical therapy for community-acquired intra-abdominal infections [21].

Carbapenemases confer the largest spectrum of antibiotic resistance since they hydrolyze not only carbapenems but practically all β-lactams. *Klebsiella pneumoniae* carbapenemases (KPC) are the most important enzymes of class A serine carbapenemases [7, 16]. The initial reservoirs of KPC were *K. pneumoniae* in the USA, Israel, Greece, and Italy, those of NDM were *K. pneumoniae* and *E. coli* in the Indian subcontinent, and those of OXA-48 were *K. pneumoniae* and *E. coli* in North Africa and Turkey; notably, NDM and OXA-48 producers may present as either nosocomial- or community-acquired pathogens [22]. Their rapid worldwide dissemination has emerged as a global medical threat. Currently, among European countries, Greece, Italy, Montenegro, Spain, and Serbia reported the highest incidence rates of carbapenems non-susceptible *K. pneumoniae* and *E. coli* [23]. DNA fingerprinting analysis of carbapenemase-producing *Klebsiella pneumoniae* isolates, have elucidated as more prevalent the *K. pneumoniae* ST258 lineage producing the KPC-2 enzyme in most countries, whereas the ST512 lineage related to KPC-3 production predominates in Italy [23–25]. Increased use of colistin, which is frequently the only available treatment option in the aforementioned clinical scenarios, has led to the emergence of colistin-resistant KPC-producing strains [26]. Although initial reports were about chromosomal mechanisms of resistance, recent emergence and dissemination of plasmid-borne colistin resistance (discussed below in detail) represents one of the most alarming threats in infectious diseases [27, 28]. Class B carbapenemases are metallo-β-lactamases (MBLs) conferring resistance to all beta-lactams except monobactams. Chromosomally encoded MBLs are primarily found in *Aeromonas* and *Stenotrophomonas* spp., *P. aeruginosa*, and *A. baumannii*, and *Enterobacteriaceae* harbor MBLs transmitted by mobile gene elements (VIM, IMP, NDM, SPM, GIM), which are frequently co-transmitted with additional resistance genes inactivating aztreonam as well [7, 16]. Finally, class D oxacillinases (OXA-β-lactamases) possess a variable hydrolyzing spectrum of activity. Among them, OXA-23 and OXA-48 are able to inactivate carbapenems; dissemination of OXA-48 among *Enterobacteriaceae* is currently an important cause of resistance particularly in the Mediterranean [7, 16, 23, 29]. In a recent initiative directed by the European Centre for Disease Prevention and Control (ECDC), 455 sentinel European hospitals from 36 countries collected contemporary carbapenem-resistant *K. pneumoniae* and *E. coli* isolates between 2013 and 2014, illustrating a significant problem centered around the Mediterranean and Balkan area. Worrisomely, colistin resistance among reported isolates heralds the loss of the last frontier, with resistance ranging from 8% in the UK to 70.5% in Romania [23].

18.2.1.2 Resistance to Fluoroquinolones, Aminoglycosides, and Colistin

Chromosomal mutations in DNA gyrase (*gyrA*) and topoisomerase IV (*parC*) are the main resistance mechanism, conferring high-level resistance against quinolones and fluoroquinolones. First-step mutants may exhibit in vitro susceptibility to fluoroquinolones, but in vivo, and in the presence of high inoculum, they develop rapidly full resistance. Other mechanisms are mediated through chromosomal overexpression of efflux pumps or decreased permeability. Recently described

qnr-encoded proteins confer low-level resistance through plasmid-mediated mechanism. These genes are usually linked to other antibiotic resistance determinants (most frequently ESBL), resulting in MDR phenotypes [7, 16, 30].

Aminoglycoside-modifying enzymes (AMEs) are the major mediators of aminoglycoside resistance in *Enterobacteriaceae* (chromosomal in *Serratia marcescens* and *Providencia stuartii*). Plasmid-borne AME genes are often co-transmitted with ESBLs being associated with resistance rates as high as 60% for gentamicin and 20% for amikacin among nosocomial isolates of *Enterobacteriaceae*. Plasmid-mediated methylation of 16S rRNA subunit is now recognized as a major mechanism of resistance to all parenteral aminoglycosides with global dissemination particularly in NDM-producing strains. At least seven genes have been associated with methylase production (*armA*, *rmtA*, *rmtB*, *rmtC*, *rmtD*, *rmtE*, and *npmA*) [31].

18.2.2 Non-fermenting Gram-Negative Bacteria

18.2.2.1 *Pseudomonas aeruginosa*

Agents with activity against *P. aeruginosa* include ticarcillin (+/− clavulanate); piperacillin (+/− tazobactam); ceftazidime; cefepime; imipenem, meropenem, and doripenem; and (variably) aztreonam. Ticarcillin-clavulanate is less active compared to piperacillin-tazobactam owing to the strong induction of AmpC by clavulanate. AmpC hyperproducing variants remain susceptible to carbapenems. The most common mechanisms of carbapenems resistance in *P. aeruginosa* resulting in MDR phenotypes is overexpression of efflux pumps (most commonly the MexAB-OprM system involving multiple antibiotics) and mutations of the OprD porin, hijacking antimicrobial passage through the outer membrane (affecting mainly imipenem) [7, 16]. Acquisition of various MGEs may result in resistance to a wide range of β-lactams and aminoglycosides [32]. Resistance mechanisms for *P. aeruginosa* are schematically presented in Table 18.1.

18.2.2.2 *Acinetobacter baumannii*

Natural expression of AmpC cephalosporinase and OXA-51-like carbapenemase by *A. baumannii* confers intrinsic resistance to aminopenicillins, first- and second-generation cephalosporins, and aztreonam. In the context of AmpC hyperproduction, acquired resistance broadens and includes carboxypenicillins, ureidopenicillins, and third-generation cephalosporins [7, 16]. Dissemination of carbapenem-resistant (CR) strains is of major clinical importance since their prevalence continues to increase especially in Southern European countries [33]. CR may result from acquisition of carbapenemases (e.g., OXA-23-like, IMP, VIM, and more recently NDM-1) or through overexpression of OXA-51-like oxacillinases (Table 18.1).

Acquired resistance to other agents such as fluoroquinolones or aminoglycosides often accompanies ESBL-producing and CR-*A. baumannii* strains, narrowing significantly therapeutic choices which in the majority of cases reside on the use of colistin [33]. Extended use of colistin in hospital settings with high prevalence of CR has resulted in colistin-resistant isolates through reduction of the negative

Table 18.1 Resistance mechanisms for non-fermenting gram negative causing cIAIs [19–23]

Gram-negative non-fermenting	Resistance phenotype	Resistance mechanism
Pseudomonas aeruginosa	β-Lactams	Enzyme inhibition (AmpC, ESBL, MBLs), active efflux (MexAB), decreased permeability (loss of OprD)
	Aminoglycosides	Enzyme inhibition (AMEs), efflux (MexxYY), target modification (ribosomal methylation)
	Fluoroquinolones	Efflux (MexAB, CD, EF, XY, GH, VW), target modification (gyrA)
	MDR	Overexpression of active efflux pumps (MexA, MexB, OprM)
	Polymyxins	LPS modifications
Acinetobacter baumannii	β-Lactams	Enzyme inhibition (AmpC, plasmid-borne TEM-, SHV-, CTX-M, MBLs, OXA-type carbapenemases), target modification (PBPs), efflux pumps, reduced permeability
	Aminoglycosides	AMEs, target modification (16S rRNA methylases)
	Fluoroquinolones	Efflux pumps, target modification (DNA gyrase
	Tigecycline	Efflux pumps
	Polymyxins	LPS modifications—mcr-1
Stenotrophomonas maltophilia	β-Lactams	Inducible MBLs, impermeable outer membrane
	TMP–SMX	Target modification (plasmid-borne sul1, sul2)
	Fluoroquinolones	Target modification, efflux pumps
	MDR	MDR efflux pump

ESBL extended-spectrum β-lactamases, *MBL* metallo-beta-lactamases, *MDR* multidrug resistant, *AME* aminoglycoside-modifying enzymes, *PBPs* penicillin-binding proteins

charge of lipopolysaccharide, therefore lowering the affinity for the positively charged colistin [27]. Until now colistin resistance occurred through chromosomal mutations which imposed significant fitness cost upon the bacterium. Recent reports on the emergence of transmissible, plasmid-mediated colistin resistance in the form of MCR-1 gene are of major global significance and concern. The gene has been repeatedly isolated from the environment thus indicating possible transmission to *Enterobacteriaceae* regardless of selection pressure, rendering extensively drug-resistant pathogens, pandrug resistant [27, 28]. In this challenging scenario, data regarding optimal treatment are lacking. Rifampin has demonstrated in vitro synergy with colistin; however, clinical data of the combination including a randomized-controlled trial have shown only a marginal beneficial effect on microbiologic eradication without effect on mortality [34]. In vitro synergy has been demonstrated between colistin and glycopeptides; clinical data mostly from retrospective studies

were encouraging. Therefore, the addition of a glycopeptide to colistin might represent an option for salvage treatment [35, 36]. Sulbactam has variable in vitro activity against *A. baumannii*; clinical data are still scarce. Tigecycline exhibits an acceptable in vitro susceptibility profile without established breakpoints of resistance; its clinical use off-label in *A. baumannii* infections is jeopardized by the lack of solid clinical data and particular risks for superinfections and breakthrough infections. Monotherapy is discouraged and double dose is advisable with careful follow-up of liver function [36].

18.2.3 Enterococci and *Bacteroides fragilis*

Overexpression of low-affinity PBPs by enterococci, or less often acquisition of beta-lactamases, results in increased resistance against penicillins. Intrinsic low-level resistance of enterococci against aminoglycosides precludes their use as monotherapy, and high-level resistance is being disseminated with acquisition of MGEs carrying AMEs. Of major clinical importance however is the development of glycopeptide-resistant enterococci, which have emerged as a major cause of nosocomial infections. Strains of *E. faecium* and *E. faecalis* with high-level resistance to vancomycin and teicoplanin harbor the *vanA* gene, resulting in reduced affinity of the bacterial peptidoglycan with the glycopeptide. Strains harboring the *vanB* gene display variable MICs against vancomycin (from 1024 to 4 μg/ml) and in vitro susceptibility to teicoplanin without direct association with clinical efficiency. *E. gallinarum*, *E. casseliflavus*, and *E. flavescens* are characterized by chromosomal expression of the *vanC* gene complex, resulting in low-level resistance to vancomycin and susceptibility to teicoplanin [37] (Table 18.2).

Resistance against beta-lactams for *B. fragilis* isolates is mediated through production of β-lactamases, most commonly cephalosporinases, which may be inhibited in the presence of lactamase inhibitors. High-level carbapenem resistance in *B. fragilis* is rare, being usually associated with overexpression of the *cfiA* gene which encodes for a metallo-β-lactamase. Resistance against metronidazole still remains at low prevalence. The most common mechanism described is through expression of 5-nitroimidazole nitroreductases that are located both on chromosomal genes or MGEs [38] (Table 18.2).

18.3 Epidemiology of Resistance in Intra-abdominal Infections

Resistance trend in IAIs follows the data presented in the section of mechanisms of resistance. Due to geographic and epidemiologic variations, it is important that each country collects and analyzes its own data, in order to issue treatment guidelines. Compiled data from international registries and studies focused on IAIs are presented below.

Table 18.2 Resistance mechanisms of Gram-positive and anaerobes causing cIAIs [27, 28]

Microorganism	Resistance phenotype	Resistance mechanism
Staphylococcus aureus	β-Lactams—penicillin	Enzyme inhibition (penicillinase)
	β-Lactams—methicillin, oxacillin, nafcillin, cephalosporins (MRSA)	Target modification (PBP2a–mecA)
	Glycopeptides—GISA	Thickened cell wall-drug prevention from binding
	Glycopeptides—GRSA	Alteration of cell wall precursor targets—plasmid-borne transfer of VanA genes from VRE
Enterococci	β-Lactams (ampicillin)	Target modification (PBP5—*E. faecium*), enzyme inhibition (penicillinase—*E. faecalis*)
	Aminoglycosides	Enzyme inhibition (high-level resistance AMEs), target modification
	Vancomycin	Alteration of cell wall precursor target (Van A,B,D—high-level resistance, Van C,E,G—low-level resistance)
	Linezolid	Target modification (23S rRNA mutations)
Bacteroides spp.	β-Lactams	Enzyme inhibition (CepA cephalosporinases, MBLs—cfiA), efflux, target modification (PBPs)
	Macrolides, lincosamides, streptogramin B	Target modification (ribosomal)
	Metronidazole	Efflux, overexpression of DNA repair protein (RecA), expression of 5-nitroimidazole nitroreductases (nimA-G)
	Quinolones	Target modification (DNA gyrase—gyrA), efflux

MRSA methicillin-resistant *S. aureus*, *GISA* glycopeptide-intermediate *S. aureus*, *GRSA* glycopeptide-resistant *S. aureus*, *VRE* vancomycin-resistant *Enterococci, MBL* metallo-beta-lactamases, *AME* aminoglycoside-modifying enzymes, *PBPs* penicillin-binding proteins

18.3.1 ESBL and Carbapenem-Resistant *Enterobacteriaceae*

The SMART study (The Study for Monitoring Antimicrobial Resistance Trends) recording in vitro susceptibility patterns of Gram-negative isolates from IAIs, since 2002 reported a notable worldwide dissemination of ESBL-producing *Enterobacteriaceae*, both within hospital settings and within the community [39]. From 2002 to 2008, ESBL-producing *E. coli* isolates from IAIs in European centers rose from 4.3% to 11.8%, whereas the prevalence of *K. pneumoniae* ESBL-producing strains remained relatively stable (from 16.4% to 17.9%). As expected, among ESBL producers hospital-associated isolates predominated [40]. An increasing prevalence has been documented also in Asia and North America [41, 42]. Data from the CIAOW Study (Complicated Intra-Abdominal infections Worldwide

Observational study), reported that among intraoperative isolates collected worldwide from October 2012 to March 2013, ESBL producers represented 13.7% of all *E. coli* isolates and 18.6% of all *K. pneumoniae* isolates [43]. A particularly high percentage of ESBL producers (42.8%) was recorded among hospital-acquired *K. pneumoniae* isolates.

The increasing prevalence of *K. pneumoniae* carbapenemases (KPCs) worldwide is becoming one of the major challenges in hospital settings [23]. An analysis in the context of the SMART study reported that 6.5% of *K. pneumoniae* worldwide isolates from intra-abdominal infections were ertapenem resistant based on the 2010 CLSI breakpoints (MIC ≥ 1 μg/ml) [44]. Among ertapenem-resistant strains, a wide variety of carbapenemase genes was found, in addition to numerous ESBL and/or AmpC beta-lactamases backgrounds. These strains were clonally related, and when a separate analysis was performed, carbapenem-resistant isolates from the Asia-Pacific region were almost exclusively collected from India and expressed NDM-1 carbapenemases [45, 46].

18.3.2 *Pseudomonas aeruginosa*

Based on the results from the SMART study, *P. aeruginosa* was the third most common isolated pathogen from IAIs [39]. In North America, resistance against fluoroquinolones has significantly risen over the years from approximately 22% in 2005 to 33% in 2010, compared to the relatively unchanged imipenem resistance (approximately 20%). Relatively unchanged during the same study period remained also the resistance rates against piperacillin-tazobactam, cefepime, and ceftazidime, ranging from 23% to 26% [47]. It should be highlighted however that various geographic variations of antimicrobial resistance exist and should be taken into account accordingly [39].

18.3.3 Enterococci

Enterococci have emerged as a significant pathogen of hospital-acquired infections, associated with significant mortality [48, 49]. Results from the EBIIA study (Etude épidémiologique Bactério-clinique des Infections Intra-Abdominales) reported significantly higher prevalence of enterococcal infections in hospitalized patients compared to community-acquired infections (33% for hospital-acquired infections compared to 19% for community-acquired infections) without isolation of VRE strains, indicating the sustained suitability of vancomycin or teicoplanin use in both types of infections [50]. The preponderance of enterococci isolation for hospital-acquired IAIs compared to community-acquired infections was also demonstrated by the CIAOW study (22.3% vs. 13.9%), with *E. faecalis* and *E. faecium* being the most prevalent Gram-positive aerobic isolates accounting for 15.9% of total pathogens cultured from intraoperative samples [43].

18.3.4 *Bacteroides fragilis*

The exact prevalence of MDR *B. fragilis* is not easy to be determined due to technical difficulties related to transfer and processing of clinical specimens for culturing in anaerobic conditions. Therapy is always started empirically since the majority of *B. fragilis* strains remain susceptible to metronidazole, β-lactam/β-lactamase inhibitor combinations, and carbapenems. However individual isolate testing should be considered for highly virulent microorganisms, such as *Bacteroides*, *Prevotella*, and *Fusobacterium* spp. [51]. Data from a national United States survey on the antimicrobial resistance in *Bacteroides* spp. strains from 1997 to 2007 reported resistance rates ranging from 0.9% to 2.3% against carbapenems and piperacillin-tazobactam. Antimicrobial resistance was greater among *non-fragilis Bacteroides* species, than among *B. fragilis*, with very high resistance rates against moxifloxacin (especially for *B. vulgatus*) and clindamycin [52]. The importance of geographic variations is highlighted by a study from Asia, where higher non-susceptibility rates of *B. fragilis* of 7%, 12%, and 90% for imipenem, meropenem, and moxifloxacin, respectively, were reported [53].

18.4 Risk Factors for Acquiring Resistant Strains and Unusual Pathogens as Guide to the Selection of Empirical Regimen

Peritonitis, the most common type of IAI is classified as primary, secondary, and tertiary. Primary peritonitis is a rare usually monomicrobial IAI generated by hematogenous spread of bacteria or translocation from the gut, particularly in hosts with a predisposing condition [54, 55]. Secondary peritonitis, accounting for 80–90% of IAIs is most often due to gastrointestinal perforation or invasion by adjacent infected viscera. It is further classified as community acquired (70%) and postoperative (30%), the latter being most frequently attributed to anastomotic dehiscence. Community-acquired peritonitis is a mixed infection caused by bacteria of the patient's gastrointestinal flora, mainly *E. coli*, streptococci, and anaerobes with *B. fragilis* as the predominant species. In postoperative peritonitis, however, after patient's exposure to the hospital environment and antibiotics, causative pathogens tend to display MDR phenotypes (i.e., ESBL or AmpC or CR Gram-negatives, or MRSA [55]); *E. coli* and streptococci are less frequent compared to community infections [50]. Enterococci including *E. faecalis* and VRE as well as *Candida* species may also participate. Empirical treatment decisions should be based on local antimicrobial resistance data and patient's personal risk factors. After pathogen's identification, treatment can be adapted [56, 57]. Tertiary peritonitis develops when secondary peritonitis persists after failure of source control procedures. Fueled by prolonged hospital stay and antibiotic use, causative pathogens resemble those of postoperative peritonitis, including enterococci (and VRE), staphylococci (and *methicillin-resistant Staphylococcus aureus*/MRSA), *Enterobacteriaceae* with

multiple MDR phenotypes, difficult-to-treat non-fermenters (*P. aeruginosa*, *A. baumannii*), anaerobes, and *Candida* species. No surgical intervention is usually required [58].

General factors predisposing to poor patient outcomes in IAIs include severe disease, severe comorbidities, inadequate source control, non-appendicular origin, healthcare-acquired infection, and inadequate empiric antimicrobial regimen [59, 60]. Minimum turnover time of 48–72 h is required from specimen to susceptibility testing with conventional microbiological methods; therefore, initial antimicrobial therapy is usually empirical. Empirical treatment decisions must target the presumed pathogens, taking into account the infectious source, risk factors for resistance, and patient's severity of illness [55]. Studies in critically ill patients have clearly demonstrated the importance of early recognition of risk factors for resistant pathogens since adequate and timely treatment has been associated with reduced mortality [61]. In this sense, the distinction between community-acquired or healthcare-associated IAI is an important element. Classification of IAIs as "complicated" and "uncomplicated" seems to be less relevant to the implication or not of difficult-to-treat bacteria [62].

As mentioned above, community-acquired infections are likely caused by bacteria of the patient's gastrointestinal flora. As an exception to this rule, ESBL producers can be the cause of community infections, either without risk factors or associated with prior use of antibiotics (particularly the class of third-generation cephalosporins). It is therefore important to recognize patients exposed to antibiotics, especially those who were pretreated with prolonged or multiple antibiotic courses due to comorbidities [63–66]. Another important factor jeopardizing the distinction between community and nosocomial IAIs is an increasing volume of patients who reside in the community but are in close contact with the healthcare system. This group comprises nursing home residents, people receiving intravenous therapy at home, and people undergoing hemodialysis, chemotherapy, or irradiation as outpatients. These hosts tend to develop infections by pathogens that resemble to the nosocomial patterns of resistance, the so-called healthcare-associated infections (HCAIs) [67–69]. In a study of 2049 healthcare-associated IAIs, MDR pathogens accounted for 79% of those recovered [70]. HCAIs portend substantial morbidity and mortality; nevertheless, early and adequate empirical treatment proved to reduce complications and mortality [71].

Box 18.1 summarizes the most important risk factors for the acquisition of resistant strains in IAIs. Evidently, the most in-risk clinical settings are that of tertiary and postoperative peritonitis, with several factors predisposing to infections by MDR *Enterobacteriaceae*, *Pseudomonas* spp., *Acinetobacter* spp., enterococcal infections including VRE, MRSA, and *Candida* spp. It is important to consider also moving patients/populations as potential carriers of MDR bacteria harboring sometimes alarming resistance determinants [8–12]. In Southeast Asia, NDM-1 has been detected from sewage waters; in China, *Enterobacteriaceae* harboring mcr-1 gene carrying plasmid-mediated resistance to colistin were isolated from the food chain; KPC-producers and XDR

A. baumannii colonize/infect frequently inpatients in the Mediterranean region; ESBL may unexpectedly colonize healthy subjects from Mediterranean and Asian countries [22–24]. MRSA is not a frequent pathogen in IAIs and should be considered in hospital-acquired (particularly wound) infections and in patients with known previous colonization. Other pathogen-specific predisposing factors in IAIs are detailed in Table 18.3 [11, 58, 62, 65, 66, 69, 70, 72–76].

Box 18.1 Risk factors and clinical scenarios with increased likelihood of multidrug-resistant (MDR) pathogens in intra-abdominal infections [65–70]

Risk factors for recovery of multidrug-resistant bacteria in patients with intra-abdominal infections
Healthcare-associated infection (outpatient intravenous treatment, wound treatment, antineoplastic therapies, hemodialysis, nursing home residents)
Recent exposure to broad-spectrum antibiotics (<3 months)
Length of hospitalization >5 days
Prior or current admission in intensive care unit
Liver disease
Pulmonary disease
Diabetic foot infection with antibiotic use
Organ transplantation
Corticosteroid use
Patient receiving immunosuppressive agents
Patient with recent exposure in areas with MDR prevalence in the community or in environmental sources
Patient hospitalized in areas with MDR prevalence
Postoperative peritonitis Long time between first and second surgery
Tertiary peritonitis
Recurrent interventions in the biliary tract
Pretreated necrotizing pancreatitis

In general, broad-spectrum regimens are recommended in critically ill patients. Although coverage of enterococci and MDR bacteria is not recommended in patients with community-acquired peritonitis, enterococci should be considered in patients with septic shock, immunosuppression, and recurrent IAIs among other predisposing conditions listed in Table 18.3. Local epidemiology is a crucial factor to consider when selecting antimicrobial therapy. Surveillance strategies are important to guide selection of empirical treatment, particularly for severely ill patients [1, 2, 72]. Box 18.2 provides some useful pearls integrating microbiology into clinical practice that might assist clinicians in the selection of the correct antibiotic.

Box 18.2 Clinical pears integrating microbiology into clinical practice of intra-abdominal insections

- Identify patient's risk factors for resistant pathogens
- Get familiar with local epidemiology
- Third-generation cephalosporins should be avoided for treating wild-type inducible AmpC-producing *Enterobacteriaceae*—piperacillin and ticarcillin should be preferred
- ESBL[b]-producing *Enterobacteriaceae* are often resistant to other antimicrobial classes besides β-lactams (e.g., aminoglycosides or quinolones)
- BLBLI[c] should preferably be avoided unless MIC[d] ≤ 4 mg/L; bacteremic patients with inadequate source control have an increased risk to fail such treatment
- If susceptibility is confirmed, cefepime can be considered as a suitable carbapenem-sparing option for AmpC hyperproducing mutants, only if adequate source control is feasible because of the [a]inoculum effect
- Carbapenems remain active against AmpC hyperproducing and a potent agent against ESBL[b]-producing *Enterobacteriaceae*
- KPC[e] enzymes inactivate all β-lactams; ceftazidime/avibactam represents a new option
- Colistin remains currently the milestone for combination treatment of KPC[e] producing strains
- Selection of [f]colistin-resistant KPC-producing strains is an emerging global threat, mandating judicious colistin use
- Agents potentially effective against *Pseudomonas aeruginosa* are ticarcillin (±clavulanate); piperacillin (±tazobactam); ceftazidime; cefepime; meropenem, imipenem, and doripenem; ceftolozane/tazobactam; and ceftazidime/avibactam. Susceptibility against aztreonam varies
- Clavulanate is a strong inducer of AmpC production in *P. aeruginosa*
- Enterococci exhibit intrinsic resistance to some penicillin, all cephalosporins, and low-level resistance to aminoglycosides. Quinolones should not be considered adequate coverage
- Glycopeptide-resistant enterococci (GRE) are a significant cause of nosocomial infections with the majority of infections attributed to *E. faecium*
- *Bacteroides fragilis* is the most frequently isolated anaerobe from cIAIs[g]; it displays low resistance rates against metronidazole

a: In vitro studies showed that when a higher inoculum was used, the MIC for cefepime was significantly increased, b: ESBL; extended-spectrum β-lactamases c: BLBLI; β-lactam/β-lactamase inhibitor d: MIC; Minimum inhibitory concentration e:KPC; *Klebsiella pneumoniae* carbapenemase f: Colistin exposure is a risk factor for colistin resistance emergence in carbapenem-resistant Gram-negative bacilli g: cIAIs; complicated intra-abdominal infections

18.5 Prevention of Resistance

18.5.1 Antibiotic Stewardship and Implication of Surgeons

Currently published guidelines for the management of IAIs prioritize patients' safety and optimization of outcomes [2, 77, 78]. Antimicrobial stewardship is a novel approach intended to optimize antibiotic selection while minimizing

Table 18.3 Characteristics and predisposing factors for specific resistant phenotypes among pathogens recovered from intra-abdominal infections and guide for empirical coverage [11, 58, 62, 65, 66, 69, 70, 72–76]

	Bacteria with MDR phenotype or unusual bacteria in intra-abdominal infections				
	Enterobacteriaceae with resistant phenotype (ESBL or AmpC- or CR-producing *Escherichia coli, Enterobacter* spp., *Klebsiella* spp., *Serratia* spp., *Proteus* spp. etc.)	Non-fermenting Gram-negative bacteria (*Pseudomonas aeruginosa, Acinetobacter baumannii, Stenotrophomonas maltophilia*, etc.)	*Enterococcus faecium E. faecalis* including vancomycin-resistant *E. faecium*	*Staphylococcus aureus*	*Candida* spp.
Predisposing conditions	Healthcare-associated infection; local epidemiology considered	Healthcare-associated infection; local epidemiology considered	Recent antibiotic exposure (particularly prolonged cephalosporin treatment)	Abdomen left-open (compartment syndrome)	Postoperative peritonitis
	Patients with a history of recent travel (tourism and trade) in regions with high prevalence (Egypt, Thailand, India)	Length of hospital stay >5 days	Postoperative peritonitis	Postoperative infections	Prolonged antibiotic exposure
	Medical tourism or medical emergencies with hospital procedures in geographic areas with prevalent MDR and XDR *Enterobacteriaceae*	Recent antibiotic exposure	Tertiary peritonitis	Wound infections	Tertiary peritonitis following failure of source control
	Otherwise healthy migrants and refugees from countries with prevalent MDR and XDR *Enterobacteriaceae*	Chronic underlying conditions leading to antibiotic exposure (diabetic foot, chronic ulcers, chronic pulmonary conditions)	Septic shock and failure of early surgical source control	Patients receiving immunosuppressive agents	Upper GI tract perforation
	Patient with known colonization with resistant bacteria	Recent ICU admission	Immunosuppression and liver transplantation	Posttransplantation	Prior administration of fluconazole predisposes for fluconazole resistance

	Pretreated necrotizing pancreatitis	Immunocompromised status (*P. aeruginosa, S. maltophilia*) and corticosteroid use (*P. aeruginosa*)	Prosthetic heart valves	Previously colonized	Immunodeficiency
	Recurrent operations of biliary tract with obstruction	Pretreated necrotizing pancreatitis	Recurrent intra-abdominal infections		

ESBL extended-spectrum β-lactamases, *MDR* multidrug resistant, *XDR* extensively drug resistant, *GI* gastrointestinal

unnecessary antibiotic use along with its undesirable effects on further promotion of resistance [1]. Basic components of an antimicrobial stewardship program (ASP) are surveillance of resistance, implementation of infection control practices, and rational antibiotic use. The latter relies upon repetitive educational approaches to improve prescribers' ability to understand and conform to antimicrobial treatment principles. Optimal use of perioperative prophylaxis is a pillar of every ASP, mandating administration of narrow spectrum antibiotics for the shortest possible duration to prevent postoperative infections. Timing and possible repeat dosing of antibiotics as prophylaxis should follow national or local protocols and take into consideration duration of surgical procedures and antibiotic pharmacokinetics [1, 79, 80].

Although highly referenced, ASPs have not yet reached a universally accepted structure; therefore they are mainly based to local capacities and practices. Interventions may include antibiotic restriction, mixing, cycling, clinical guidelines, and practice algorithms. De-escalation is an important strategy to limit unnecessary use of broad-spectrum antibiotics after receipt of susceptibility results. Treatment duration is well established in IAIs and rarely should exceed 7 days, in complicated infections [1, 2, 79, 80]. Despite diversity of ASPs, observational studies have demonstrated a beneficial effect on antimicrobial resistance after implementation of ASP in surgical and trauma intensive care unit, which decreased in parallel with broad-spectrum antibiotic orders [81].

The Infectious Diseases Society of America has identified two types of approaches in the implementation of ASPs [1]. First, a persuasive-proactive approach requiring restriction formulary or pre-approval for select antibiotics or both. Second, a restrictive approach consisting of prospective audit with intervention with subsequent feedback of the prescribers. Both types of interventions have been associated with reduction of restricted antibiotics along with cost [1, 81, 82]. A Cochrane meta-analysis of 89 studies encompassing ASPs showed that the restrictive approach had more immediate results compared to the proactive one and was associated with reduction of antimicrobial resistance; on the other hand, persuasive approach was associated with better patients' outcomes. Nevertheless, after 6 months, no difference could be demonstrated. Despite the rapid results obtained with restrictive measures, after a short period of a few months, physicians were able to bypass obstacles to deliberate prescription of antibiotics [79].

Acceptance of ASPs is not straightforward; surgeons are frequently reluctant to share responsibility of their patient and "obey to restrictions." The success of every ASP relies on the building of confidence and the strong participation of all stakeholders in joint efforts. Adherence to surveillance practices and infection control measures may pose an additional obstacle in "conformation with restrictions." Both are important elements for containment of antimicrobial resistance. As far as infection control measures are concerned, surgeons may represent the most relevant specialties to understand the rationale and the procedure, since they are familiar with surgical procedures under aseptic conditions. Baseline educational activities may be decisive as well as the strong implication of a surgeon with well-appreciated knowledge and skills in both communication and management of surgical infections.

Equally important is the provision of continuous feedback to the surgeons with the results of strategies taken in order to improve antibiotic prescription and tackle antimicrobial resistance in their setting [83–85].

18.5.2 The Value of Targeted Therapy

It is very important to guide treatment decisions by appropriate cultures taken before empirical treatment initiation. There is discordance between published guidelines by the IDSA and the WSES [2, 62, 78] regarding the necessity of intraoperative cultures in uncomplicated IAI from the community. The issue has been very clearly addressed in the AGORA position paper [3]. In terms of clinical benefit on a patient basis, microbiologic confirmation might not affect clinical outcome in mild community IAIs [3, 86, 87]. However, it helps understanding microbiological trends in the community and survey antimicrobial resistance, given the fact that many resistance mechanisms in *Enterobacteriaceae*, namely, ESBLs and NDM-1, are now recovered from otherwise healthy persons without healthcare-associated risk factors [8–12]. Furthermore, microbiological documentation will enable de-escalation decisions, in order to curtail unnecessary use of broad-spectrum antibiotics selected as part of the empirical regimen. On the other hand, in case of a pathogen with unexpected pattern of resistance, antibiotic testing will enable prompt adaptation of treatment. Blood cultures are very rarely positive in IAI; nevertheless, in critically ill patients and particularly those with previous ICU admission and having implanted devices and central lines, a set of two blood cultures before initiation of treatment is highly advisable [3].

Perioperative tissue and pus specimens are also advisable in every patient with community-acquired IAI. Notably, perioperative and pus specimens are considered standard of care in hospital-acquired IAI or complications of previous surgery, recurrent bile duct surgeries, and necrotizing pancreatitis [2, 62, 78]. In view of escalating resistance and in patients not responding to the administered regimens, properly obtained and transported samples for anaerobic cultures should be ordered in select cases. It is also important to seek advice from infectious diseases physicians, clinical microbiologists, and possibly clinical pharmacologists in order to customize treatment in difficult-to-treat MDR pathogens. Finally, after almost two decades of dry pipeline, launching of a handful of new antibiotics with activity against some of the most cumbersome MDR/XDR pathogens mandates a prudent use of them by the clinicians. For these new antibiotics empirical use should be kept to a minimum, and their use as targeted treatment should be clinicians' priority.

Conclusion

Antimicrobial resistance is a worldwide expanding phenomenon with unprecedented consequences in morbidity, mortality, and healthcare expenditures. Evidently, surgical departments follow the global alarming trends with less than a handful antibiotics active against bacteria with pandrug-resistant phenotypes. Surgeons are by definition in the frontline of emergencies; now, they have to

confront the obstacle of antimicrobial resistance. Enhancing surgeons' knowledge on antibiotics and resistance will help the acceptance of ASP and all other measures targeting the containment of the problem. Antibiotic stewardship is not just a restriction for prescribers; it is an integrating model to lead hospitals in preservation of antibiotics while maximizing clinical efficacy. Frontline physicians are (by definition) part of the solutions.

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The Role of *Candida* in Abdominal Sepsis

19

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19.1 Introduction

Candida is frequently isolated on microbiologic samples from patients with abdominal sepsis. A very large number of studies have been published on candidemia, but only limited data are available concerning abdominal sepsis. The management of patients with *Candida* peritonitis is largely extrapolated from that proposed for candidemia. In addition, many definitions have been proposed for *Candida* peritonitis, reflecting the variety of clinical circumstances in which *Candida* spp. are reported. The broad definition proposed by Bassetti et al. takes into account the specificities of *Candida* in abdominal sepsis (Table 19.1) [2].

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Table 19.1 Circumstances in which detection of *Candida* is defined as an episode of invasive abdominal candidiasis

Candida detection by direct microscopy examination
Candida growth in culture from purulent or necrotic intra-abdominal specimens obtained during surgery or by percutaneous aspiration
Candida growth from bile, intra-biliary duct devices
Candida growth from biopsy of intra-abdominal organs
Candida growth from blood cultures in a clinical setting of secondary and tertiary peritonitis in the absence of any other pathogen
Candida growth from drainage tubes only if placed less than 24 h before cultures

Adapted from Bassetti et al. [1]

19.2 What Is the Impact of *Candida* in Intra-abdominal Infections

19.2.1 Circumstances of *Candida* Isolation in Intra-abdominal Infections

The pathogenicity of *Candida* spp. in intra-abdominal infections is a controversial issue due to the diverse effects observed when *Candida* spp. are involved. *Candida albicans* and *C. glabrata* are saprophytic hosts of the digestive tract in healthy subjects and are reported in 23 up to 76% of the population, in low concentrations (between 10^2 and 10^4 CFU/mL or g depending on the site) throughout the digestive tract [3]. In animal models of infection, the pathogenicity of *Candida* is only reported at high concentrations and in mixed bacterial and fungal infections [4]. In typical cases of community-acquired peritonitis, perforation of a hollow viscus releases these *Candida* cells present in the gut flora into the peritoneum, consequently raising the issue of whether these organisms need to be taken into account in management.

In other circumstances, such as recurrent or tertiary peritonitis, *Candida* colonization emerges progressively. Infection usually develops over several days in a limited number of colonized cases, but the mechanisms of transition from colonization to invasive intra-abdominal candidiasis remain unclear. Broad-spectrum antibiotic agents obviously play a key role in enhancing *Candida* colonization of mucosal surfaces, but many other risk factors have also been described [2] (Table 19.2). The most common source of confusion concerns difficult cases, such as patients undergoing a first reoperation for postoperative peritonitis, in which the process described for invasive candidiasis might be less significant than in recurrent peritonitis and for which the evidence in favor of the benefits of early empiric antifungal treatment remains debated.

Table 19.2 Risk factors for intra-abdominal candidiasis

Surgery-related risk factors
– Recurrent abdominal surgery (open and laparoscopic procedures)
– Recurrent gastrointestinal perforation
– Gastrointestinal anastomosis leakage
Multifocal colonization by *Candida* spp.
Nonspecific risk factors
– Acute renal failure
– Central venous catheter placement
– Total parenteral nutrition
– ICU stay
– Severity of sepsis
– Diabetes
– Immunosuppression
– Prolonged broad-spectrum antibacterial therapy

Adapted from Bassetti et al. [1]

19.2.2 Types of *Candida* Involved in Intra-Abdominal Infections

Due to their presence in the normal gut flora, *C. albicans* is the most common causative yeast, and *C. glabrata* is the leading *Candida* non-*albicans* pathogen in intra-abdominal infections [1, 5–9]. Other *Candida* species are reported in small numbers of cases. De Ruiter et al. reported up to 41% of positive cultures of abdominal fluid yielding *Candida* obtained from gastroduodenal injuries compared to 8.7% in biliary tract and 11.8% in colorectal perforations [10]. These authors observed the same trends when comparing community-acquired and postoperative infections. High proportions of *Candida* have been reported in some specific subpopulations, such as patients with postoperative peritonitis following bariatric surgery [11, 12], more commonly in late-onset peritonitis and often associated with multidrug-resistant bacteria [12]. The frequency of *Candida* spp. in persistent and tertiary peritonitis remains stable over time and reaches proportions ranging between 40% and 50% of isolates during repeated surgery [10, 13].

19.2.3 Role of *Candida* in the Prognosis of Intra-abdominal Infections

The pathogenic role of *Candida* has been debated for decades, but many reports suggest a potential pathogenic role of *Candida*. Candidemia during intra-abdominal infection is a factor of poor prognosis, although positive blood cultures are rare in most series, ranging between 6% and 15% of patients [14, 15]. In a cohort of patients with candidemia, an intra-abdominal source was associated with an increased risk

of death (OR = 8.15; 95% CI, 1.75–37.93; $p = 0.008$) compared to other sources of sepsis [16]. In addition, the detection of *Candida* on direct examination of peritoneal fluid, indicating a heavy fungal inoculum, is associated with an increased mortality rate (OR = 4.7; 95% CI, 1.2–19.7; $p = 0.002$) [6]. However, this analysis is not systematically performed in routine clinical practice.

Septic shock complicating intra-abdominal candidiasis is also associated with high mortality rates. In a large international observational study comprising 481 patients with intra-abdominal candidiasis, the risk factors for death identified on multivariate analysis were age, high APACHE II score, secondary peritonitis, septic shock, and absence of adequate abdominal source control [1]. In these patients with septic shock, absence of source control was correlated with mortality rates higher than 60% irrespective of administration of adequate antifungal therapy. Similarly, in a prospective observational study involving 180 patients with secondary generalized peritonitis (community acquired and postoperative), septic shock complicating intra-abdominal candidiasis was associated with high mortality rates [17]. In addition, yeasts cultured from peritoneal fluid of patients with postoperative peritonitis were an independent risk factor for death in patients with septic shock.

In healthcare-associated (mainly postoperative) peritonitis, intra-abdominal candidiasis is associated with increased mortality rates. In an observational case-control study, isolation of *Candida* spp. was an independent risk factor for death in nosocomial peritonitis patients [8]. On the contrary, the role of *Candida* spp. in the prognosis of community-acquired infections is difficult to demonstrate. Indirect evidence suggesting the low pathogenicity of *Candida* in this setting is provided by published data suggesting that antifungal treatment is not necessary in patients with community-acquired peritonitis [18–20]. In a multicenter case-control study in intensive care unit (ICU) patients, the mortality rate was not increased in cases of community-acquired peritonitis [8].

19.3 When and How to Treat Intra-abdominal Candidiasis?

19.3.1 Early Recognition of Intra-abdominal Candidiasis

Diagnosing invasive candidiasis is often difficult and often takes several days [21, 22]. Intra-abdominal candidiasis is associated with bacterial co-infection in the majority of cases, complicating analysis of the symptoms related to bacterial and/or fungal infection [1, 14, 15, 23]. In addition, blood cultures have insufficient diagnostic performances [24, 25] and are only reported in small proportions of patients with invasive candidiasis, ranging from 1–3% of cases in a recent study [15] to 28% of patients [23], but usually ranging between 10% and 15% of cases [1, 7, 15]. Clinical and laboratory criteria are not sufficiently relevant to discriminate *Candida* peritonitis from non-microbiologically confirmed suspicion [15]. Antifungal therapy is therefore often initiated empirically, despite the lack of consensus on decision-making criteria [16, 21]. A large proportion of these patients suspected of having *Candida* peritonitis unduly receives empiric antifungal therapy. Overuse

of antifungal therapy has been described in patients suspected of having invasive candidiasis [26] including intra-abdominal infections [15].

19.3.2 Value of Clinical Scores

Several risk factor-based predictive scores have been proposed to improve the early recognition of intra-abdominal candidiasis by clinicians [27–32] (Table 19.3), but the value of these scores remains debated. A major limitation to the use of several scores is the need for fungal mapping [28, 31], which cannot be obtained in emergency patients and/or patients transferred from another institution. These scores have a high

Table 19.3 Criteria used in the clinical scores for prediction of intra-abdominal candidiasis

Pittet [31]	Number of distinct body sites colonized with *Candida* spp. Two sites or more More than two sites Three sites or more *Candida* colonization index *Candida* corrected colonization index
Dupont [27]	Cardiovascular failure Upper gastrointestinal tract origin Female Ongoing antimicrobial therapy
Leon [33]	Multifocal *Candida* species colonization Surgery on ICU admission Severe sepsis Total parenteral nutrition
Ostrosky [29]	Any systemic antibiotic (days 1–3) Or presence of a central venous catheter (days 1–3) And at least two of the following: Total parenteral nutrition (days 1–3) Any dialysis (days 1–3) Any major surgery (days −7–0) Pancreatitis (days −7–0) Any use of steroids (days −7–3) Use of other immunosuppressive agents (days −7–0)
Ostrosky [30]	Mechanically ventilated for at least 48 h Antibacterial antibiotic use (days 1–3) Central venous catheter (days 1–3) At least one of the following: Any surgery (days −7–0) Immunosuppressive use (days −7–0) Pancreatitis (days −7–0) Total parenteral nutrition (days 1–3) Any dialysis (days 1–3) Steroid use (days −7–0)
Dupont [32]	Length of stay ≥48 h before surgery Intraoperative cardiovascular failure Generalized peritonitis Upper gastrointestinal tract perforation

negative predictive value, allowing intra-abdominal candidiasis to be ruled out, while their positive predictive value remains insufficient [34, 35]. In contrast, the efficacy of these scores for the detection of intra-abdominal candidiasis has rarely been assessed in non-selected surgical populations. In a prospective, multicenter, observational study comprising 204 patients receiving antifungal therapy for suspected intra-abdominal candidiasis, the *Candida* and peritonitis scores failed to discriminate patients with *Candida* peritonitis from those without *Candida* infection [15].

19.3.3 Place of Nonspecific Biomarkers

The operative value of biomarkers such as C-reactive protein and procalcitonin has been evaluated in intra-abdominal candidiasis. These tests are more reflective of the inflammatory response to surgical injury than fungal infection. In a prospective cohort of 176 non-neutropenic ICU patients, CRP and PCT assays were performed twice a week [36]. CRP and PCT concentrations could not be used to differentiate patients with invasive candidiasis from those who were neither colonized nor infected, or who presented *Candida* colonization, regardless of sample collection times.

19.3.4 Value of Non-culture-Based Tests

The use of non-culture-based tests has been proposed to help clinicians discriminate cases of colonization from cases of infection and to select patients requiring early antifungal therapy. However, the use of these tests is associated with considerable confusion. Most studies assessing the efficacy of these tests have included mixed cases of candidemia and invasive candidiasis, but few studies have specifically focused on intra-abdominal candidiasis. Evaluation of these tests is rarely performed in real time, and their results are not available during the decision-making process. Despite the potential improvement of clinical management that could be provided by these tests, they are only rarely used in routine clinical practice because of their limited distribution and their high cost when repeated assays are required.

BD-glucan assay has been reported to be useful in ICU patients with complicated abdominal surgery, abdominal leakage, and acute pancreatitis [36, 37]. Various cut-offs for the detection of intra-abdominal candidiasis have been discussed. The sensitivity of BD-glucan assay at a positive cutoff of 80 pg/mL was 76.7% (95% CI, 57.7–90.1), with a specificity of 57.2% (49.9–64.3) and a negative predictive value of 94.1% (89.1–96.8) [38]. In order to improve the accuracy of this parameter, several authors have proposed repeated samples, at least twice weekly [36, 37]. Positive BDG on two consecutive samples had a sensitivity of 76.7% (95% CI 57.7–90.1) and a specificity of 57.2% (95% CI 49.9–64.3) [38].

More recently, there has been a growing interest in *Candida albicans* germ tube antibodies (CAGTA). The sensitivity of CAGTA at a positive cutoff of 1/60 was 53.3% (95% CI, 34.3–71.7) with a specificity of 64.3% (57.2–71.0) and a negative

predictive value of 90.1% (86.0–93.2) [38]. These authors also proposed a combination of two or possibly more than two tests to increase the performance for the detection of intra-abdominal candidiasis. The combination of positive CAGTA and BDG in a single sample or at least one positive biomarker in two consecutive samples improved the performance of the test with a sensitivity of 90.3% (95% CI 74.2–98.0), a specificity of 42.1% (95% CI 35.2–98.8), and a negative predictive value of 96.6% (95% CI 90.5–98.8) [38]. These results have been confirmed in a study of a general population including ICU and non-ICU patients that reported a sensitivity and negative predictive value of the combination of CAGTA and BDG of 97% for the entire population [39]. The best performance was observed in ICU patients with a sensitivity and negative predictive value of 100% [39].

Mannan antigens and anti-mannan antibodies have been rarely evaluated in intra-abdominal candidiasis. The combination of these two tests increases their specificity and sensitivity. However, in a prospective study evaluating 233 non-neutropenic ICU patients, mannan antigens (≥60 pg/mL) and anti-mannan antibodies (≥10 AU/mL), assayed twice a week, demonstrated a low discriminating capacity [38].

The value of polymerase chain reaction (PCR) remains debated because of the major drawbacks of this technique. The absence of any commercially available test and the lack of methodologic standardization and multicenter validation are key issues limiting the interest for this test. Several studies have reported a good correlation between PCR and other tests, such as BD-glucan [24, 40], while other studies have reported a low discriminating capacity [38].

19.3.5 Adequacy of Source Control

Before addressing the issue of antifungal therapy, the fundamental importance of source control must be stressed. Recently, Bassetti et al., in a large cohort of 216 patients with septic shock attributable to *Candida*, demonstrated the critical role of source control in the outcome of these patients [41]. In multivariate analysis, a 2.99-fold increased mortality rate was reported in the case of inadequate source control. The issue of source control is of particular importance in patients with septic shock with mortality rates as high as 60% [1] and has been confirmed in another study with a 77.40-fold (95% CI 21.52–278.38) increased mortality rate [42].

19.3.6 Adequate Timing of Antifungal Therapy

The need for adequate antifungal therapy is the second key point in the anti-infective management of intra-abdominal candidiasis. However, the optimal timing of initiation of antifungal therapy in intra-abdominal candidiasis has been poorly addressed. Over the last decade, several reports have demonstrated that delayed empiric antifungal therapy in patients with candidemia and invasive candidiasis significantly worsened the prognosis and survival of these high-risk cases [42–44]. By extension based on these observations, early initiation of systemic antifungal therapy is

recommended for patients with suspected intra-abdominal candidiasis by experts and the most recent guidelines. However, the deleterious impact of delayed initiation of systemic antifungal therapy has never been formally demonstrated for *Candida* intra-abdominal infection. In a recent prospective observational study in 158 patients with intra-abdominal candidiasis, including patients receiving empiric therapy and patients with documented antifungal therapy, the time to initiation of antifungal therapy ranged between the day of surgery and six or more days after surgery [15]. The time to initiation of antifungal therapy did not appear to influence the outcome in these two groups of patients, except for the less severely ill patients (SOFA score < 7), who displayed an increased mortality in the case of delayed therapy ($p = 0.04$).

This concept of early antibiotic therapy has led to the definition of pre-emptive therapy and empiric therapy [21]. According to the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines, a pre-emptive approach is a diagnosis-driven prescription defined as therapy triggered by microbiological evidence of candidiasis without proof of invasive fungal infection. The empiric approach is a fever-driven prescription in the clinical situation of a patient at risk for invasive candidiasis who is persistently febrile with no microbiological evidence of infection. However, these definitions are a source of confusion in the field of intra-abdominal infections, conditions that differ considerably from the context surgical patients, except possibly for ICU patients with tertiary or recurrent peritonitis. Interestingly, the recently updated Infectious Diseases Society of America (IDSA) guidelines no longer mention pre-emptive therapy [25].

While early antifungal therapy for microbiology-proven infection makes sense, few pre-emptive therapies have been assessed in patients at risk of developing intra-abdominal candidiasis. In an exploratory, randomized, double-blind, placebo-controlled trial, Knitsch et al. evaluated a pre-emptive antifungal approach with micafungin or placebo in intensive care unit patients requiring surgery for intra-abdominal infection [45]. This study was unable to provide any evidence that pre-emptive administration of an echinocandin was effective in preventing intra-abdominal candidiasis in high-risk surgical intensive care unit patients with intra-abdominal infections. Interestingly, patients with positive plasma BD-glucan assay were 3.66 (95% CI, 1.01–13.29) times more likely to have confirmed invasive candidiasis than those with a negative result [45].

19.3.7 Adequate Spectrum of Antifungal Therapy

The adequacy of antifungal therapy is the second major prognostic factor.

Susceptibility to antifungal agents of *Candida* strains cultured from peritonitis is rarely assessed in the literature [1, 6, 8, 15, 18, 23]. Most studies report good susceptibility of *C. albicans* to antifungal agents and decreased susceptibility of

C. glabrata to azoles. Bassetti et al. reported 98% of *Candida* strains susceptible to echinocandins, 89% to fluconazole, and 96% to voriconazole [1]. Sartelli et al. in a large multicenter international study observed 98% of *C. albicans* strains susceptible to fluconazole and 97% of *C.* non-*albicans* strains [9]. These data were confirmed in a recent multicenter study reporting the susceptibility profile of 125 peritoneal isolates: 100% of *Candida* spp. were susceptible to echinocandin and 84% were susceptible to fluconazole, while only 40% of *C. glabrata* strains were susceptible to fluconazole [15].

The EUCAST guidelines consider *C. glabrata* to be resistant to azoles [46]. These organisms are the second most common isolates among surgical isolates, ranging between 12% and 22% of all *Candida* strains [1, 12, 15, 23, 27, 41].

According to the IDSA and ESCMID guidelines, appropriate management of IC includes administration of an appropriate antifungal agent [21, 25]. For suspected invasive candidiasis as well as proven candidemia, IDSA guidelines recommend the use of fluconazole or an echinocandin (caspofungin, micafungin, or anidulafungin) and preferably an echinocandin for critically ill patients or for fluconazole-resistant *Candida* species [25, 47]. Fluconazole is an appropriate choice for treatment when *Candida albicans* is isolated. Finally, amphotericin B is not recommended as initial therapy for toxicity reasons [47], but a lipid formulation should be considered in the presence of intolerance, limited availability, or resistance to other antifungal agents [25]. On the contrary, ESCMID guidelines do not modulate their recommendations according to patient severity, but also recommend the use of echinocandins as first-line therapy [21].

Several guidelines define the profile of patients who should receive empiric antifungal therapy (Table 19.4). Two IDSA guidelines have addressed this issue, the first focusing on the diagnosis and management of complicated intra-abdominal infections [47] and the second corresponding to the 2016 updated guidelines for the management of candidiasis [25]. Interestingly, the ESCMID guidelines do not provide a real picture of the patients requiring treatment for intra-abdominal candidiasis [21]. The recommendations of the consensus of multinational experts differ from the other guidelines by proposing broad criteria for initiation of empiric therapy [2]. The World Society of Emergency Surgery (WSES) more clearly defines immunosuppressed patients [48].

However, these recommendations for intra-abdominal infections are a source of concern, as they are based on a very limited level of proof. No study has ever specifically evaluated the efficacy of antifungal therapy in intra-abdominal candidiasis. In recent randomized trials focusing on antifungal therapy of invasive candidiasis, the proportion of patients with a diagnosis of intra-abdominal candidiasis was extremely low [50–53], and it is impossible to draw any solid conclusions concerning these surgical cases or to recommend any agent based on clinical results. In summary, the extensive use of echinocandins in surgical patients suspected of intra-abdominal candidiasis deserves additional proof.

Table 19.4 Type of patients in whom empiric antifungal therapy is recommended according to recent guidelines

IDSA 2010 [47]	Patients with severe community-acquired or healthcare-associated infection if *Candida* is grown from intra-abdominal cultures
	Not recommended for adult and pediatric patients with mild-to-moderate community-acquired intra-abdominal infection
IDSA 2016 [25]	Patients with clinical evidence of intra-abdominal infection and significant risk factors for candidiasis, including recent abdominal surgery, anastomotic leaks, or necrotizing pancreatitis
WSES [48]	Patients with nosocomial infection and critically ill patients with community-acquired infections Patients with community-acquired intra-abdominal infections recently exposed to broad-spectrum antimicrobials and immunocompromised patients (due to neutropenia, concurrent administration of immunosuppressive agents such as glucocorticosteroid chemotherapeutic agents and immunomodulators)
	Not recommended for patients with community-acquired intra-abdominal infections with no risk factors
Consensus of multinational experts [2]	Patients with a diagnosis of intra-abdominal infection and at least one specific risk factor for *Candida* infection Patients with intra-abdominal infection with or without a specific risk factor for *Candida* infection, empiric antifungal treatment should be administered if a positive mannan/anti-mannan or BDG or PCR test result is present
French consensus [49]	In severe peritonitis (community-acquired or postoperative), in the presence of at least three of the following criteria: hemodynamic failure, female gender, upper gastrointestinal surgery, antibiotic therapy for more than 48 h In healthcare-associated intra-abdominal infection when a yeast is detected on direct examination In all cases of healthcare-associated IAI in which peritoneal fluid culture (apart from closed suction drains and drainage systems, etc.) is positive for yeasts
	Not recommended for patients with community-acquired intra-abdominal infections in the absence of signs of severity

19.3.8 Adequate Dose of Antifungal Therapy

Recent data assessing plasma concentrations of fluconazole and echinocandins have suggested that trough concentrations are highly variable and could be quite low in ICU patients [54, 55]. The peritoneal concentrations of antifungal agents have rarely been determined. A peritoneal fluid/plasma ratio of 0.3 and a median (interquartile ratio IQR) maximal peritoneal concentration of 0.9 (0.6–1.5) mg/L were observed between 5 and 8 h after the start of micafungin infusion [55]. Surprisingly, no data are available regarding the peritoneal diffusion of fluconazole in patients with peritonitis. Overall, the daily dose of fluconazole should be considered cautiously, especially in patients with renal replacement therapy, in whom daily doses higher than 200 mg may be required [54].

19.3.9 De-escalation of Antifungal Therapy

De-escalation of empiric antifungal therapy is a safe procedure as recently illustrated in two studies. A multicenter prospective observational study analyzed 158 ICU patients receiving systemic antifungal therapy for documented or suspected

intra-abdominal candidiasis [15]. Antifungal therapy was fairly rapidly (after 3–5 days) modified in 42% of cases, including de-escalation in 49 (31%) patients, and escalation in 16 (10%) patients. The SOFA score at D7 after antifungal initiation was similar in patients who underwent de-escalation and those who did not (3 [2;5.75] versus 3.5 [1;6], respectively, $p = 0.529$). In a study based on 206 patients with healthcare-associated intra-abdominal infections, de-escalation was performed in 53% of cases, including de-escalation of antifungal agents in 49% of the cases receiving antifungal therapy [56]. De-escalation was not a risk factor for mortality on multivariate analysis. These results suggest that antifungal de-escalation may be safe in these patients.

19.3.10 Duration of Antifungal Therapy

The adequate duration of antifungal therapy for patients with CP has not been established. The IDSA guidelines provided recommendations for patients with fungal cIAI, but no clear recommendations for duration of therapy [25]. Similarly, ESCMID guidelines did not specifically address intra-abdominal candidiasis [21]. French experts recommended a duration of antibacterial therapy of 7–15 days for severe bacterial healthcare-associated intra-abdominal infections [49]. Due to the high rates of recurrence and relapse in intra-abdominal candidiasis, experts recommended longer durations of therapy, around 2–3 weeks [57]. In recent observational studies, patients received antifungal therapy for 17 days (median, IQR 13–21) in a multicenter prospective study [15] and 14 (range: 1–88) days in a single-center retrospective analysis [14].

Conclusions

Despite progress in the understanding of the mechanisms driving intra-abdominal candidiasis, the diagnosis and decision-making process for this disease remain highly complex. The physician in charge of a patient with suspected intra-abdominal candidiasis remains torn between over-response with ecological and financial issues and delayed therapy with life-threatening complications. The next goal to achieve will be to find rapid response tools for differentiating colonization from infection allowing early initiation of antifungal therapy.

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The Value and Interpretation of Microbiological Specimens in the Management of cIAI

20

Warren Lowman

"There is nothing more deceptive than an obvious fact".
Sherlock Holmes, in Arthur Conan Doyle: The Boscombe Valley Mystery

Sir Arthur Conan Doyle put it to us through his fictional master of observation and deduction yet we remain deceived. In the context of complicated intra-abdominal infections (cIAI) the fact is we are dealing with a diverse and complicated ecosystem of micro-organisms, a world we are only recently beginning to understand. The complexity of this ecosystem confounds us in managing patients with cIAI because we do not fully appreciate the microbial milieu and its impact on a healthy gut. Yet we blindly throw antimicrobials at patients in abundance, hoping to clear the offending pathogen(s). We need to understand the role of the microbe(s) in this complex interaction and to do this we need to identify the microbe(s) involved. This coupled with advances in microbial identification, the escalation of multidrug resistant organisms (MDRO), and the difficulty in identifying patients at risk of harboring MDRO make the appropriate collection of microbiological specimens of paramount importance.

20.1 Microbial epidemiology of cIAI

Many studies have sought to establish the microbiological epidemiology of cIAI, and similar trends have emerged from these various studies. Table 20.1 highlights the data from recent multicentre surveillance studies, and in summary the salient findings are:

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Table 20.1 The global microbial epidemiology of cIAI—multicentre surveillance studies from 2002–2014

Region	Period	No. and type of micro-organisms	Patient type	Clinical breakpoint guidelines	HAI vs CAI	ESBL rates	Agents not included	Ref.
Middle East and Africa	2007–2012	255 Isolates *E. coli*—*72* *Klebsiella* spp.—*53*	Adult and paediatric	CLSI	NC	11.4% *E. coli 36%* *Klebsiella* spp. *45%*	Ertapenem and imipenem	[1]
China	2002–2011	*E. coli*—*3074* *K. pneumoniae*—*1025*	Adult and paediatric	CLSI	Yes	*E. coli* CAI[a]: 19.1–61.6% HAI[a]: 52.2–70%	Meropenem and tigecycline	[2]
Vietnam	2009–2011	905 isolates *E. coli*—*697* *K. pneumoniae*—*129*	Adult and paediatric	CLSI	NC	46.7% *E. coli* 48.1% *K. pneumoniae* 39.5%	Meropenem and tigecycline	[3]
Latin America	2008–2012	*K. pneumoniae*—1511	Adult and paediatric	CLSI	NC	42%	Meropenem and tigecycline	[4]
Europe	2011–2014	1259 isolates *E. coli*—819 *P. aeruginosa*—133	Paediatric	EUCAST	Yes	*E. coli* CAI: 5.5% *E. coli* HAI: 10.7% *K. pneumoniae* CAI: 18.2% *K. pneumoniae* HAI: 39%	Meropenem and tigecycline	[5]
United States	2011	1442 isolates *E. coli*—516 *K. pneumoniae*—268	Adult and paediatric	CLSI	NC	10.7% *E. coli* 9.7% *K. pneumoniae* 12.7%	Meropenem and tigecycline	[6]

United States	2012–2013	1285 isolates *E. coli*—434 *K. pneumoniae*—231	Adult and Paediatric	CLSI	Only HAI	11.9% *E. coli* 8.9% *K. pneumoniae* 17.3%	Meropenem and tigecycline	[7]
Global	2012–2013	1330 isolates[b] *E. coli*—548 *Enterococcus* spp.—211 *K. pneumoniae*—140	Adult and paediatric	EUCAST and CLSI	Yes	*E. coli* CAI: 12.3% *E. coli* HAI: 20.7% *K. pneumoniae* CAI: 10.5% *K. pneumoniae* HAI: 42.9%	Not reported	[8]

The majority of these studies follow the SMART surveillance system methodology and are thus directly comparable (Refs. [2–7])
HAI hospital-acquired infection, *CAI* community-acquired infection, *ESBL* extended-spectrum ß-lactamase, *NC* not categorized
[a]Range given as this was a 10-year surveillance study with varying rates over the study period
[b]Initial intraperitoneal specimens collected from 1190 patients; excludes subsequent samples

(1) *Enterobacteriaceae* predominate, specifically, in descending order, *E. coli* and *Klebsiella pneumoniae*.

(2) Extended spectrum ß-lactamase (ESBL)—producing isolates are predominantly found in the two aforementioned isolates.

(3) ESBL rates vary regionally but collectively for *E. coli*, and *K. pneumoniae* rates are greater than 10% (range: 10.7–46.7%).

(4) The distinction between community-acquired (CA) and hospital-acquired (HA) still remains relevant given the higher risk of MDRO in the setting of HA-cIAI.

(5) A marked increase in carbapenem resistance in *Enterobacteriaceae* compared with surveillance data from the turn of the millennium [1–7].

Pseudomonas aeruginosa, Candida species and enterococci are less common pathogens but should always be considered in the context of HA-cIAI and protracted infections, e.g. tertiary peritonitis. These observations are supported by the largest multicentre study to date examining the epidemiological profile of cIAI, the CIAOW study [8]. This study evaluated intraperitoneal specimens from 1190 patients worldwide and demonstrated the prevalence of micro-organisms associated with cIAI, in descending order, as follows: (1) *Enterobacteriaceae*, (2) *Enterococcus* species, (3) anaerobes, (4) *Candida* species and (5) *Pseudomonas aeruginosa.* The ESBL rate for *E. coli* and *Klebsiella* species was 16.9% and 21.4%, respectively, with higher rates for both in patients with HA-cIAI.

20.1.1 Contextualization of Surveillance Studies

Surveillance studies of this nature suffer from some specific limitations, and it is important to contextualize the findings. Firstly, many are industry-driven, and thus specific predefined objectives relevant to targeted antimicrobial agents are incorporated into the methodology. This does not make the data inaccurate or irrelevant but rather less comprehensive. The omission of certain antimicrobial agents means that the full armamentarium of agents for management of cIAI is not assessed, and thus we are often left wondering if and what the relationships are between certain phenotypes and agents. An example is the SMART (Study for Monitoring Antimicrobial Resistance Trends) surveillance system which was initiated in 2002 and continues to deliver excellent global surveillance data on pathogens involved in cIAI and the activity of antimicrobial agents used to treat these pathogens. SMART surveillance studies are funded by Merck & Co., and all follow a very standardized method which allows for comparison over time with trend analysis of resistance rates. However, the omission of certain key antimicrobial agents like meropenem and tigecycline does not allow for adequate comparison of different carbapenem susceptibilities and the relationship between various MDRO and tigecycline susceptibility, respectively. Similarly, the Tigecycline Evaluation and Surveillance Trial (TEST) programme funded by Pfizer Inc. does not include meropenem or ertapenem. Secondly, many of these studies do not distinguish between community-acquired and hospital-acquired infections. The basis for many of these studies is isolate submission to a central testing facility so the clinical relationship of the

isolate is limited to patients having an IAI. This applies even to those studies that do categorize into CA and HA, as this is usually done on the basis of the widely accepted 48 h rule. It thus becomes evident that the surveillance data essentially gives a very broad picture of what pathogens are involved in cIAI but does not allow for sufficient stratification into what micro-organisms are involved with specific types of cIAI and what specific risk factors are associated with MDRO. At a patient level, it means that the ability to choose an appropriate empiric antimicrobial agent is compromised and that without targeted culture it will remain best "guesstimate" work.

It is largely accepted that the need to send specimens for microscopy, culture and susceptibility (MC&S) testing should be confined to patients with HA-cIAI or patients at risk of harbouring MDRO. Although in essence I would agree with this in the context of uncomplicated IAI (especially in situations where source control is the primary management tool, and antimicrobials are merely ancillary and in some cases not even necessary, e.g. uncomplicated appendicitis), in cIAI there are caveats to this. These caveats are based largely on the preceding discussion around the limitations of current surveillance data. Firstly, the regional differences in rates of resistance mandate knowing specifically what is happening in the context of your own practice. This requires local data, data that is unlikely to be readily available in the form of a publication, and thus establishment of a localized (site/hospital-specific) antibiogram is essential. This can only be achieved through regular submission of specimens and frequent analysis of cumulative antibiogram data. Secondly, ESBL rates in CA-cIAI can be as high as 61.6%, as reported in China [2]. In a European paediatric population, the *K. pneumoniae* ESBL rate in CA-cIAI was reported as 18.2% [5]. Thirdly, although risk factors for MDRO are well established, they lack specificity, and considering the varied MDRO that are now prevalent, it becomes impossible to discern without MC&S. I would thus advocate, especially in the absence of robust localized surveillance and antibiogram data, submission of specimens for MC&S in all patients with cIAI.

20.1.2 Indicator Micro-organisms Requiring Special Consideration

Apart from Gram-negative bacilli (*Enterobacteriaceae* and *P. aeruginosa*) and enterococci which usually predominate as bacterial pathogens in cIAI, there are a number of other pathogens involved. A few of these deserve special mention due to particular clinical or pathogenetic peculiarities that impact on management.

20.1.2.1 *Candida*

An important consideration in the management of cIAI is that of fungal infection, primarily *Candida* species. Intra-abdominal candidiasis is associated with high mortality [9], and thus empiric antifungal regimens are often used in the management of cIAI. Furthermore, early source control and directed antifungal treatment are important in reducing mortality [10]. Fungal epidemiology of cIAI is not

particularly well described and is infrequently isolated, with only 6.4% of all isolates in the CIAOW study being yeasts [8]. This rate increased slightly to 8.9% in the subset of follow-up peritoneal samples suggesting an association with more complex HA-cIAI. The distribution of *Candida* species involved in cIAI is also not well studied, but the common species appear to predominate, with *C. albicans* rates ranging from 57% to 77% [8–10]**.** The emergence of new *Candida* species such as *C. auris* and increasing multidrug resistance in *Candida* species [11] has meant that definitive diagnosis and management of intra-abdominal candidiasis necessitates submission of microbiological samples for MC&S. It is imperative that local epidemiology of *Candida* species is well understood as the prevalence of different species can vary from unit to unit.

20.1.2.2 *Streptococcus bovis* Group

The *Streptococcus bovis* group has undergone extensive taxonomic revisions in the last decade and now includes a number of species and subspecies. These group D streptococci are natural inhabitants of the bowel of vertebrates causing disease in many animals. An important consideration in the context of human disease and cIAI is the isolation of *Streptococcus gallolyticus* subsp. *gallolyticus* which has a strong association with colorectal carcinoma [12]. A number of studies have demonstrated an association between invasive disease (bacteraemia, meningitis and endocarditis) due to this micro-organism and colonic neoplasia. Similarly *S. gallolyticus* subsp. *pasteurianus* has also been more commonly found in patients with gastrointestinal malignancies. Thus, isolation of any group D streptococcus reported as *S. bovis* should ideally be speciated further to interpret its significance in the clinical context. A clinically significant isolation of *S. bovis*/group D streptococcus/*S. gallolyticus* warrants further investigation of the patient for a possible gastrointestinal malignancy.

20.1.2.3 *Streptococcus anginosus* Group

The *Streptococcus anginosus* group, previously termed *S. milleri*, is also an important indicator organism as it has the propensity to behave like other pyogenic streptococci and form abscesses. The *S. anginosus* group is subdivided into three species: *S. anginosus, S. constellatus and S. intermedius*. These are further subdivided into subspecies but all are natural inhabitants of the human oral cavity and thus may be isolated from a variety of clinical specimens [12]. In the context of cIAI, isolation of one of these streptococci should prompt investigation for a possible localized abscess.

20.1.2.4 Anaerobic Bacteria

Anaerobes (Gram positive and Gram negative) are important pathogens in cIAI as they often form part of the polymicrobial milieu associated with many of these infections. The relative infrequency of isolation probably has more to do with issues of specimen collection and transport (see below, section on specimen collection); nevertheless, they remain important especially in the colon where anaerobic bacteria exceed all other bacteria by a factor of 10^2-10^3 [13]. Gram-negative bacilli, in

particular *Bacteroides* species, predominate, and resistance in this group is generally higher [8, 14]. It has also been demonstrated that resistance rates in the non-*B. fragilis* group is usually higher than in the *B. fragilis* group [15]. In instances of poor clinical response (where an agent with anti-anaerobic activity is being utilized), it thus becomes important and useful to speciate these organisms further. Additionally there are specific associations with anaerobic bacteria: (1) *Clostridium* species and gas gangrene, (2) *Clostridium difficile* and antibiotic-associated diarrhoea and (3) *Actinomyces* species and abscesses or suppurative draining sinus tract lesions. As alluded to above, antimicrobial therapy is often not specifically directed at these isolates, especially when part of a polymicrobial infection, and thus it is important to be aware of the anaerobic activity of agents commonly used in the treatment of cIAI (see below, section on interpretation AST). Few studies have systematically addressed the issue of resistance in anaerobic bacteria, and current treatment regimens are usually empiric, based on the acceptance that there is anaerobic activity of the agent rather than susceptibility. This arises in part because of the difficulty in performing antimicrobial susceptibility testing (AST) of anaerobes [16]. A survey performed in the early 2000s of microbiology laboratories in the USA highlighted that whilst 89% performed culture, only one in five laboratories performed AST [17]. There is, however, clinical data to link poor clinical response with inappropriate anaerobic therapy; thus, it would seem prudent to monitor resistance in anaerobes at local, regional and national levels. Current surveillance data suggests that there are emerging patterns of resistance with multidrug resistant strains of the *Bacteroides fragilis* group circulating [14].

20.1.2.5 *Salmonella* Species and Other Bacteria Causing Enteric Fever-Like Syndromes

Salmonella species deserve special mention given the classic syndrome of enteric fever and the important distinction between typhoidal and non-typhoidal *Salmonella,* both of which can present with gastrointestinal surgical complications. Enteric fever is typically caused by ingestion of *Salmonella* serovar Typhi or Paratyphi, and complications include gastrointestinal bleeding, abscess formation and intestinal perforation. Isolation of this micro-organism and establishment as the cause of disease is important from a management perspective, both at an individual level and public health level. Non-typhoidal *Salmonella* species can also cause enteric fever and are not exclusively carried by humans, with transmission usually through contamination of food by animal excreta. An important association is that of invasive non-typhoidal salmonellosis and HIV infection, especially in sub-Saharan Africa. In African adults, >95% of cases have been associated with HIV infection [18]. Thus, in this setting, isolation of a non-typhoidal *Salmonella* species mandates further investigation for HIV. Recurrent salmonellosis also requires further workup to exclude possible occult sources of infection, e.g. endovascular and biliary. Other bacteria that cause an enteric fever-like syndrome include *Yersinia enterocolitica*, *Yersinia pseudotuberculosis* and *Campylobacter* species [19]. Enteric fever is more commonly diagnosed through isolation of the causative bacterium from blood cultures, an important diagnostic consideration (see below).

There are a number of other specific micro-organisms associated with various cIAI presentations, and these may require specialized diagnostics and/or treatment. In these instances, a high degree of clinical suspicion and consultation with an infectious disease specialist or clinical microbiologist may be warranted. Examples include parasites, specifically intestinal nematode- and helminth-related infections and mycobacterial and fungal infections of the GIT. These are usually initially diagnosed histologically from tissue samples, but definitive microbiological diagnosis often remains elusive if no tissue is submitted for culture. This highlights the importance of submitting a tissue specimen for microbiological MC&S together with the sample for histology.

It must be borne in mind that almost any gut commensal can be associated with cIAI, as can any potentially pathogenic organism that may gain access to the gastrointestinal tract through procedure or device. Thus, isolation of any bacterium from a clinically relevant GIT specimen must be carefully considered.

20.2 Specimen Collection and Processing

The value derived from microbiological sampling of any site follows the simple principle of "rubbish in = rubbish out". In our current state of symbiosis with our own microbiome, it is often considered, "Who parasitizes who?" A microbiological sample provides a snapshot of the multitude of living micro-organisms that coinhabit every crevice of our anatomy. Therefore it is imperative to sample the most representative site of the disease process when trying to establish microbial aetiology. Considering that the majority of cIAI are attributable to endogenous flora, this becomes a very critical step in management of patients. The isolation of a micro-organism essentially has no bearing unless the site sampled is reflective of the disease process.

In the context of cIAI, the most commonly submitted specimens are fluids/pus from aspirates and tissue. Table 20.2 outlines the specific criteria and guidelines associated with each sample type [20]. The submission of swabs should generally be discouraged although there are relatively few indications for submission. The main drawback to swabs is that they are often not representative of the disease process and may reflect colonization only. Swabs are also very limited in terms of the repertoire of testing that can be performed. For example, they are inappropriate for anaerobic culture, fungal culture or where more than one type of culture is requested (both aerobic and fungal). In general, the principle for cIAI should be that if fluid/pus or tissue is available, it should always take preference over a swab.

20.2.1 Aspirates

Aspirates are appropriate for any fluid collection and are usually deposited in a sterile container for further testing. If anaerobic bacteria are specifically being considered, then a suitable anaerobic container/transport medium is required. This needs to be specifically requested from the microbiology laboratory. Increasingly

Table 20.2 Prerequisites for specimen types in microbiological diagnostics

Specimen type	Sampling recommendations	Transport	Comments
Swabs	– Avoid touching noninvolved surfaces – Only use when tissue or aspirates/fluid cannot be collected – Roll over affected area with pressure to maximize adsorption	– Generally require transport medium to enhance recovery and prevent desiccation	– Flocked swabs can improve yield – Swabs are limited in terms of yield: not recommended for anaerobic or fungal cultures
Aspirates	– Disinfect overlying skin/surface with 70% alcohol and chlorhexidine preparation – Submit as much fluid as possible (>1 ml)	– Sterile transport container – Inoculate blood culture bottles with fluid (1–10 ml); useful for recovery of anaerobes	– Do not inoculate frank pus into blood culture bottles – Do not submit a swab dipped in a fluid aspirate
Tissue	– Disinfect overlying skin/surface with 70% alcohol and chlorhexidine preparation – Use fresh sterile scalpel, after surface incision is made, for sampling of infected site – Submit at least 1 ml/1 g of tissue; for quantitative cultures 1cm^3	– Submit in sterile container with tight-fitting lid – Instil few drops of sterile saline to keep tissue moist – For anaerobic culture, use anaerobic transport vial	– Do not disturb the integrity of the tissue sampled Do not add formalin to microbiological tissue samples

Formulated and adapted from Ref. 20

the value of blood culture bottles is becoming evident for submission of aspirates [21]. Recovery of micro-organisms from blood culture bottles is faster than conventional media and can also potentially eliminate false negatives where patients are on antimicrobials which may suppress growth, thus enhancing yield [22]. There is a wide variety of blood culture bottles available, and some include resin or charcoal to bind any inhibitors such as antimicrobial agents. The advantage of the modern-day blood culture system is that it is highly automated, it can detect low numbers of micro-organisms and it is less prone to contamination when collected appropriately. It is recommended to inoculate blood culture bottles with 1–10 ml of fluid/aspirate but not abscess contents or frank pus [21, 22]. There are a variety of suppliers, and if used it is important to familiarize oneself with the specific bottle types (different for aerobic and anaerobic cultures) that may be available.

20.2.2 Blood Cultures

Blood cultures as a distinct entity should not be ignored as they can add immense value to the management of cIAI, especially in patients with bacteraemic disease. The 2010 IDSA guidelines on diagnosis and management of cIAI blood cultures do

not routinely recommend blood cultures as an adjunct to diagnosis due to low rates of bacteraemia and in the setting of CA-cIAI are often not useful from a management perspective [21]. However, the secondary seeding of bacteria to the bloodstream allows for a unique opportunity to establish a microbial aetiology prior to performing a definitive surgical procedure or whilst awaiting culture results from intra-operative specimens. It thus becomes reasonable to submit blood cultures in any patient who presents with features of sepsis, according to the revised definitions of sepsis, and where sepsis as an entity mandates the submission of blood cultures [23]. Submission of two to three sets of blood cultures, the first prior to administration of any antimicrobial agent, is essential in the workup of a septic patient. The volume of blood drawn has been shown to be the most crucial determinant of yield, and thus multiple sets of adequate volume (20–30 ml in adults; 1–5 ml paediatrics) are usually required [24, 25]. In the context of cIAI, blood cultures should ideally include submission of both aerobic and anaerobic culture bottles. In patients who have already received a dose of antimicrobial, or are on existing treatment, it is imperative that blood cultures with a binding agent are utilized. It is of particular importance when considering the information that blood cultures provide when specific bacteria are isolated (e.g. *Salmonella* species and *S. bovis* group; see above).

20.3 Interpretation of Microscopy, Culture and Susceptibility Results

When interpreting an MC&S result, clinical contextualization is imperative. As stated above, the value of the result is entirely dependent on the integrity of the specimen. Good-quality, representative samples are of immense value in managing patients. The most crucial information relates to the susceptibility testing, and there are a number of issues to consider in this regard. However, in order of sequence of events, the microscopy is performed first and provides the first indication of microbial aetiology.

20.3.1 Microscopy

Amongst the most important clues to be garnered from microscopy is whether fungi are involved, and the presence of yeasts in a sample would provide support for empiric antifungal cover [21]. The presence of parasites may also be detected through microscopy although this is usually accompanied by a distinct clinical entity where suspicion of a parasitic infection may already be high, e.g. amoebic liver abscess.

20.3.2 Culture

The process of culture, i.e. what general and selective media to use, what atmospheric conditions to incubate cultures at, etc., is largely determined by the laboratory and would usually follow recommended guidelines for processing of specific sample

types. When a specific microbiological diagnosis is suspected or actively being pursued, it is best to liaise with the laboratory to facilitate the process as this may involve use of special/additional stains and media and/or different incubation conditions. A common example would be mycobacteria or *Nocardia* species where a special stain (acid-fast stains) can be applied. The laboratory relies entirely on the clinical information supplied; thus, it is crucial to be specific and provide as much detail as possible.

20.3.3 Susceptibility

Antimicrobial susceptibility testing (AST) performed by the laboratory would usually follow one of two guidelines, the European Committee on AST (EUCAST) or the Clinical & Laboratory Standards Institute (CLSI). These guidelines are updated annually and provide guidance on how to perform AST, what antimicrobials to test for specific micro-organisms and how to interpret these results. It is important to realize that laboratories cannot test all relevant antimicrobials because of practical and financial constraints. Thus, clinically relevant antimicrobials are chosen to be included in panels which then encompass the various organism groups, e.g. Gram negative, Gram positive, anaerobic, and fungi. Panels are also stratified by specific specimen types, e.g. urine, blood culture, etc., as certain antimicrobials are not relevant for the treatment of specific types of infections, e.g. daptomycin would not be tested on lower respiratory tract specimens as daptomycin is inactivated by surfactant and thus not appropriate for treatment of pneumonia. The choice of antimicrobials will vary widely and is usually guided by local requirements depending on what AST systems are available, what antimicrobials are available for clinical use and what guidelines are being utilized.

Nevertheless there are always certain antimicrobials that may be omitted but are clinically relevant for a particular organism/infection type. In this case, either inference is needed or additional AST would have to be requested. A classic example of inferring results is that of *S. aureus*, which when susceptible to oxacillin/cefoxitin (i.e. a methicillin susceptible *S. aureus* [MSSA]) is considered susceptible to all ß-lactam agents. Yet laboratories would usually report as susceptible to cloxacillin/nafcillin and may not routinely report susceptibility to cephalosporins or carbapenems; this must be inferred from the cloxacillin susceptibility. This is in essence an example of a class effect, where one antimicrobial in the class is tested and the susceptibility of other agents in the same class can be inferred from the result of the one. Some inferences related to micro-organisms commonly involved in cIAI are shown in Table 20.3. A contentious issue of implied results and inferring susceptibility relates to that of ESBL detection. In the past, it was considered the norm to modify extended-spectrum cephalosporin results to resistant upon detection of an ESBL phenotype, irrespective of the actual AST results. The revision (lowering) of the cephalosporin breakpoints by both EUCAST and CLSI has meant that this practice is no longer relevant as the breakpoints will now reliably detect clinically relevant resistance in this class of antimicrobials. It is now recommended to report the cephalosporin AST results as is irrespective of phenotype [26, 27]. Similarly, the ß-lactam-ß-lactamase inhibitor (BLBLI) combinations, e.g. amoxicillin-clavulanic acid and

Table 20.3 Interpreting AST reports and the inferences based on selected antimicrobials

Micro-organism	Reported antimicrobial result	Inference
Enterococcus faecalis	Ampicillin susceptible	Piperacillin-tazobactam susceptible Imipenem susceptible (CLSI only, EUCAST specifies a breakpoint)
Enterobacteriaceae	Ciprofloxacin or levofloxacin resistant	Class effect: resistance/reduced susceptibility to one implies resistance to the other
Staphylococcus aureus	Cefoxitin/oxacillin resistant	Resistant to all ß-lactams with exception of fifth-generation cephalosporins (ceftaroline/ceftobiprole)
	Cefoxitin/oxacillin susceptible	Susceptible to all BLBLI, cephalosporins and carbapenems
Anaerobic GNB	May not be routinely reported on and AST is often not standardized	BLBLI, carbapenems and tigecycline generally have good anti-anaerobic activity[a]

BLBLI ß-lactam ß-lactamase inhibitor, i.e. amoxicillin-clavulanic acid, piperacillin-tazobactam
[a]These agents are often used as part of a treatment regimen in cIAI because of aerobic Gram-negative cover but may not be routinely reported on anaerobic isolates; if used it may not be necessary to add an additional anti-anaerobic agent

piperacillin-tazobactam, should be reported as tested (EUCAST). The ß-lactamase inhibitors clavulanic acid and tazobactam have inherent activity against ESBL enzymes, and there is now considerable clinical data to support the use of these agents in the treatment of infections, including bacteraemia, caused by these micro-organisms [28]. This issue remains contentious from a clinical perspective as there is conflicting data, but the important point is that the laboratory should allow for a choice and not simply report as resistant [29]. This practice has led to an over-reliance on carbapenems which have reflexively been used in the treatment of ESBLs, a practice which is thought to have contributed to the rise of carbapenemase-producing *Enterobacteriaceae* (CPE). Antimicrobial prescription must be guided by appropriate AST which allows for more tailored therapy according to site and type of infection. It is important to be aware and understand local practices of AST and reporting so that informed clinical decisions can be made.

In the context of MDRO and extensively drug-resistant (XDR) micro-organisms, an additional consideration related to AST is that of site-specific breakpoints. Antimicrobial choices are often limited in this context, and the choice of agent needs to take into consideration the pharmacokinetic and pharmacodynamic parameters associated with that particular agent. The breakpoint development process unfortunately largely ignores the issue of drug levels at the particular site of infection, and most breakpoints are developed based on achievable serum levels. An exception is meningitis where different breakpoints do exist for meningeal isolates. In the context of cIAI, site-specific tissue levels are crucial and must be considered when treating MDR or XDR isolates. Thus, the reporting of resistant may not be sufficient and an actual MIC value may be required. A good example is the case of carbapenems,

where the current susceptible breakpoint for meropenem is ≤2 μg/ml and ≤1 μg/ml for EUCAST and CLSI, respectively. However, the MICs to meropenem for many CPE isolates are in the region of 2–16 μg/ml, and pharmacological studies have demonstrated that serum levels well in excess of 2 μg/ml can be achieved with optimized dosing regimens [30]. This has also translated into positive clinical response when treating CPE-associated infections with carbapenems [31–34]. This observation is relevant to cIAI when considering the tissue penetration of agents such as piperacillin-tazobactam in the biliary tree and tigecycline in the colon, where concentrations are a significant order of magnitude above the current susceptible clinical breakpoints [35, 36]. The importance of pharmacokinetics and pharmacodynamics in the setting of clinical breakpoints has been extensively reviewed, and future work into the development of site-specific clinical breakpoints is an important strategy to prolong the longevity of our current antimicrobial armamentarium [37].

20.3.3.1 How to Select an Appropriate Antimicrobial Agent?

From a clinical perspective when confronted with a list of antimicrobials on an AST report, and there are a number of choices available, it is important to select the most appropriate agent based on the type of infection, the micro-organism isolated, the pharmacokinetics of the agent and the risk of adverse events. Pharmacodynamic parameters are also relevant and become even more important when considering the actual dose and method/frequency of administration (see elsewhere, chapter dosing). What is crucial to understand though is that not every "S" (susceptible) on the report is equivalent. As mentioned above, the "S" on the report is a translation of the MIC, which, although less than or equal to the susceptible MIC breakpoint value, does not give an actual MIC value. The DALI study has clearly demonstrated the importance of MIC values where it has been shown that critically ill patients treated with a ß-lactam are 2.3 times more likely to have a positive outcome if the MIC of the pathogen is ≤2 μg/ml [38]. This can be translated back to the relationship between clinical outcome and optimization of pharmacodynamic parameters, where the pharmacodynamic parameter of any antimicrobial agent is inextricably linked to the MIC. Thus, generally speaking, antimicrobial agents with MICs that are an order of magnitude lower than the susceptible breakpoint would be preferable to an agent that is susceptible but has an MIC on the breakpoint. An example to illustrate this point would be the case of a *Klebsiella pneumoniae* isolate that is reported as susceptible to the aminoglycosides, gentamicin and tobramycin. However, the gentamicin MIC is 0.25 μg/ml and the tobramycin MIC is 2 μg/ml. Both are considered susceptible using current EUCAST or CLSI breakpoints. Aminoglycosides are concentration-dependent agents, and thus the higher the serum/tissue concentration above the MIC (C_{max}:MIC), the better the antimicrobial activity. The gentamicin MIC is three- to twofold dilutions lower, and thus at similar dosing regimens, one would expect to achieve a C_{max}:MIC ratio of greater than 10 with greater likelihood using gentamicin over tobramycin. The issue of MIC-directed therapy becomes far more pertinent in the setting of difficult-to-treat/complicated infections, critically ill patients and MDRO/XDR micro-organisms.

Table 20.4 Principles in considering what antimicrobial agent to choose according to provided antibiogram

Duplicity in spectrum of cover	The polymicrobial nature of cIAI often results in use of multiple antimicrobials. The spectrum of an agent must be considered in terms of its Gram-negative, Gram-positive and anaerobic cover. Where a single agent can be used to cover all isolates, this is preferable
All susceptible results are not created equal	Where MICs are available or there is local data on MIC_{50} and MIC_{90} cumulative susceptibility, the choice of agent should take this into account to maximize the probability of optimizing pharmacodynamic parameters
Distribution and penetration to the site of infection	Tissue penetration is critical in optimizing pharmacodynamic exposures, especially in the context of MDRO
Foreign body in situ and definitive source control, i.e. removal is not an option	Agents with anti-biofilm activity are preferable in this setting and should be used in combination
Pathogen-directed therapy	Consider whether there may be a particular drug that is more "potent" than another for a specific pathogen
Implications of antimicrobial side effects	In the setting of existing problems, try avoid agents that may compound the problem, e.g. use of aminoglycosides in patient with existing renal dysfunction

Additionally when assessing the options, it is worthwhile considering the distribution and penetration of antimicrobials to the site of infection. This differs between agents and can influence the choice of agent. The inherent activity of certain antimicrobials against specific pathogens is also a factor to consider, and in terms of potency, one agent may be preferable to another, e.g. treatment of MSSA with a ß-lactam versus a glycopeptide [39]. Factors such as anti-biofilm activity should also be considered where foreign objects or devices are in situ, and an agent that is active against biofilm is required. In cIAI the polymicrobial nature of many infections must always be considered, and thus despite the actual MC&S result, cognizance of the potential role of uncultured isolates must be maintained. This primarily refers to anaerobes, and therefore the anti-anaerobic spectrum of activity of each agent should be considered (refer Table 20.3). Lastly one must consider the adverse effects of antimicrobials, which are largely ignored due to the generally safe profile of most agents. Many antimicrobial agents cause gastrointestinal disturbances themselves, nausea and vomiting being the commonest. However, in the setting of pre-existing renal dysfunction, hepatic dysfunction and bone marrow suppression, there are a number of agents that must be carefully assessed, and if used necessary dose adjustments made. If an alternative agent that meets all other criteria exists, then rather use that agent. Table 20.4 summarizes the salient points in interpreting an antibiogram and deciding which antimicrobial to use. It is evident that the choice of antimicrobial requires careful consideration, and when faced with a laboratory report, there is a significant amount of thought that needs to go into deciding which of the reported agents should be used for that patient. This decision-making process allows for more tailored, patient-specific therapy, an approach that aligns itself with the global movement of antimicrobial stewardship.

The management of cIAI is a complex entity, requiring a combined surgical and chemotherapeutic approach. The surgery itself is a critical component; not only does it allow for source control, it also provides a unique opportunity to sample appropriately which ultimately guides the medical management. It is this sampling process, with subsequent microbiological testing from which we gather all the facts and which determines the future course. It is thus fitting that we seek to gather all the evidence in managing these patients, so that we do not continue to be deceived:

> *"It is a capital mistake to theorise before you have all the evidence. It biases the judgment"*.
> Arthur Conan Doyle: Sherlock Holmes, in *A Study in Scarlet*

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Appropriate Antimicrobial Therapy in Critically Ill Patients

21

Fekade B. Sime and Jason A. Roberts

21.1 Introduction

Beyond the selection of the most suitable agent(s), appropriate antimicrobial therapy should ensure adequacy of dosing to ensure maximal patient outcomes. Guidelines are available to aid appropriate selection of agents for most of the commonly encountered infections, including complicated intraabdominal infections, and consider the epidemiology of pathogens at the geographical locality, source of infection, type of infection and patient population [1, 2]. Treatment guidelines also provide dosing recommendation which are usually universal for most target patient populations except some attempts of due consideration for patients with special dosing needs such as the paediatrics and those with renal or hepatic impairment. Such dosing considerations are however based on gross categorisation for ease of clinical application, for example, dosing based on mild, moderate and severe renal impairment. Although such an approach in guidelines appears adequate for stable patient, in special patient population such as the critically ill where there is highly

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unpredictable pharmacokinetic alteration, standard recommendation frequently fails to meet the dosing targets [3, 4]. In some ways, it is understandable why guidelines err on the side of simplicity, but in contemporary medicine, it is likely that a more individualised approach to dosing will result in improved patient outcomes.

An appropriate dosing regimen of antimicrobials is required to achieve therapeutic concentrations at the site of infection such that exposure of the etiologic organisms to bactericidal concentrations achieves rapid resolution of infection. To achieve this goal, dosing regimens may need to be tailored based on the antibacterial kill characteristics. Some antibiotics (so-called time dependent) require prolonged time of exposure of the free drug concentrations above the minimum inhibitory concentration (MIC) of the pathogen, $fT_{>MIC}$ [5], for some antibiotics the peak (maximum) concentration relative to the MIC (C_{max}/MIC) best relates exposure to bacterial killing (termed concentration dependent) [6], and for others the magnitude of exposure over time relative to the MIC described by ratio of area under the concentration time curve to MIC (AUC/MIC) relates to bacterial killing and/or efficacy [7]. Importantly, different strategies may be necessary for each type of kill characteristics when designing or optimising dosing regimens [3].

Equally important is the understanding the physiologic and pathologic factors that affect the relationship between the administered dose and exposure. Marked changes in physiologic phenomena that govern drug disposition occur in severely ill patients such as those with intraabdominal sepsis altering antibiotic exposure from conventional dosing regimens [8]. To the challenge of clinicians, critical illness-driven derangements in dose-exposure relationships are hardly predictable making it difficult to define dosing requirements based on the usual dose-finding studies that are performed in noncritically ill patients. Regardless, there is a widespread use of the dosing regimens validated in noncritically ill patients, which potentially contributes to the significant failure rates of antimicrobial therapy in critically ill patients. Increasing evidence from clinical studies suggests that suboptimal exposure frequently occurs compromising treatment outcomes and risking emergence of resistance or reduces susceptibility of pathogens [9].

Indeed there has been a reduction in the susceptibility of pathogens implicated in complicated intraabdominal infections that led to recent efforts to develop novel drug for this condition [10]. However, despite the accumulating evidence in support of special dosing considerations in the critically ill, the ongoing introduction of new agents is not based on adequate clinical data that confirm appropriateness of suggested dosing regimens. For example, the novel agents ceftolozane-tazobactam [11] and eravacycline [12] are being considered/developed for the treatment of complicated intraabdominal infections, although there is yet inadequate information on the appropriateness of approved/suggested dosing regimens for complex critically ill patients such as those with severe sepsis and/or being treated with extracorporeal therapies. Comparative clinical trials that provide the principal evidence of regulatory approvals are merely non-inferiority trials often comparing novel agents with conventional dosing regimen of comparators. Given the substantial evidence available to date that conventional dosing regimens (used as comparators) frequently result in subtherapeutic exposure in the critically ill and possibly achieving

submaximal outcomes [4, 13], non-inferiority trials cannot therefore provide evidence for dosing regimens of the novel agents that maximise patient outcomes. Without comprehensive clinical evaluation integrating pharmacokinetic (dosing appropriateness) and outcome assessment, the novel agents still remain at risk of treatment failure and/or emergence of resistance when used in the critically ill. This also holds true to most of the established agents which passed through similar processes of drug development. Therefore, addressing the special dosing needs of the critically ill will be essential to prolong the life span of existing drugs and preserve the novel agents for the treatment of multidrug-resistant infections.

This book chapter aims to summarise the most important consideration for dosing of antimicrobials commonly indicated in the treatment of critically ill patients with intraabdominal sepsis.

21.2 Why Do Critically Ill Patients Require Unique Considerations for Antimicrobial Therapy?

In the critically ill, important physiological processes that affect drug disposition are markedly perturbed. The degree of such pathologic derangements is particularly intense in septic patients. The progression of (intraabdominal) sepsis is driven by an overwhelming systemic inflammatory response, mediated by proinflammatory cytokines (e.g., TNF-α, IL-1, IL-6, IL-8, IL-18) [14]. Particularly, severely ill patients with very poor prognosis exhibit higher degree of proinflammatory cytokine activity. For example, Wakefield et al. [15] observed very high level of interleukin-6 in patients with intraabdominal sepsis exhibiting high APACHE and organ failure scores. Trauma from surgical intervention for the control of source of infection may further accentuate the inflammatory host response. For example, Sautner et al. [16] observed a post-operative surge of interleukin-6 in patients with severe peritonitis. Increased activity of such proinflammatory cytokines results in diverse pathophysiological changes. Particularly relevant to drug disposition, these include a supranormal cardiovascular activity characterised by high cardiac output, capillary extravasation, fluid accumulation, accelerated glomerular filtration and acute organ damage. The resulting altered body water dynamics affects the disposition of primarily hydrophilic antibiotics such as beta-lactams which form the backbone of empiric therapy for intraabdominal sepsis. Capillary extravasation, fluid accumulation and/or acute organ (kidney) damage increase the volume of distribution and reduce target site concentrations of some drugs [8]. Increased renal elimination of solutes due to elevated glomerular filtration rate (GFR) during sepsis results in distinctly higher clearance of renally eliminated antibiotics (termed augmented renal clearance) and is associated with subtherapeutic concentrations [17, 18]. Further, proinflammatory cytokines such as interleukins mediate pathologic fluid accumulation, intraabdominal abscess formation [19], also contributing to the expansion of the volume of distribution. The abscess presents further challenge of impaired antibiotic penetration into this site of infection. The outermost layer of the abscess is often very thick for diffusion of drug molecules due to its morphological makeup

consisting of a collagen layer [20]. Layers of leucocytes and cell debris within the abscess also render the abscess fluid viscus and thus probably affect the diffusion of antibiotics [20, 21]. Further, interventional percutaneous abscess drainage provides an extra route of drug elimination not accounted in the design of conventional dosing regimens and thus can contribute to reduced antibiotic exposure. Although evidence of significant effect is outstanding, large volume abdominal lavage in peritonitis has also been examined as a cause for altered antibiotic disposition [22]. Another common intervention, aggressive fluid resuscitation, significantly contributes to an increased drug volume of distribution [4, 8]. Further, up to one-third of patients with complicated intraabdominal infection develop acute kidney injury that necessitates the use of renal replacement therapy (RRT) [23]. RRT results in difficult-to-predict clearances of antibiotics that are significantly eliminated via renal excretion [24].

The collective consequence of such various factors that alter antibiotic pharmacokinetics in the critically ill is that these patients exhibit distinct dose-exposure relationships. Therefore, dosing regimens that would normally be expected to achieve optimal exposure can frequently result in inappropriate exposure. Antibiotic dosing in this population should consider the unique dose-exposure relationships to adapt conventional regimens based on novel clinical data that define these unique relationships [4].

21.3 How Significant Is Consequence of Pharmacokinetic Alterations on Dosing Requirements of Antimicrobials in the Critically Ill?

There is strong evidence from clinical studies confirming that the altered pharmacokinetics of antimicrobials in the critically ill can result in subtherapeutic exposures when standard dosing regimens are used. The largest study on defining antibiotic levels in the intensive care unit (the DALI study) [13] analysed exposure of eight beta-lactam antibiotics in 68 hospital ICUs across the world (361 patients). The results highlighted very high variation (up to 500-fold for some antibiotics) in the unbound plasma concentration at mid of the dosing interval and the trough. Consequently, there was a large variation in the attainment of pharmacokinetic/pharmacodynamic (PK/PD) targets. In this study, 20% of patients did not achieve even the conservative PK/PD target of 50% $fT_{>MIC}$, whereas in 50% of the patients, the PK/PD target recommended for severely ill patients, 100% $fT_{>MIC}$, was not achieved. The observed high failure rates in this study underline the inadequacy of contemporary beta-lactam dosing regimens for significant proportion of critically ill patients. There being a clear relationship between PK/PD target attainment and patient outcomes, also illustrated from the DALI data, failure to attain target goals is highly likely to contribute towards poor patient outcomes.

The DALI study also showed poor PK/PD target attainment for vancomycin [25]. Target trough concentrations were not achieved in 43% of the study population (42 patients from 26 ICU across the world). Data from previous studies [26–28]

shows that exposures associated with low trough concentrations (<10 mg/L) not only lead to poor outcomes but also risks the emergence of resistant organisms such as vancomycin-resistant *Staphylococcus aureus* (VRSA). Another large pharmacokinetic study by Roberts et al. [29] illustrated that a higher than usual loading dose (35 mg/kg vs the standard 15 mg/kg) of vancomycin may be necessary to avoid subtherapeutic exposure in the initial phase of therapy. Even larger doses (including the maintenance dose) may be required in patients with augmented renal clearance [29, 30].

Studies that have assessed tissue antimicrobial exposure from conventional regimens also suggest that standard dosed may be inadequate in septic patients to achieve adequate tissue exposure. For instance, a study [31] describing interstitial tissue exposure of fluconazole reported that despite the likelihood of achieving the desirable plasma PK/PD target of *f*AUC/MIC ≥100, tissue exposure would be far less for the majority of patients unless higher than standard doses are administered. Data on the penetration of antibiotics into the peritoneal fluid (important target site in intraabdominal sepsis) is generally limited; however, some studies highlight that penetration could be variable and insufficient particularly for less susceptible pathogens. For instance, Karjagin et al. [32] reported that standard 1 g meropenem dosed eight hourly achieved adequate penetration into peritoneal fluid only against low MIC pathogens (<4 mg/L) and is likely to be suboptimal against pathogens with intermediate susceptibility. Another study by Galandiuk S et al. [33] showed that concentration of antibiotics such as ceftriaxone and cefoxitin in the abscess fluid could fall well below the MIC of likely pathogens.

It is therefore important to acknowledge that appropriate selection of antibiotics without consideration of dosing appropriateness does not guarantee success of antimicrobial therapy in the critically ill. Indeed patients with complicated intraabdominal sepsis have been shown to be subject to higher risk of mortality despite appropriate selection of standard antibiotic regimens for directed therapy guided by in vitro susceptibility testing [32]. An appropriate directed or empiric antibiotic therapy should also aim to achieve therapeutic antibiotic exposure in the plasma and/or target tissue of infection.

21.4 How Can We Optimise Antimicrobial Dosing in the Critically Ill to Ensure Appropriate Therapy?

21.4.1 Beta-Lactam Antibiotics

The beta-lactam antibiotics remain a mainstay of initial empiric therapy in intraabdominal sepsis, either alone or in combination with other agents [1]. Owing to the very short half-lives (about 1–5 h) of these agents, disease-induced changes in volume of distribution and clearance significantly reduce the $\%\, fT_{>MIC}$ achieved with standard intermittent dosing regimens [13]. Theoretically, increasing the frequency of administration of an intermittent dosing schedule can increase the $\%\, fT_{>MIC}$; however, even those schedules with increased frequency (e.g. every six hourly vs eight

hourly for piperacillin-tazobactam) may still result in antibiotic underexposure and more frequent dosing schedules (every four hourly or more frequent) are not only inconvenient but also inefficient cost wise due to the increased total daily dose and staffing requirements. The use of an extended infusion over about half of the dosing interval of the conventional dosing schedule is a useful approach to increase exposure ($fT_{>MIC}$) with lower total daily dose [34]. A combination of increasing the frequency of administration but using an extended infusion may be employed to maximise exposure. For example, instead of every eight hourly dosing, every six hourly dosing with 3 h infusion can be used. Sime et al. previously demonstrated this approach for piperacillin-tazobactam in randomised controlled study [35], in which the extended infusion regimens achieved conventional PK/PD target in 94% of the patients vs 31% of the control. Other authors also have illustrated the significantly better exposure ($fT_{>MIC}$) achieved with extended infusion [34, 36, 37]. Increased exposure is highly likely to contribute to better patient outcomes. For instance, in the study by Cutro et al. [38], clinical failure rates in patients with intraabdominal sepsis treated with extended infusion of piperacillin were lower compared to intermittent administration (14.5% vs 25%; $P = 0.184$). Other studies also reported that shorter duration of therapy was required with extended infusions presumably due to improved outcome [39–41]. It may also be reasonable to anticipate a reduced mortality rate from the improved exposure, although available studies have important design and power limitations that preclude any conclusion from the inconsistent reports [38, 39, 41–45]. For highly susceptible infections (caused by low MIC pathogens), it is highly likely that equivalent exposure in terms of $fT_{>MIC}$ will be observed between extended vs intermittent infusions, and therefore the relative outcome benefits are more likely to be pronounced when intermediate to high MIC organisms are targeted for treatment. Thus, in clinical practice, the use of extended infusion should be preferred over intermittent dosing at least for empiric treatment of very sick patients and directed therapy of less susceptible and/or high MIC pathogens.

Not all patients receiving extended infusion are expected to achieve targeted exposures due to the high pharmacokinetic variability between patients and within a patient, in one study [46] estimated to be as high as 57% and 40%, respectively. The cumulative fractional target attainment against high MIC bacteria may be lower than the recommended cutoff value >85% [34]. The exposure, $fT_{>MIC}$, can further be maximised with continuous infusion administration as has been demonstrated by a number of clinical studies conducted in critically ill patients [47–49]. Continuous infusion also achieves higher exposure in interstitial fluid (tissue) of septic patients [50] as well as within local sites in intraabdominal infections. For example, Buijk et al. [51] compared peritoneal exudate exposure between 1 g loading dose plus 4.5 g continuous infusion regimen of ceftazidime, with 1.5 g every eight hourly dosing. They found that for most common pathogens, $fT_{>4xMIC}$ was greater than 90% for continuous infusion versus 44% for the intermittent administration. Therefore, continuous infusion would be highly advantageous in intraabdominal infection where drug penetration into peritoneal abscess collection (an important site of action) is minimal [52].

Outcome benefits of continuous infusion for a better control of bacteraemia are supported by laboratory models of septic peritonitis [53]. However, the clinical benefit of continuous infusion may be more pronounced if less susceptible organisms are involved; many etiologic bacteria, the Gram-positives in particular, are likely to have lower MIC, and therefore patient outcomes may appear equivalent despite the significant difference in $fT_{>MIC}$ [49]. Indeed previous outcome assessment for piperacillin-tazobactam by Lau et al. [54] and also Li et al. [55] found no impact of the mode of delivery in patients with intraabdominal infection. However, even in such cases, there is evidence suggesting that the high concentrations achieved with continuous infusion (albeit more than necessary considering conventional targets) are likely to benefit in suppression of regrowth of resistant subpopulations [56–58].

A definitive outcome benefit from continuous infusion of beta-lactams still remains to be illustrated. However, it is important to underling that most of the existing studies that failed to identify the anticipated outcome benefit from continuous infusion suffer from serious limitation in study design and/or power. Studies are heterogeneous in terms of patient population, types of antibiotics, outcome end points and dosing regimens employed [48, 59]. For example, in the largest randomised controlled trial by Dulhunty et al. [60], recruitment of patients with heterogeneous organ function was suggested to have confounded the lack of benefit reported in the study. This was later elaborated by another large trial from the same group which was designed to exclude patients on renal replacement therapy and was able to identify significant improvement in clinical cure rate (56 vs 34%, $p = 0.011$) [61]. Similarly, a subsequent individual patient-level data meta-analysis by Roberts et al. [62] that analysed homogenous data from three trials showed higher clinical cure rates (RR 1.20, 95% CI 1.03–1.40, $p = 0.021$) and also found reduced hospital mortality rates (RR 0.74, 95% CI 0.56–1.00, $p = 0.045$), a finding different from older meta-analyses of heterogeneous trials [63–67]. Therefore, the odds of significant outcome benefits from continuous infusion are apparently substantial.

Only to some extent, the use of continuous infusion may offset the influence of pharmacokinetic variability on inconsistency of PK/PD target attainment, but practically it is very difficult to achieve desirable treatment targets in every patient by implementing a uniform dosing regimen [35, 46]. Appropriateness of dosing adequacy can only be ascertained by monitoring actual concentrations in every patient. The utility of beta-lactam therapeutic drug monitoring (TDM) has been well described in literature and is a useful tool to guide dose adaptation [35, 59, 68–70]. At the moment, only few ICUs have implemented TDM programme for beta-lactams, and experience from existing practice suggests trough concentration monitoring at steady state may be sufficient to assess target attainment (100% $fT_{>MIC}$). Dosing can subsequently be adjusted either by empiric considerations in reference to the measured TDM concentration or by applying Bayesian forecasting method using a computer software. The empiric adjustment involves dose adaptation by increasing dosing frequency and/or magnitude or mode of delivery (prolonged infusion). The review by Wong et al. [71] describes the practical issues that prevent beta-lactam TDM being used more widely. An important limitation of empiric

adjustment is that it may not be uncommon to see concentrations below the target concentrations even after dose adjustment [35, 68, 69]. Apparently, it is impossible to account for the poorly predictable pharmacokinetic variability with just a concentration versus MIC reference. However, the success of interventional TDM can be maximised by using population pharmacokinetic models that account for between patient and within patient variability. Patient-specific covariates and TDM concentration can be fed to Bayesian estimation software to develop patient-specific pharmacokinetic model and precisely predict dosing requirements [3, 72]. This approach is likely to be the future of TDM if the various softwares being developed are clinically validated [4, 73].

21.4.2 Vancomycin

Given the time-dependent pharmacodynamic activity of vancomycin, there has been an interest in the use continuous infusion to ensure consistent attainment of therapeutic targets [74, 75]. However, the benefit of continuous infusion of vancomycin is yet to be clarified. Studies suggest that in terms of achieving therapeutic exposure (an AUC/MIC ratio $\geq$ 400), continuous infusion is not any better than intermittent infusion and therefore does not demonstrate any improvement in patient outcomes [29, 76–78]. On the other hand, a meta-analysis by Cataldo et al. [79] suggested a potential benefit of reduced risk of nephrotoxicity in patients treated for Gram-positive infections. The authors discussed that this probably relates to daily lower doses required to achieve a similar trough concentration targeted with conventional intermittent regimens. However, targeting the same trough concentration for these two modes of delivery may not be appropriate given the fact that higher steady-state (trough) concentration are required (20–25 mg) for continuous infusion than conventionally targeted for intermittent administration (15–20 mg/L) to achieve the target exposure of AUC/MIC ratio $\geq$ 400; or otherwise it is likely to result in underexposure especially when targeting high MIC pathogens (e.g. MIC > 1 for *S. aureus*) [80, 81]. Therefore, there being no evidence of superiority, continuous infusion may only be considered as an alternative approach, and intermittent infusion remains the preferred mode of delivery. In the critically ill, it is important to ensure that an adequate loading dose is used to avoid initial subtherapeutic exposure with both continuous infusion [29, 82, 83] and intermittent infusion (25–30 mg/kg) [84]. The initial intermittent dose could be determined based on actual body weight due to large volume of distribution of vancomycin, and subsequently doses can be adjusted based on trough concentrations [85]. Clearance-based, rather than weight-based, dose initiation has recently been proposed as a reasonable alternative based on the concept of AUC/MIC dosing target giving rise to AUC-based dosing chart. Though pharmacokinetically rational, this approach has not been clinically validated, and the consensus is still to base initial dosing on body weight [84, 86].

In the critically ill, achieving consistent vancomycin concentrations within the therapeutic range, particularly with intermittent dosing, is hardly possible such that TDM-guided individualisation of therapy is advocated to minimise toxicity and

maximise efficacy [84, 87]. The widely endorsed TDM approach involves trough concentration monitoring, even though the best PK/PD index that relate to vancomycin clinical efficacy is AUC/MIC, which would require multiple samples for accurate estimation, thus is practically inconvenient. Trough concentrations were assumed to correlate well with AUC [84, 88] that for intermittent administration, the target AUC/MIC ratio of ≥400 was generally considered to be attainable with trough concentration of 15–20 mg/L for susceptible organisms (MIC values of ≤1 mg/L) [84, 87]. However, a relatively recent population pharmacokinetic analysis by Neely et al. [89] suggested that trough concentrations are poor predictors of AUC. According to their assessment, AUC will be under predicted on the average by 25%, and estimates are unreliable due to high between patient variability of AUC (up to 30-fold). Further, their analysis showed that up to 60% of patients with trough concentration < 15 mg/L may achieve the target AUC/MIC (for MIC 1 mg/L) ≥ 400. These interesting findings probably explain the lack of consistent report on the correlation between trough concentrations and nephrotoxicity [90–97] or treatment outcome [28, 97–100].

Therefore, the conventional TDM approach as described by the consensus guidelines [84, 87] may have some shortcomings in the overall outcome benefit. The level of evidence remains poor although a later meta-analysis indicated potential benefit [101]. However, given the significant variability of concentration in critically septic patients, particularly those with unstable renal function and receiving renal replacement therapy, the current TDM may be warranted to prevent the risk of toxicity from high drug concentration. On the other hand, the high variability in exposure from conventional therapy risks treatment failure due to subtherapeutic exposure and thus warrants further investigation of robust methods for dose individualisation to maximise treatment outcomes. The Neely et al. study [89] demonstrates that Bayesian forecasting based on a trough concentration can provide a high precision estimate of AUC (3% failure rate) and dosing requirement. Thus, this should be considered a valuable tool pending further validation of its utility in larger outcome trials [102].

21.4.3 Quinolones

Unlike other hydrophilic antibiotics such as the beta-lactams and glycopeptides, the quinolones may not be expected to be highly affected by the sepsis-driven physiological changes due to their physiochemical nature (lipophilicity). Although data is limited for many fluoroquinolones, ciprofloxacin is relatively well studied. For example, Gous et al. [103] showed that fluid shifts do not significantly affect the pharmacokinetics of ciprofloxacin in patients with intraabdominal infections. As a result, the volume of distribution is often not affected, and therefore no adjustment may be necessary for initial dosing relative to maintenance dosing. However, pharmacokinetic variability could occur due to other reasons such as changes in organ function. Clinically significant pharmacokinetic variability that affects target exposure attainment has been reported for ciprofloxacin in general ward patients [104],

burn patients [105] and ICU patients [106–109]. In a study by Haeseker et al.[104], target exposure of AUC/MIC ratio > 125 was not achieved with a commonly used 400-mg-twice-a-day dosing of ciprofloxacin in 75% of patients when the MIC of target organisms was high (0.5 mg/L). Even with a lower MIC of 0.25 mg/L, the authors observed a significant (21%) failure rate in target attainment. Another retrospective study by Matsuo et al. [110] found that standard dosing (300 mg IV twice a day) with ciprofloxacin did not reach the target AUC/MIC ratio in large proportion of the study cohort, and treatment was ineffective in more than 50% of the patients. Therefore, higher doses of ciprofloxacin (such as 400 mg every eight hourly or 600 mg twice daily) are recommended in the critically ill. These higher doses are highly likely to improve exposure (AUC/MIC ratio) in most patients, more so when relatively low MIC organisms are involved (≤0.25 mg/L). For example, in the Haesker et al. [104] study, data simulation showed that for a MIC of 0.25 mg/L, target attainment was improved to 99% with a higher dose (400 mg every 8 h); however, this was only 63% when MIC was 0.5 mg/L.

Generally the use of the traditional low dosing regimens recommended for ciprofloxacin in guidelines [1] may not be appropriate for critically ill patients, particularly with empiric therapy or directed therapy for high MIC organisms (≥0.5 mg/L). However, it may be difficult to ascertain adequacy of therapy with a uniform dose. Some authors have recommended a role for TDM-guided dose adjustment, although the level of evidence justifying the need is limited [104–109]. Perhaps as one example of a relevant patient group, TDM may be indicated when infections are caused by organisms with a high MIC (≥0.5 mg/L) and in patient with renal dysfunction requiring extracorporeal renal replacement therapy (RRT) [71]. In critically ill patients with reduced renal function but not undergoing RRT, empiric dose reduction should be avoided due to high pharmacokinetic variability that risks underexposure as well as limited accumulation due to potential upregulation of the alternative biliary elimination pathways. Furthermore, this intestinal pathway of elimination is not necessarily affected in patients with intraabdominal infection [103]. Therefore, dose reduction is unnecessary in most cases, and accumulation is generally rare [70, 71]. When all major elimination pathways are likely to be impaired (renal, hepatic and gastrointestinal dysfunction), accumulation may be likely, and dose reduction guided by TDM would be advantageous to ensure appropriateness of dosing [71].

21.4.4 Aminoglycosides

Given that aminoglycosides exhibit concentration-dependent activity with C_{max}/MIC ratio describing bactericidal effects, dosing of these agents may be significantly affected by alterations in volume of distribution. Particularly in the early phase of sepsis when intense pathologic changes occur, and also urgent fluid resuscitation is initiated, the volume of distribution rises [111]. Consequently, despite the use of normal loading doses, the initial C_{max} can be subtherapeutic, and thus a higher than normal loading dose may be necessary in these patients [112, 113]. Further, the

predominant renal clearance of aminoglycosides means that in septic patients, maintenance doses will also be affected due to either augmented renal clearance or acute kidney injury and with high variability in drug clearance when RRT is used. While conventional TDM may address the issue of reduced clearance and toxicity, the subtherapeutic exposure due to augmented renal clearance may often be overlooked. Thus, suboptimal dosing may be particularly frequent in young septic patients that exhibit augmented renal clearance [30, 113].

TDM of aminoglycosides should be used not only for monitoring toxicity but also to avoid potential underexposure/treatment failure. TDM based on measuring two samples, the first at 1 h and the second between 6–18 h after administration, would be required to estimate C_{max} [114]. The traditional TDM guided by nomogram and a single random concentration measurement between 6 and14 h post dose is likely to give erratic estimate of the C_{max} since most nomograms are developed based on data from noncritically ill patients [71].

Of note, previous studies that observed the likelihood of underexposure with conventional aminoglycoside dosing in young patients with normal renal function recommend increasing dosing frequency to optimise exposure [113], perhaps as careful approach given concerns of toxicity with the high-dose requirements. However, accumulation of aminoglycosides in renal tissue largely follows a zero-order kinetics, and high peak concentrations are unlikely to increase risk of nephrotoxicity [115]; thus, a higher dose with a single daily regimen should be considered in critically ill patients. Further, nephrotoxicity correlates well with trough concentrations and that lower troughs with the once daily schedule may reduce the risk of toxicity [116–119]. Therefore, when subtherapeutic exposure is identified, it is reasonable to use higher doses provided that more frequent TDM is performed to minimise any untoward effects due to the intra-patient variability in pharmacokinetics that occurs with the progression of sepsis. Preferably dosing should be guided based on estimation of exposure in individual patients using Bayesian forecasting tools that enable precise estimation of dosing requirements [120].

The benefit of individualised aminoglycoside dosing that also aims to optimise efficacy may perhaps extend to redefining the place of therapy of these agents in the treatment of intraabdominal sepsis. Unfortunately, previous comparative clinical trials and meta-analysis [121] that report that aminoglycosides combined with anti-anaerobic agents were less effective in intraabdominal infections relative to other broad-spectrum antibiotics may have been confounded by underexposure of drugs. Given most of the broad-spectrum first-line agents recommended in contemporary guidelines are more expensive, individualised aminoglycoside therapy may provide an effective alternative in resource-limited settings.

21.4.5 Metronidazole

Metronidazole is a lipophilic antimicrobial agent predominantly eliminated by hepatic metabolism with only up to 18% of the parent drug excreted unchanged via urine [122]. Therefore, given hepatic function is unaffected, most of the

sepsis-driven pharmacokinetic alterations that affect body water dynamics have no significant effect on the disposition of this agent. The study by Karjagin et al. [123], for instance, showed that both plasma and tissue pharmacokinetics are not altered in patients with septic shock. Consequently, no change in loading dose is required to account for fluid shift-related increase in volume of distribution, and no adjustment to maintenance dose is necessary in patients with augmented renal clearance or acute kidney injury [124]. Likewise, although metronidazole is efficiently cleared (sieving coefficient up to 0.97) by the different RRT modalities [122, 125], dose adjustment is considered mostly unnecessary considering the relative contribution towards total clearance. Data is generally limited to explicitly describe any requirements of dose modification, particularly a potential need of supplementation in critically ill patients with less susceptible infections [122]. In patients with hepatic failure, toxic accumulation of metronidazole can occur and necessitates dose reduction [126]. Nevertheless, no standardised approach of dose reduction is available with mostly empiric reduction of dosing to 500 mg once daily or twice daily observed in practice; given the relatively wide margin of safety of metronidazole, this may be adequate to control adverse effects. Accumulation of metabolites in renal impairment is also reported [127]; however, although some of the metabolites are pharmacologically active [128], there is no evidence of toxicity that necessitates dose adjustment.

21.4.6 Tigecycline

The originally approved dosing regimen of tigecycline, 100 mg loading dose with 50 mg twice daily maintenance dose, is still recommended in guidelines [1, 129] despite strong concerns of its adequacy arising from reports of high treatment failure rates [130–132]. This has caused subsequent regulatory restriction of tigecycline use only for cases where alternatives are not available [133]. In line with this, dosing simulation studies show suboptimal exposure with standard dosing against common pathogens such as *P. aeruginosa*, *Klebsiella* spp., *Enterobacter* spp. and *Acinetobacter* spp. [134]. As a possible solution, higher dose regimens were evaluated in few studies given the linear dose-exposure-response relationship of tigecycline [135], although heterogeneity of the available studies and lack of complete safety data precludes any conclusion on the relative efficacy and safety [136]. Nonetheless, in terms of PK/PD exposure required for complicated intraabdominal infections (AUC/MIC > 6.96), higher doses (100 mg twice daily) are more likely to achieve optimal exposures against many Gram-negative pathogens which have relatively higher MICs [137]. Therefore, if tigecycline has to be used in the critically ill, which often will be in the case of complicated infections not responding to first-line agents, the standard doses may risk treatment failure, and as such use of higher doses (e.g. 200 mg loading dose followed by 100 mg twice daily) are suggested with careful monitoring of side effects. There has been an increasing off-label use of this high dose in the critically ill [138], and subsequent retrospective evaluations suggest doses are well tolerated given the most common dose-related increases in

gastrointestinal side effects (nausea and vomiting) are unlikely to be dose-limiting in sedated critically ill patients [139]. Doses may need to be reduced (even lower that standard doses) in patients with severe hepatic impairment to avoid potential accumulation and toxicity [140]. However, tigecycline does not undergo significant metabolism, and thus dose modification in mild to moderate liver dysfunction may not be necessary [141]. Similarly renal excretion is limited (up to 15% in healthy volunteers [142]), and the predominant pathway of elimination is via faeces (about 60%) [143]; thus, no dose adjustment is required in renal failure [141]. There is limited data on the effect of extracorporeal therapies, RRT or ECMO. A case report of a patient receiving ECMO found similar plasma and tracheal aspirate concentration, suggesting no influence of the ECMO on dosing requirements [144]. Sequestration in RRT circuit is yet to be clarified, and it is unclear if dose supplementation is required to compensate for possible loss [145].

21.4.7 Antifungal Agents

Fluconazole is one of the most commonly prescribed agents for the management of invasive candidiasis in complicated intraabdominal infections [146–148]. Data in the critically ill remains limited, with the available evidence suggesting that alterations in the pharmacokinetics of fluconazole can be significant, necessitating dose optimisation [149]. For example, in a recent multicentre study [150], conventional doses of fluconazole failed to provide empiric coverage ($fAUC_{0-24}$/MIC $\geq$ 100) at a clinical susceptibility breakpoint of 2 mg/L in one-third of the study population (n = 15 patients). Further, tissue penetration in septic patients has been shown to be highly variable and incomplete; the majority of patients receiving conventional dosing are likely to exhibit low tissue exposure (fAUC/MIC < 100) compared to that of plasma, thus requiring higher than normal doses to maximise exposure at the sites of infection [31]. Patients receiving RRT in particular may be subject to suboptimal exposure due to the extensive clearance of fluconazole by the different RRT modalities that may even exceed the normal renal clearance in healthy volunteers [149, 151, 152]. For example, a recent study [152] in patients undergoing sustained low-efficiency diafiltration reported that 72% of the administered dose was removed leading to exposures that failed to attain the target $fAUC_{0-24}$/MIC $\geq$ 100. Designing dosing regimens to account for the effect of RRT is however a challenge due to the range of RRT modalities and high inconsistency in the operational setting, which means that dosing requirements are different between patients and RRT modalities and settings [153]. The role of TDM to guide optimisation is therefore invaluable, though is yet to be established for fluconazole [154]. Nonetheless, if TDM is not possible, higher does should be used, and dosing should be individualised in the critically ill at least on the basis of weight, i.e. loading dose 12 mg/kg instead of 800 mg and maintenance dose of 6 mg/kg daily rather than 400 mg/day. Weight-based dosing has been shown to correlate well with increased probability of attaining dosing target [147, 155].

Echinocandins are another class of antifungal agents likely to be prescribed in complicated intraabdominal infections of fungal involvement. Recent guidelines recommend the echinocandins as drug of initial choice for invasive candidiasis [147, 148]. Although pharmacokinetic data is generally limited, these agents are generally considered not to be affected by pathophysiological alteration due to their lipophilicity. However, some of the available recent studies have indicated that low exposure may be likely. For example, low exposure of anidulafungin and caspofungin has recently been reported (AUC_{0-24} of 55 and 52 mg/L * h respectively) in ICU patients [150]. A population pharmacokinetic analysis by Grau et al. [156] showed that, in patients with severe peritonitis, the standard 100 mg/kg dosing of micafungin results in suboptimal exposure against less susceptible stains. However, the lack of clinical data that define PK/PD exposures for these agents impair further dosing recommendation. Moreover, based on existing data, in patients receiving RRT, no special dosing consideration may be necessary. For instance, Maseda et al. [157] showed micafungin is not cleared by haemofiltration, and the standard 100 mg/day dose offers adequate exposure. Similarly, another study by Weiler et al. [158] showed that caspofungin clearance by continuous heamodialysis and heamodiafiltration techniques was very low to affect dosing requirements.

21.5 Optimised Antibiotic Dosing and Duration of Therapy

The duration of antibiotic therapy for intraabdominal sepsis has been a subject of controversy. While the concern of emergence of resistance following prolonged course of therapy has led to the advocacy of short course therapy, in clinical practice treatment often takes longer courses than even recommended in guidelines [159]. On the average treatment duration is about double that of the advocated short-duration therapy of 4–5 days [160]. The STOP-IT trial by Sawyer et al. [161] was the recent largest randomised study that evaluated the impact of duration of therapy on patient outcomes. The study randomised 518 patients with complicated intraabdominal infection for whom adequate control of source of infection was confirmed. Patients received antimicrobial therapy either for 3–5 days (experimental group) or until 2 days after resolution of signs of infection including fever, white cell count and presence of ileus (median of 8 days). The primary endpoint of the trial was a composite of occurrence of surgical site infection or recurrence of intraabdominal infection or mortality within 30 days. The results of the study identified no significant difference between the groups either in the composite or individual endpoints. The study, therefore, concluded that a fixed short course of therapy (4 days) may be sufficient provided that adequate source control is achieved. In agreement with these findings, recent guidelines recommend a shorter duration of therapy with careful monitoring of clinical response, i.e. no signs of further infection persistence [129]. However, experts suggest that prognosis of critically ill patients who present with severe abdominal sepsis is poorly predictable, and thus the duration of treatment should be based on evaluation of each patient's response [162]. In addition to monitoring response, such patient would require monitoring of antibiotic dosing

appropriateness. If adequate source control is confirmed, inappropriate dosing is likely to be one of the major reasons for treatment failure in the critically ill. Therefore, TDM-guided dose individualisation should be considered to maximise the outcomes of these short durations of therapy and avoid unnecessarily prolonged antibiotic exposure that risks recurrence of infection due to emergence of resistance.

Indeed recurrence of intraabdominal infection could be very frequent; for instance, rates as high as 37–50% have been observed in patients with Crohn's disease [163]. Although this could be partly due to lack of adequate source control, undoubtedly inappropriate antibiotic exposure and reduced susceptibility may lead to regrowth of organisms despite drug therapy. To minimise the rate of recurrent infection and maximise the efficacy of short duration of therapy, higher than usual doses may be required in the critically ill. Emerging studies indicate that despite exposure to concentration above the MIC, growth of resistant organisms may occur with prolonged treatment [164]. A recent in vitro study (data submitted) found that for meropenem and piperacillin, regrowth of *Pseudomonas aeruginosa* and *Escherichia coli* clinical isolates occurs despite exposure to concentration above but close to the MIC. The study further showed exposure to several multiples of the MIC may be required to suppress regrowth. Thus, particularly for antibiotics with wide margin of safety, administering high dose for a short duration may be advantageous in the critical patients to maximise patient outcomes.

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Hemodynamic Support

22

Pedro Povoa and António Carneiro

22.1 Introduction

According to several epidemiological studies, abdominal sepsis is the second most prevalent site of infection in intensive care units (ICU) being responsible for about 20% of admissions [1–3]. In addition, some acute abdominal sources of infection are associated with very high mortality rates, namely, when caused by ischemic bowel disease, *Clostridium difficile*-associated colitis and disseminated intra-abdominal infections [4].

Septic shock secondary to abdominal sepsis has all the characteristics of septic shock of other origins plus two additional problems: (a) high intra-abdominal pressure (IAP) and risk of abdominal compartment syndrome with (b) compromise of splanchnic perfusion that makes the sepsis approach slightly different [5].

22.2 Principles of Hemodynamic Support in Severe Sepsis/Septic Shock

The pathophysiologic hallmark of sepsis is maldistribution of distal circulation. It also includes hypovolemic component (decreased preload), cardiogenic dysfunction (decreased contractility), and profound vasodilation when inflammatory

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mediators are massively liberated into the circulation (great fall in afterload) [6, 7]. Additionally the endothelium is a preferential target of systemic inflammation provoking increase capillary permeability that results in relative and absolute hypovolemia, severe circulatory heterogeneity, and vasodilation and capillary obstruction (micro thrombi) resulting in a distributive type of shock [5, 8].

In sepsis-induced hypotension, several neurohormonal mechanisms are activated. Sympathetic stimulation is the main host response intending to provoke vasoconstriction, namely, in skin, muscle, kidney, and splanchnic vascular beds, and inducing higher left ventricular compliance and tachycardia that increases cardiac output and indirectly also mean arterial pressure (MAP).

Currently the systemic effects of shock on tissue perfusion are clinically evaluated through different "windows," namely, the skin, kidney, brain, and lactate [5]. However, organ dysfunction can occur without signs of global hypoperfusion. Besides, there are no "windows" to assess the adequacy of splanchnic circulation in particular of the liver and the gut.

22.3 Perfusion Pressure, Intra-Abdominal Pressure, and Splanchnic Blood Flow

The blood flow and the perfusion pressure of each organ are regulated by two systems. The systemic or "extrinsic" system regulates the systemic circulation that results from the activity of different neuroendocrine systems, namely, the autonomic nervous system, the renin-angiotensin-aldosterone system, and the antidiuretic hormone [9]. Moreover, each organ possesses its own autoregulation. Preservation of an adequate systemic blood pressure is crucial for adequate tissue perfusion. In a wide range of MAP, the autoregulatory range, the organ blood flow remain constant; in other words, organ blood flow is independent of MAP [10]. When MAP falls below this autoregulatory threshold, the blood flow decreases and ensues tissue ischemia with reduction in oxygen transport (DO_2) and organ dysfunction as a consequence. Below that critical MAP level, organ blood flow becomes linearly dependent of MAP [11]. There is also some dependence of previous levels of blood pressure, since hypertensive patients usually need higher MAP than hypotensive/normotensive ones [12].

Patients with abdominal sepsis can present additional problems that aggravate even further this clinical scenario. Some causes of abdominal sepsis are associated with severe absolute hypovolemia. The peritoneal cavity (peritonitis) and the gut (colitis, occlusion), depending on the disease process, can collect large amounts of volume [13] and are a potential cause of severe absolute hypovolemia, imposing aggressive fluid infusion.

Besides, intra-abdominal sequester of large amount of fluids can contribute to an increase in IAP and evolve to an abdominal compartment syndrome. The increase in IAP can further compromise splanchnic and kidney perfusion in particular if MAP is low, since splanchnic perfusion pressure is equal to the MAP minus IAP. Since the gut is full of bacteria, gut ischemia can facilitate bacterial

translocation perpetuating sepsis syndrome [14]. The venous return from inferior vena cava can also be compromised, decreasing preload and inducing further hemodynamic deterioration.

22.4 Hemodynamic Targets and Therapeutic Approach

The supportive approach of septic shock includes an adequate fluid resuscitation, preferably with fluid challenge strategy intending to achieve rapidly the hemodynamic needs of that particular patient but avoiding excessive fluid infusion [7]. The preferred fluids are crystalloids [7]. It is not clear if buffered solutions are better; however, exclusive use of normal saline is associated with hyperchloremia and metabolic acidosis [15].

If hypotension persists, patients should be treated with vasopressors to increase MAP and maintain a minimal perfusion pressure. However, increase in MAP is not always associated with a better blood flow. In patients with abdominal sepsis, there is a balance between volume resuscitation and the risk of worsening IAP, and the right balance is frequently difficult to achieve.

There is also an interaction between timing for fluid infusion and timing of vasoactive drug initiation [16]. In hypotensive conditions, late initiation of vasoactive drugs (>6 h) seems to be associated with higher mortality than early (within the first hour). Another cohort study of septic shock patients from two surgical ICU concluded that early administration of norepinephrine was associated with better survival [17].

In the individual patient, optimal MAP is still unknown. Vasopressor support should be focused on achieving the target MAP to restore adequate tissue perfusion with the intention of optimizing DO_2. Oxygen delivery has three components: adequate arterial O_2 saturation, sufficient hemoglobin level (Hb > 7 g/dL), and adequate cardiac output. Based on this concept, we can define as treatment objectives the surveillance and repeated reassessment of 2O + 2C, as follows:

- Oxygen optimization: monitor SaO_2, PaO_2, $PaCO_2/ETCO_2$, and respiratory rate
- Circulation: monitor blood pressure, cardiac output, central vein diameter variation during respiration, and central venous pressure
- Organ function: the brain (mental state), kidney (diuresis and creatinine evolution), and skin (temperature, mottling scores, capillary refill time)
- Cell homeostasis: lactate, pH, HCO_3^-, and base excess, repeatedly

The target MAP depends on the usual patient blood pressure [18, 19]. From a clinical point of view, the individual MAP should be kept at the level necessary to maintain urine output, usually between 65–70 mmHg. Unfortunately, some patients remain oliguric despite an adequate resuscitation, which could reflect that renal damage has become established.

Increased MAP with vasopressors could improve organ perfusion pressure, but it simultaneously carries a risk of regional vasoconstriction, namely, of splanchnic

vascular bed. So proper fluid infusion should go in parallel with vasopressor [20]. In a recent trial on septic shock (17% of the patients have abdominal sepsis), targeting vasopressors for a MAP of 80–85 mmHg compared with 65–70 mmHg did not result in significant different mortality, but previously hypertensive patients may need higher MAP [12]. However, in abdominal sepsis the splanchnic perfusion pressure is dependent not only of MAP but also of IAP. As a result, the titration of MAP should take into account the IAP in order to have a splanchnic perfusion pressure >65 mmHg.

22.5 Vasopressor and Inotropic Support in Septic Shock

The vascular tone is regulated by the activity of the sympathetic nervous system, via endogenous catecholamines (dopamine, norepinephrine, and epinephrine) and the renin-angiotensin-aldosterone system (vasopressin and angiotensin) [21]. So far, in clinical practice, endogenous as well as synthetic catecholamines and vasopressin and its synthetic analogue terlipressin have been used and evaluated [22, 23].

Inotropes are agents that increase myocardial contractility, whereas vasopressors are agents that increase vascular tone [21].

The expression of adrenergic receptors in capillaries is minimal but increases moving away from capillary bed to arterioles and venules [24]. In addition, the response of the vascular beds to adrenergic agents seems to be different, for example, of mesenteric and skeletal muscle beds. However, the α- and β-receptors are susceptible to downregulation and desensitization [25, 26] which is particularly important in shock, namely, septic shock [27].

During septic shock there are important changes of the vascular control at the microvascular level characterized by decreased responsiveness to vasoconstrictor agents, mainly mediated by nitric oxide. The administration of vasopressors at "common" pharmacological doses to restore the target MAP results in serum concentrations reaching 100 times the physiological levels [28].

22.6 Endogenous Vasoactive Hormones

22.6.1 Adrenergic Agents

The hemodynamic effects of the adrenergic agents depend on their relative affinity to the adrenergic receptors, ranging from pure α-agonists to pure β-agonists and the rates of metabolism (Fig. 22.1 and Table 22.1). Those with predominant α-agonist activity produce more vasoconstriction and are classified as inoconstrictors (norepinephrine, epinephrine, and dopamine), while those with predominant β-agonist stimulation increase cardiac performance and are called inodilators (dobutamine, dopexamine, and isoproterenol) (Table 22.2) [23, 28, 29].

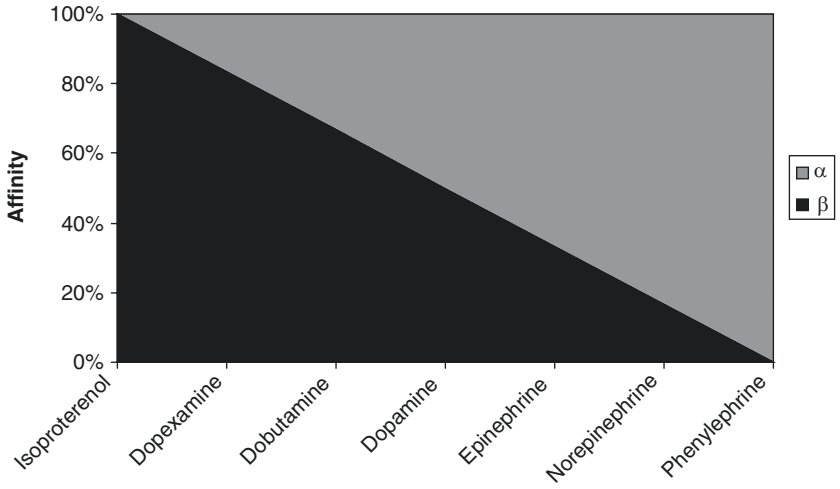

Fig. 22.1 Graphic representation of the relative α-adrenergic and β-adrenergic effects of different catecholamines used to treat patients with shock. Reproduced with permission from [23]

Table 22.1 Affinity of catecholamines for adrenergic receptors

	Dose	α_{1art}	α_{1ven}	β_1	β_2	D_{1A}
Dopamine	Low dose	0	+++	+++	+++++	++++
	High dose	++++	+++	+++++		
Norepinephrine		+++++	+++++	+++	?	0
Epinephrine	Low dose	+	+	++++	++++	0
	High dose	++++	++++			
Dobutamine	5 μg/kg/min	+	?	++++	++	0

Reproduced with permission from [23]

Table 22.2 Cardiovascular effects of commonly used vasoactive agents

		Cardiac		Vascular		
	Dose	Heart rate	Contractility	Vasoconstriction	Vasodilation	Dopaminergic
Dopamine	Low dose	+	+	0	+	++++
	High dose	++	++/+++	++/+++	0	++
Norepinephrine		+	++	++++	0	0
Epinephrine	Low dose	+	++	++	++	0
	High dose	+++	++++	++++	0	0
Dobutamine	5–20 μg/kg/min	++	+++/++++	0	++	0
Vasopressin	0.01–0.03 U/min	0	0	++++	0	0

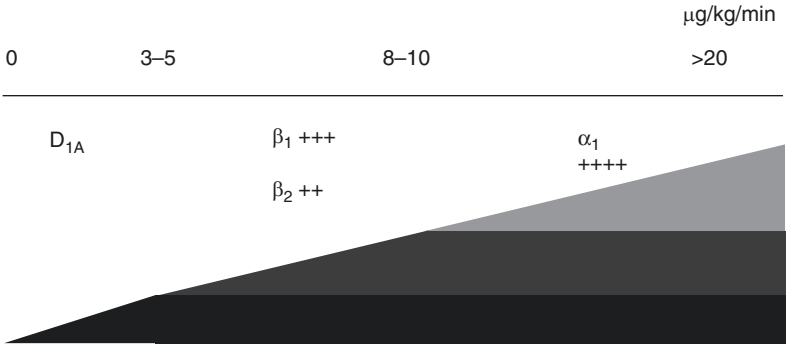

Fig. 22.2 Representation of the predominant effects of dopamine infusion. Reproduced with permission from [23]

22.6.1.1 Dopamine

Dopamine has a complex cardiovascular response profile. Several experts have classified it as the "complete" catecholamine [30], since, depending of its dose, it could have DR_1–DR_5, β_1, β_2, and α_1 activity, whereas the other catecholamines are active only in β_1, β_2, and α_1 [7, 31]. Dopamine is the immediate precursor of norepinephrine. About 50% of its activity is indirect through its biotransformation to norepinephrine. As a result, during dopamine infusion, even at low dose (3 μg/kg/min), plasma norepinephrine concentration increases likewise [32].

The effects of dopamine according to its infusion dose, in μg/kg/min, result to the different receptor interactions (Fig. 22.2) [29, 33]. At low dose, up to 3–5 μg/kg/min, the so-called dopaminergic dose, dopamine activates in a nonselective way dopaminergic receptors, leading to the vasodilatation of renal and mesenteric vascular beds [34, 35]. With doses between 5 and 10 μg/kg/min, dopamine also activates β-adrenergic receptors, leading to positive inotropic and chronotropic effects on the myocardium. Attempting to increase dopamine inotropic effect, by increasing its dosage above 10 μg/kg/min, usually results in tachycardia, tachyarrhythmia, and increasing α_1-adrenergic stimulation and, therefore, systemic vasoconstriction. Since norepinephrine levels parallel dopamine infusion dose, at high doses (>20 μg/kg/min), the effects of dopamine are almost indistinguishable from those of norepinephrine [32].

22.6.1.2 Norepinephrine

Norepinephrine is the endogenous mediator of sympathetic nervous system. It is a potent α-adrenergic agonist and to a less extent a β_1-adrenergic agonist [36]. At low doses, norepinephrine has clearly effects on myocardial contractility, via stimulation of β_1-receptors and also a vasoconstrictor effect by activation of α_1-receptors, leading to an increase in systemic blood pressure with minimal or absent tachycardia [29, 33]. At high doses, vasoconstriction predominates due to predominant activation of α_1-receptors. However, the cerebral and coronary vascular beds are protected to a certain extent of these vasoconstrictor effects owing to the relative

paucity of vascular adrenoreceptors. There is data showing that noradrenaline has minor effects on pulmonary, cutaneous, and also splanchnic blood flow [37, 38].

Given this systemic vasoconstrictive effect of norepinephrine at high doses, there was the fear of precipitating acute renal failure secondary to renal vasoconstriction. However, septic shock patients present a marked vasodilatation, related to α-adrenergic hyporesponsiveness, and therefore infusion of norepinephrine; although causing some renal vasoconstriction, the net effect of raising MAP is the restoration of renal perfusion pressure followed by increase in urine output, increase in creatinine clearance, and consequently decrease in serum creatinine [18, 19].

22.6.1.3 Epinephrine

Epinephrine is produced and released by the adrenal medulla and is a potent agonist of all adrenoreceptors resulting in increase in cardiac output, heart rate, MAP, and coronary blood flow [21]. At equipotent doses, it is 8–10 times cheaper than norepinephrine.

At low doses, epinephrine is a potent nonselective β_1- and β_2-receptor agonist providing positive inotropic effect with an increase in cardiac output without marked vasoconstriction [22, 33, 39]. However, epinephrine has potent chronotropic, dromotropic, and bathmotropic actions, leading to an increase in myocardial work and oxygen consumption that may augment the risk of ischemia and malignant arrhythmias. At higher doses (0.15–0.3 μg/kg/min), the α-receptors are activated, resulting in potent vasoconstriction and increase in systemic blood pressure. Epinephrine administration increases blood pressure in patients that were unresponsive to other vasopressors [39].

For a long time, clinicians fear to use epinephrine since it has been associated with potential detrimental effects of regional blood flow, namely, hepatosplanchnic blood flow [22, 39]. In addition, epinephrine was associated with hyperglycemia and an increase both in systemic and regional lactate levels [37]. However, this is controversial since it seems that epinephrine could even increase in hepatic blood flow [37], and the increase in serum lactate does not appear to be associated with harm, since it is the result of the β_2-receptor-mediated activation of glycolysis [40].

22.6.2 Vasopressin

For reasons not completely understood, in early septic shock, vasopressin levels are elevated and begin to decrease subsequently, sometimes markedly, reaching almost undetectable levels developing a relative vasopressin deficiency [41, 42]. Besides, the administration of vasopressin has been shown to restore vascular tone and blood pressure in patients with vasodilatory shock since it increases the vascular responsiveness to catecholamines [43, 44]. As a result the rationale to give vasopressin in vasodilatory shock patients results from the concept of relative vasopressin insufficiency [45], of the potential synergism with adrenergic agents [46], and finally from the vasopressin-mediated restoration of vascular tone [47].

Vasopressin is a hormone produced in the neurohypophysis. There are two types of vasopressin receptors, the V2-receptor, located in the kidney, responsible for the regulation of water and sodium reabsorption, and the V1-receptor, located in the vascular smooth muscle, which contributes to the regulation of vascular tone and to increase the blood pressure [48]. Consequently, the administration of vasopressin in "physiological" doses (≈0.03–0.04 U/m) can increase blood pressure, mainly mediated by inhibition of inducible nitric oxide synthase.

Terlipressin is a semisynthetic analogue of vasopressin with a greater affinity for V1-receptors compared to V2 (2:1 ratio). Thus, in septic shock, its administration is associated with a greater effect in arterial as well as in organ perfusion pressure, particularly in the kidney [49]. Simultaneously, cardiac output decreases usually from high to "physiological" values [48]. This molecule has a prolonged half-life (approximately 6 h), much higher than that of vasopressin (about 6 min). In septic shock administration of vasopressin or its analogues should be used as a replacement therapy for the relative hormone deficiency rather than as a primary vasopressor agent. It is proposed that an interaction between V1 and α_1-receptor leading to an improvement of the autonomic function, an increase in other endogenous vasoconstrictors as well as other beneficial effects on nitric oxide and glucocorticoid production, could be responsible for the reversal of vascular reactivity to catecholamines [50, 51].

22.6.3 Exogenous Vasoactive Agents

22.6.3.1 Dobutamine

Dobutamine is a synthetic catecholamine with mixed β-adrenoreceptor effects with an affinity three times higher for β_2-receptor [33]. With a dose range between 5 and 25 μg/kg/min, dobutamine is an inodilator with positive inotropic effects (β_1-receptor activation) and arterial vasodilatation (β_2-receptor activation). Besides, dobutamine possesses significant chronotropic and bathmotropic activities that result not only from the cardiac β_1- and β_2-receptor activation but also from the baroreflex response to arterial vasodilatation. In cardiogenic shock, poor tissue perfusion is usually indicative of low cardiac output, and as a result dobutamine is usually warranted and successful. In the other forms of shock, the role of dobutamine is less clear [33]. However, if dobutamine is infused in patients with septic shock, it should be always associated with a vasopressor. It should never be given alone in hypotensive septic patients [7] and should be considered only after evaluation of left ventricular function.

22.6.3.2 Other Sympathomimetics

Phenylephrine is a highly selective α_1-adrenoreceptor agonist causing vasoconstriction [52] with a reduction in cardiac output and a reflex bradycardia. This potent vasoconstriction could also affect the renal and splanchnic blood flow [38].

Ephedrine is a mixed direct- and indirect-acting sympathomimetic. Its effects result from displacing noradrenaline from vesicles and nerve terminals. Since ephedrine has a mild direct β-adrenergic activity, it causes an increase in cardiac output and bronchodilation. The prolonged use of ephedrine is associated by frequent tachyphylaxis because of noradrenaline depletion.

22.7 Alterations in Adrenoreceptors in Critically Ill Patients

The activation of adrenoreceptors is couple with G proteins, either G stimulatory or G inhibitory. Endotoxin disturbs the synthesis of G proteins that could result in poor catecholamine response [53]. In addition, prolonged adrenergic stimulation induces reduction of G stimulatory and increase in G inhibitory proteins [54, 55]. It is also know that sustained adrenergic agonism leads to receptor internalization and reduces the production of new receptors [56].

These changes occur in different types of shock but are more pronounced in sepsis [57].

22.8 Effects of Vasoactive Drugs on Splanchnic Blood Flow

Vasoactive agents increase blood pressure mainly through vasoconstriction. As a result reduction of tissue perfusion, namely, of the splanchnic vascular bed, is a concern in critically ill patients in shock. Unfortunately, early clinical manifestations of poor splanchnic perfusion are unspecific like stress ulceration, ileus, or malabsorption. Currently, there is no evidence that in adequately volume-resuscitated, hypotensive septic patients, vasoconstriction occurs when treated with noradrenaline [58]. The increase in MAP by noradrenaline may improve microvascular flow and DO_2 [59, 60]. In mild to moderate septic shock, dopamine and adrenaline present effects in splanchnic blood flow similar to those of noradrenaline. However, in the severe forms, adrenaline decreases splanchnic blood flow compared to noradrenaline [61]. The clinical impact of these differences is not well known.

Vasopressin and its analogues are known to have a negative impact on splanchnic blood flow [62].

Phenylephrine use as a vasopressor has been shown to be associated with a decrease in splanchnic blood flow and DO_2, rising concerns about its potential deleterious effect in septic shock patients. However, it seems not to be the case [52].

22.9 Comparative Studies of Vasopressors in Septic Shock

The discussion around the choice of the "best" vasopressor agent should be substituted by the discussion about what vasopressor best suits these patient pathophysiological abnormalities [33]. This is probably one of the reasons why trials on vasopressors failed to identify significant differences between different agents since they often include a heterogeneous patient population. As a result the discussion should be more about the effects than about the vasopressors in a particular septic shock patient.

In recent years several randomized controlled trials of vasopressor support in septic shock have been conducted; however, none was performed only in patients with abdominal sepsis. In addition, there is a marked variability between centers and countries on the dosing of vasoactive agents. The recent trials have mainly focused on agents and not on dose selection. It seems that the best approach involves the lowest dose of vasoactive agents during the shortest time.

Currently, the most used vasoactive drugs are probably dopamine, noradrenaline, adrenaline, and dobutamine.

The use of adrenaline declined because of the potential deleterious effects, namely, oxygen consumption, lactate elevation, and potential decrease in splanchnic blood flow. However, two trials have shown the efficacy and safety of adrenaline in septic shock [63, 64]. In both trials the mortality rate of epinephrine arm was similar to the noradrenaline. Unfortunately, neither trial assessed specifically patients with abdominal sepsis.

Finally, a large multicenter trial comparing norepinephrine with dopamine in a mixed population of critically ill patients suggests that noradrenaline has a better safety profile and is associated with better outcome in particular in cardiogenic shock [65]. These findings are attributed to harmful chronotropic effect of dopamine resulting in a higher incidence of severe arrhythmias.

Vasopressin use may be considered in refractory shock [66]. However, it is not recommended to replace norepinephrine or dopamine as first-line vasopressor agent [7]. A large trial to assess the role of vasopressin in septic shock showed no difference in mortality [67]. However, in a prespecified subgroup, less severe septic shock, mortality rate was significantly lower. Only 25% of septic shock patients presented abdominal sepsis, and no subgroup analysis was done. As a result, the potential deleterious effect of vasopressin in splanchnic blood flow cannot be clinically evaluated [68, 69].

Vasopressin is not available in several European countries. On the opposite, terlipressin is usually available, but there are no studies assessing the role of terlipressin in septic shock. Since it has a much longer half-life, terlipressin cannot be titrated so easily.

Dobutamine increases cardiac index, through increment of both stroke volume and heart rate [7]. It has been shown that in patients with severe sepsis and septic shock, an early (first 6 h) goal-directed therapy, aiming at a $ScvO_2$ >70%, after an adequate fluid resuscitation, the achievement of a MAP >65 mmHg and a hematocrit ≥30%, was associated with a reduction in mortality [70]. It is important to point out that inotropic support with dobutamine was required in a marginal group of patients, only 15% [70].

The vasodilator properties of dobutamine are believed to improve the microvascular flow, and this has been shown in patients with sepsis using sublingual polarized spectroscopy to assess microcirculation [71].

Conclusion

The hemodynamic approach of patients with abdominal sepsis encompasses the usual approach of severe sepsis/septic shock patient, plus the issue of raised IAP and the risk of worsening splanchnic blood flow. With this information our strategies to optimize DO_2 and tissue perfusion in severe sepsis and septic shock patients, namely, of abdominal origin, are depicted in Fig. 22.3.

Strategies to optimize DO_2 and tissue perfusion in severe sepsis and septic shock

Monitoring

Focus in four mains objectives: 2O + 2C

Oxygen – objective: SpO_2/ SaO_2 = 92-95% monitor lung sounds (pulmonary edema), PaO_2, $PaCO_2$, check and register respiratory rate and signs of respiratory distress / exhaustion; $SvcO_2$ (if available)

Circulation – objective: MAP >65mmHg (or higher if previously hypertensive) - check pulse, cardiac rhythm, signs of central venous congestion, and inferior vena cava diameter variation with respiration;

Organ dysfunction – evaluate and register mental state, diuresis, skin mottling, capillary refill time (extremities color and temperature)

Cell homeostasis – measure and follow evolution of arterial lactate, pH, HCO_3 and BE during resuscitation

Hemodynamic Approach

- ✓ If hypotension and/or lactate >2 mmol/L or signs of organ hypoperfusion start iv fluids
- ✓ Prefer crystalloids and "fluid challenge strategy" (iv bolus, as needed, consider at least 30 mL/kg in the first 4-6h)
- ✓ If hypotension (MAP <65mmHg) persists, start vasopressors as necessary to reach MAP>65mmHg (or higher if previously hypertensive) and monitoring frequently the response with 2O + 2C
- ✓ Assess IAP repeatedly; target MAP to achieve a splanchnic perfusion pressure >65mmHg; consult a surgeon to consider abdominal decompression.

Fluid Challenge Strategy

- ✓ Select the infusion fluid;
- ✓ Chose appropriate volume: 250-500 mL (for a 70-kg adult) according to expected cardiac function
- ✓ Define infusion time: 20-30 min
- ✓ Define intended MAP: 65–70 mmHg or systolic pressure (>90mmHg)
- ✓ Define safety limits: signs of respiratory distress, signs of pulmonary edema or CVP < 12-15 mmHg
- ✓ Prefer dynamic / continuous monitoring (at list each 5-10min), because static data are less informative

Successful Test: Desired MAP has been achieved without overcoming safety limits

Interpretation: the patient had volume depletion and fluid challenge started correcting the deficit

Unsuccessful Test: Desired MAP has not been achieved within safety limits or alarming signs occurred.

Interpretation: patient has enough fluid for the present state of his heart and could need vasoactive drugs. Do not overload with more fluids

Additional considerations:

- ➢ If Hemoglobin < 8g/dL, consider transfusion to achieve Hb >8g/dL or10 g/dL if coronary ischemia present
- ➢ If vasopressors needed: prefer norepinephrine/dopamine (take into consideration arrhythmia and tachycardia)
- ➢ If target blood pressure is not attained, consider adding epinephrine or vasopressin / terlipressin (1–2 mg IV daily perfusion)
- ➢ If signs of low CO (echocardiography), consider inotrope support: eg, dobutamine (in a septic shock setting do not start dobutamine without a vasopressor because of the risk of worsening hypotension and tachycardia)

Warning: patients with risk of pulmonary or cerebral edema should have careful monitoring before, during, and after volume infusion.

Warning: excessive fluid load is related with worst prognosis, keep fluids as needed and consider vasopressors to prevent overload

Warning: excessive vasopressor infusion without proper volume resuscitation risks to deteriorate tissue perfusion,despite normalized hemodynamic parameters.

Definitions

Hypotension is defined as a SBP <90 mmHg or MAP <65 mmHg or a SBP decrease >40 mmHg or >2 SD below normal for age in the absence of other causes of hypotension.

Abbreviations: CO -cardiac output; CVP -central venous pressure; DO_2-oxygen delivery; Hb -hemoglobin; IV -intravenous; MAP -mean arterial pressure; PaO_2-arterial oxygen -partial pressure; SaO_2-arterial oxygen saturation; SBP -systolic blood pressure; SD -standard deviation; $SvcO_2$ - central venous blood oxygen saturation.

Fig. 22.3 Proposed algorithm with the strategies to optimize DO_2 and tissue perfusion in severe sepsis and septic shock, namely, abdominal sepsis

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Adjunctive Therapies in Abdominal Sepsis

23

Thomas Ryan and John D. Coakley

23.1 Background

Intra-abdominal sepsis is a commonplace complication of a wide variety of primary gastrointestinal pathologies such as cholecystitis, diverticular disease, peptic ulcer with perforation, pancreatitis and also as an iatrogenic complication of surgical procedures. Among the iatrogenic complications, intra-abdominal sepsis from a leaking anastomosis is probably the most frequently observed, although abdominal sepsis may also arise following urinary diversion with formation of an ileal conduit or incarceration of bowel loops in an internal hernial sac.

The initial therapy for intra-abdominal sepsis should comply with internationally accepted guidelines and must include adequate resuscitation, aggressive support of failing organs, culture of relevant fluids and tissues, initiation of broad-spectrum antimicrobial cover, with early abdominal imaging in order to direct prompt surgical or radiologically guided intervention [1]. Thus, it seems appropriate that adjuvant therapy for intra-abdominal sepsis should only be contemplated once the basic interventions outlined by internationally accepted guidelines have been implemented.

Following resuscitation, source control and initiation of empiric antimicrobial cover, clinicians have come to expect the sequelae of marked systemic inflammation in the first few days after the onset of intra-abdominal sepsis. Thus, an initial period of haemodynamic instability, characterised by a requirement for high doses of vasopressors to maintain adequate mean arterial pressure, is commonly observed, along with acute hypoxic respiratory failure secondary to acute respiratory distress syndrome, a variable degree of acute kidney injury, evidence of disseminated intravascular coagulopathy and hyperbilirubinaemia indicative of hepatic impairment.

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In the absence of residual intra-abdominal infection, the extent and severity of organ failure should start to resolve within a few days of the initial onset of sepsis. Evidence of ongoing systemic inflammation, such as fever, leucocytosis and elevated biomarkers of inflammation, such as CRP and/or procalcitonin, is suggestive of residual intra-abdominal infection and mandates repeat abdominal imaging with percutaneous drainage of infected material or an open surgical intervention for repair of leaking anastomoses when necessary.

Persistent severe organ failure with sepsis of any origin is associated with an increased risk for mortality and must be addressed as a matter of urgency [2]. Although the underlying pathophysiology of progressive organ failure has yet to be finally resolved, the proximate mediations of organ damage include innate immune mediators such as complement and interleukin-6 [3]. Dysregulated systemic inflammation, driven by circulating endotoxin and/or by mitochondrial DNA, has a role in generating additional organ damage [4, 5]. However, unresolved intra-abdominal infection may be quite common and should always be a concern for clinicians [6].

Fungal infections, predominantly with candida species, are becoming increasingly common in critically ill patients and are associated with a significant increase in mortality [7, 8]. Fungal sepsis is a particular problem in patients with abdominal sepsis. Mortality with fungal sepsis increases with delayed source control and with delayed therapy of fungal sepsis. Thus, in high-risk patient groups, prophylactic anti-fungal therapy as an adjuvant sepsis therapy may be warranted [9]. Risk factors for fungal sepsis in critically ill patients include complex and complicated abdominal surgery, in patients who require central venous catheters for total parenteral nutrition, who develop renal failure and who receive broad-spectrum antimicrobial therapy [10]. Management of invasive candidiasis complicating abdominal sepsis is made more complex by the poor sensitivity of fungal cultures and the absence of reliable biomarkers [11]. Furthermore, the consequences of delayed therapy for fungal sepsis are such that both prophylaxis and empiric therapy with antifungal agents are advocated for high-risk patients [12]. Such patients include those with gastrointestinal perforation, anaesthemotic leaks and acute necrotising pancreatitis. With regard to the role of adjuvant therapies for abdominal sepsis, it is noteworthy that corticosteroids, administered in patients with septic shock, further increase the risk for invasive candidiasis [13].

Adjunctive sepsis therapies can be divided into two main groups: anti-inflammatory therapies that purport to limit the deleterious effects of systemic inflammation, and immune adjuvant therapies aimed at eradicating residual infection. While systemic inflammation and persistent infection likely coexist in human sepsis, unfortunately most adjunctive therapies targeting systemic inflammation have immune suppressive side effects which may further impede host immune response to infection. However, immune adjuvants have a potential to exacerbate systemic inflammation and thereby exacerbate existing organ failure. Furthermore, the relative roles of systemic inflammation and persistent infection in the pathophysiology of unresolved and unresolving organ failure have yet to be elucidated. In this regard, recent literature, highlighting the role of immune suppression in the pathophysiology of sepsis, and increasingly advocates immune-based adjuvant

sepsis therapies as opposed to the more conventional anti-inflammatory therapies [14]. With this background knowledge in mind, anti-inflammatory sepsis adjuvant therapies will be discussed before examining potential immune adjuvant therapies.

23.2 Anti-inflammatory Therapies

23.2.1 Steroids

Surviving sepsis guidelines include hydrocortisone as a therapy for septic shock that is refractory to bolus intravenous fluids and vasopressor infusions [1]. Although hydrocortisone was reported to significantly decrease vasopressor requirements in patients with sepsis in the Corticus study, hydrocortisone did not improve outcome and was associated with increased risk for secondary infection [15]. This haemodynamic effect of hydrocortisone in septic patients is likely meditated by inhibiting inflammation, decreasing IL-6 and IL-8 levels in blood and inhibiting nitric oxide synthesis rather than any direct adrenal effect [16]. Consequently, the use of low physiologic dose steroids advocated in the Surviving Sepsis Guidelines may not need to be guided by the results of adrenal stimulation tests as has been advocated in the past [17]. Unfortunately, hydrocortisone has well-recognised immune suppressant effects in patients with sepsis, which are mediated in part by inhibition of antigen presentation in macrophages and may account for the increased incidence of secondary infection linked with steroid usage [18]. This link between hydrocortisone as a therapy for shock and both secondary infection and immune suppression is of some concern, given the reported occurrence of unresolved infection in surgical patients who succumb to sepsis [6]. Subsequent to the Corticus study, a retrospective study of the surviving sepsis campaign database, including almost 18,000 patients with septic shock, reported an association between administration of hydrocortisone and excess mortality [19]. In the particular context of intra-abdominal sepsis and/or complex abdominal surgery, corticosteroids are a risk factor for the development of invasive candidiasis [20]. Thus, in the particular context of intra-abdominal sepsis, corticosteroids should be used sparingly, if at all.

Therefore, when using corticosteroids as a sepsis adjuvant, a prudent approach is to reserve hydrocortisone for severe shock refractory to fluid and vasopressors, and then to discontinue hydrocortisone as soon as possible.

23.2.2 Polymyxin-b Haemoperfusion (PMbHP)

Haemoperfusion with a polymyxin-b filter binds and removes circulating lipopolysaccharide and thereby purports to inhibit systemic inflammation. As nephrotoxicity limits the systemic use of systemic polymyxin-b, haemoperfusion via an extracorporeal circuit with polymyxin-b bound to polystyrene fibres in a cartridge circumvents this adverse effect. PMbHP, which is optimally delivered within the

first 24 h of the onset of sepsis, effectively clears lipopolysaccharide from the circulation, with a 20% reduction in endotoxin levels over a 2-h treatment.

PMbHP has been employed as a therapy in excess of 100,000 patients in Japan, North America and Europe. In clinical practice, thrombocytopenia is the most frequently recognised complication, but transient hypotension and allergic reactions have been reported. Despite widespread use in Japan over several decades, PMbHP has not been extensively trialled and has not entered clinical use in Europe or North America.

A recent meta-analysis of the effect of blood purification techniques upon mortality in patients with sepsis examined the use of a range of technologies including haemofiltration, plasma exchange and haemoperfusion, in 16 trials of 827 patients [21]. In this meta-analysis, overall blood purification techniques appeared to decrease mortality in patients with sepsis; however, the benefit was linked exclusively with data from ten trials of 557 patients studying the effects of PMbHP.

One such study by Cruz et al. investigated PMbHP in a small controlled multicentred trial of 64 patients with septic shock from intra-abdominal sepsis [22]. In this study, PMbHP therapy was linked with improved haemodynamics, a decrease in organ failure scores and a decrease in 28-day mortality when compared with conventional therapy. More recently, Monti et al. reported upon the use of PMbHP as a rescue therapy in 52 patients with refractory septic shock and observed a significant decrease in vasopressor requirements [23]. Similarly, Sawa et al. studied the effect of PMbHP as a rescue therapy, comparing the effects of vasopressin and PMbHP on mortality in patients with septic shock. Interestingly, in Sawa's study, patients with abdominal sepsis appeared to be more likely to benefit from PMbHP than a general population of septic patients [24] .

However, in a recent and larger study of PMbHP in patients with peritonitis and septic shock, there was no beneficial effect of PMbHP, either on the severity of organ failure or mortality [25]. The discordant results of these trials may be ultimately resolved in the current EUPHRATES trial that is recruiting to a multicentred study of PMbHP in patients with septic shock and with detectable endotoxin in the peripheral blood.

23.3 Immune Adjuvant Therapies

23.3.1 Immune Globulins

Studies investigating the role of intravenous immunoglobulin as an adjunctive therapy in sepsis were reviewed recently by the Cochrane collaboration [26]. This review concluded that administration of intravenous immune globulin improved outcome in adults with sepsis. These studies included all patients with sepsis, without any attempt to identify patients with hypogammaglobulinaemia, who might have a greater chance of responding to intravenous immunoglobulin.

What is the proposed mechanism of action for intravenous immune globulins in sepsis? While some studies have linked adverse outcome with

hypogammaglobulinaemia in sepsis [27–29], not all such studies detected this link [30]. In studies that reported such a linkage between mortality in sepsis and immune globulin levels, patients with the lowest deciles of IgM levels experience particularly high mortality rates. In addition, change in IgM levels in the first few days appears to be as important as any single IgM level [31]. Hence, when contemplating the use of immune globulins in sepsis, intravenous immune globulin should be administered at the onset of sepsis, as delayed administration appears to reduce benefit [31].

Intravenous immune globulins as a sepsis adjuvant therapy will merit further and more focused study, given that recent reports have identified a relatively small subgroup of septic patients with profound hypogammaglobulinaemia that experience a significantly greater mortality rate [29]. This subgroup of patients, representing only approximately 10–20% of all patients, may potentially benefit from individualised adjuvant therapy with intravenous immunoglobulin. This high-risk subgroup experiences a marked increase in mortality with sepsis and is characterised by a deficit in both IgM and IgA levels [32]. As a consequence, it is plausible that the existing studies of immunoglobulin in sepsis, which recruited patients without regard to underlying immunoglobulin levels, may have been underpowered to detect a beneficial effect in such a small minority of patients. Thus, the potential benefit of immunoglobulin in sepsis may be much greater than that appraised by the Cochrane collaboration review.

This area of research is both novel and promising as it offers a realistic possibility for individualised immune adjuvant sepsis therapy with a medication that currently has regulatory approval and is in widespread use in neurology and haematology, with minimal side effects.

23.3.2 Interferon-γ

Interferon-γ may act as an immune adjuvant in critically ill patients by inducing HLA-Dr expression in antigen-presenting cells, thereby enhancing T lymphocyte activation and potentially augmenting phagocyte bactericidal activity.

Historically, the potential benefit of interferon-γ as an immune adjuvant was investigated in trauma patients and patients with burns [33]. In a large study of patients with major trauma, interferon-γ did not alter outcome but was noted to decrease the incidence of intra-abdominal infections. Interferon-γ had no effect on the outcome of patients with burn injuries and did not decrease the incidence of infection in burn patients [34].

More recently, interferon-γ has been selectively administered to patients with demonstrated deficit in monocyte HLA-Dr expression, in order to enhance such expression. While interferon-γ increases HLA-Dr expression in patients with sepsis, this effect is not immediately apparent, taking at least a week to have a perceptible effect [35].

Case series have suggested a role for interferon-γ as an adjuvant therapy in patients with invasive candidiasis which may be of particular relevance given the incidence of fungal infections in patients with abdominal sepsis [35–37]. Further

study will be required to define the patients most likely to benefit for adjuvant therapy with interferon-γ. Currently a Dutch group is conducting a randomised trial of interferon-γ as an immune adjuvant in patients with sepsis, with results due in early 2017.

23.3.3 G-CSF and GM-CSF

While GM-CSF appears to upregulate HLA-Dr expression on monocytes [38] and thereby potentially augment innate immunity, these immune stimulatory effects are not universal [39] and may not translate into a survival benefit. Putative benefits include shorter ICU stay and shorter duration of mechanical ventilation [38]. However, existing studies are small in size and will need to be validated in larger multicentred studies. The existing studies of the effect of G-CSF and GM-CSF in sepsis have recently been reviewed by Bo et al. [40].

Currently there is an ongoing randomised trial of GM-CSF administered as an immune adjuvant in sepsis in order to decrease the incidence of ICU-acquired infection. This trial is due to finish recruiting in 2018.

23.3.4 PD-1

Lymphocyte populations change dramatically in patients with sepsis. In sepsis, lymphopenia is commonplace [41], lymphocyte apoptosis increases [42], T cell diversity decreases [43], and lymphocytes express predominantly inhibitory surface molecules [44]. Among these inhibitory molecules are PD-1 and respective ligands PDL-1 and PDL-2. These molecules are members of a larger class of molecules that interact to regulate adaptive immune activation by innate immune lymphocytes. Apart from PD-1 and respective ligands, the molecular class includes the B7/CD28 and CTLA-4 and BTLA-4 molecules. Of these molecules, PD-1 and respective ligands have received attention of late in their putative role as immunotherapy in oncology [45].

In humans with sepsis, surface PD-1 expression on CD4 lymphocytes is increased, and surface expression of PDL-1 is similarly increased on monocytes [46]. Furthermore, survival and occurrence of nosocomial infection are linked with expression of PD-1 and PDL-1. Interestingly monocyte IL-10 expression, an anti-inflammatory and immune suppressant cytokine, was related to PD-L1 expression by monocytes, while lymphocyte replication was inversely related to CD4 PD-1 expression.

Given these findings, anti-PD-1 antibodies have been proposed as potential immune adjuvants in sepsis. Unfortunately, prior attempts to activate T lymphocytes in humans with sepsis were counter-productive. Direct activation of CD28 by a monoclonal antibody resulted in a massive systemic inflammatory response, multiple organ failure and death in healthy volunteers, despite extensive supportive background animal data [47]. Interspecies differences between humans and laboratory

animals likely accounted for this particular failure. However, this experience has somewhat dampened enthusiasm for immune adjuvant therapy by direct T cell activation in patients with sepsis.

23.3.5 Interleukin-7

Given the well-recognised lymphocyte apoptosis that occurs in septic patients, and the adverse outcome linked with lymphopenia and lesser T cell diversity in patients with sepsis, then there is potential niche for an immune modulant that expanded T cell populations and diversity. Recombinant IL-7 is an obvious candidate for this mechanism of immune modulation.

T lymphocyte homeostasis is regulated by cytokines of the common gamma-chain family, including IL-2, IL-7 and IL-15. While IL-2 and IL-7 both expand CD4 lymphocytes, low doses of IL-2 preferentially expand CD4FoxP3 inhibitory Treg cells, whereas low doses of IL-7 preferentially expand CD4 effector cells [48]. Indeed STAT-5 gene expression in CD4 cells has been proposed as a biomarker of IL-7 efficacy in sepsis [49].

When the effects of IL-7 and PD-1 antagonism are compared on splenic lymphocytes in an animal sepsis model, IL-7 expands populations of activated CD4 lymphocytes, whereas PD-1 antagonism enhances the expression of MHC molecules in antigen-presenting cells [50]. Thus, the effects of IL-7 and PD-1 antagonist antibody may potentially be complementary in sepsis.

Recombinant IL-7 is available for human use and, when administered to lymphopenic patients following marrow transplantation, appears to preferentially expand memory T lymphocytes [51]. Thus, IL-7 of itself or in combination with PD-1 Ab offers an exciting prospect for immune modulation as an adjuvant therapy in sepsis.

Currently, a phase II study of the effects of recombinant IL-7 on lymphocyte populations and patient outcome in sepsis has a completion date of early 2017.

23.4 Summary

Standard medical care as outlined in international guidelines for patients with sepsis should be applied to all patients with abdominal sepsis. In profoundly shocked patients, hydrocortisone may be administered to attenuate shock severity. As steroids are a risk factor for invasive candidiasis, a major problem with abdominal sepsis, the dosage and duration of steroid therapy should be minimised.

Profound hypogammaglobulinaemia is a risk factor for mortality in sepsis. Prior studies of intravenous immune globulins in sepsis suggest a benefit in terms of decreased mortality; however, such benefit may potentially be much greater in the select group of patients with marked hypogammaglobulinaemia. The role of blood purification as an adjunct therapy in patients with sepsis remains to be established.

Novel sepsis-specific immune adjuvant therapies are currently under investigation and will in time change sepsis management and outcomes.

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Impact and Management of Abdominal Compartment Syndrome in Patients with Abdominal Sepsis

24

Jan J. De Waele

24.1 Introduction

Intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) have evolved from incompletely understood and inconsistently reported concepts to universally accepted contributors to organ dysfunction in various categories of critically ill patients [1]. IAH is a continuous process with a dose-dependent effect on different organ systems, and ACS is the final result of prolonged increased intra-abdominal pressure (IAP), resulting in a clinical picture of multiple organ dysfunction. Initial reports described IAH and ACS in trauma and acute surgical patients—mostly postoperative—but IAH and ACS have now been described in various kinds of critically ill patients [2]. Decompressive laparotomy and open-abdomen therapy were once the sole treatment option, but better insights in the pathophysiology of the disease have led to the current understanding that both preventive strategies and therapeutic interventions for IAH exist and may defer or avoid a decompressive laparotomy. This chapter will focus on the role of IAH and ACS in patients with abdominal sepsis, as well as current treatment options.

24.2 IAH and ACS Definitions

IAP is defined as 'the steady-state pressure in the abdominal cavity', which is determined by two components: the intra-abdominal volume and compliance of the abdominal wall [3]. Normal IAP values are expected to be around 5–7 mmHg in critically ill adults, although it is difficult to define what 'normal' is in this setting, and some degree of increased IAP will go unnoticed. This 'normal' IAP is higher in

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(morbidly) obese patients but rarely higher than 15 mmHg; any IAP higher than 15 mmHg in an obese patient should not be attributed to the patient's appearance alone [4].

IAH is characterized by a sustained or repeated pathological elevation of IAP greater than or equal to 12 mmHg [1]; IAH is graded from 1 to 4 depending on the level of IAH, with grade 1 (12–15 mmHg) and 2 (15–20 mmHg) being most common.

WSACS—the Abdominal Compartment Society defines ACS in adults as a sustained IAP of 20 mmHg or higher that is associated with new organ dysfunction/failure. It should be underlined that organ dysfunction—often clinically unnoticeable—may start at lower values than 20 mmHg. IAH affects organ function in a dose-dependent way, but will ultimately lead to the full clinical syndrome of ACS if left to progress.

IAH/ACS may be further classified as primary, secondary or recurrent with primary IAH/ACS associated with injury or disease in the abdominopelvic region and secondary IAH/ACS referring to conditions that do not originate in the abdominopelvic region. Abdominal sepsis patients are as such to be considered primary ACS. Furthermore, recurrent IAH/ACS may often complicate the disease in this setting; it is characterized by the redevelopment of IAH/ACS following a previous treatment of IAH/ACS.

24.3 IAP Measurement

Intermittent IAP measurement via the bladder with a maximal instillation volume of 25 mL of sterile saline is now the reference method to measure IAP in most intensive care units (ICU) [5]. It should be measured at end expiration, in the supine position, while ensuring that abdominal muscle contractions are absent. The transducer needs to be zeroed at the level of the mid-axillary line, not the symphysis pubis. IAP measurement is most reliable in completely sedated, mechanically ventilated patients. However, many mechanically ventilated patients in the ICU are now less sedated, and spontaneous breathing movements or pain may affect IAP measurement. Although there are no specific data on this, it has been reported that in awake, noncritically ill patients without the suspicion of IAH, IAP can be increased without impact on organ function. The impact of high positive end-expiratory pressure (PEEP) on IAP is considered to be mild and clinically insignificant.

24.4 Pathophysiology

The two main causes of increased IAP that contribute to the development of IAH and eventually ACS are increased intra-abdominal volume and decreased abdominal wall compliance (Table 24.1).

In the setting of abdominal sepsis, intra-abdominal volume on the one hand may increase due to ischemia-/reperfusion-related oedema, postoperative fluid accumulation and ileus, whereas abdominal wall compliance may decrease due to surgical

Table 24.1 Factors contributing to IAH in abdominal sepsis patients

Increased intra-abdominal volume	Decreased abdominal wall compliance
• Bowel wall oedema	• (Postoperative) pain
• Mesenteric and retroperitoneal oedema	• Abdominal wall oedema
• Intraperitoneal fluid (ascites, pus)	• Abdominal wall closure
• Ileus with GI tract dilatation	• Abdominal bandages

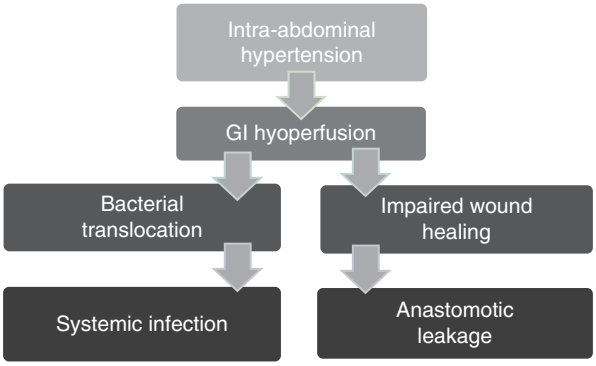

Fig. 24.1 Impact of IAH on intestinal function

trauma, oedema and postoperative pain. It is important to realize that both the abdominal infection and the treatment, namely, fluid resuscitation and surgery, play a role in the development of IAH.

A typical feature of the factors contributing to IAH and ACS is that they are not all that easy to treat. Interstitial oedema formation, for example, is the most challenging to tackle. It is linked to fluid resuscitation, and for this a pre-emptive strategy, using fluid restriction is more likely to be successful in avoiding ACS (see below).

The effects of IAH of course are multiple and will spread well beyond the peritoneal cavity, and these are beyond the scope of this chapter. The effects specifically related to abdominal infection are represented in Fig. 24.1.

The effects of IAH on the gut have been studied mainly in animal models. Studies have found increased IAP (a) to impair gut perfusion [6], (b) to lead to structural changes in the gut [7] as well as (c) to cause bacterial translocation [8], all of which are important drivers of systemic inflammation and subsequent organ dysfunction. In animal studies IAH has been found to delay the healing of colonic anastomoses [9]. It is unclear how these phenomena translate to clinical practice and at which level this effect starts to have a major impact.

24.5 Epidemiology

Although initially only reported in (abdominal) surgical and trauma patients, in recent years it has become clear that IAH/ACS can affect any type of critically ill patient. The reported incidence in general ICU patients ranges between 21% and

58% for IAH and between 1% and 12% for ACS, depending on the study period and case mix [10]. This variation in incidence and prevalence estimations across studies may also be explained by differences in IAP monitoring frequency, as well as the use of preventive or therapeutic measures for IAH, as many ICUs now have been integrating these concepts in daily care. A large individual patient data meta-analysis from 21 centres in 11 countries reported that 28% had IAH, and 3% had ACS, at ICU admission [2]. A pre-emptive strategy towards ACS (integrating restrictive fluid resuscitation, prophylactic open-abdomen management by the surgical team and IAP targeted interventions) has allowed some hospitals to greatly reduce the incidence of ACS.

Several studies have demonstrated that IAH and ACS are associated with an independently increased risk of acute renal failure, multiple organ dysfunction syndrome (MODS) and death among mixed populations and certain subgroups of adult ICU patients [2]. A prospective study reported that patients with IAH had a significantly higher number of organ dysfunctions in the first 3 days after admission [11]. Furthermore, an individual patient data meta-analysis of 1669 general ICU patients recruited into 14 studies suggested that absolute ICU mortality was 13% higher among those with IAH at admission as compared to those without IAH [2].

In a series of 78 patients with secondary peritonitis undergoing serial measurements of the IAP, 32 (41%) developed IAH postoperatively [12]. 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.

24.6 Prevention of IAH and ACS

The prevention of IAH and particularly ACS is highly desirable. As the risk factors have been better described in recent years, identifying patients at risk for IAH in the setting of abdominal sepsis is not difficult. In these patients, many of the established risk factors for IAH are present and even more so when patients present with organ failure [10]. Risk factors that are typically present in patients with abdominal sepsis are summarized in Table 24.2.

Clinicians who are aware of the problem of IAH and ACS in other settings will have no problems detecting the problem early in peritonitis patients. Although this may be an oversimplification, the combination of an abdominal catastrophe such as severe peritonitis requiring emergency surgery and the need for fluid resuscitation should point the clinician in the right direction. IAH should be anticipated, and IAP monitoring is advised in IAI patients presenting with severe sepsis or septic shock requiring emergency surgery or other source control procedures.

Preventing IAH and ACS is a joint responsibility for all involved in the care of the patient and will surpass classical hospital organization. This starts with a rapid diagnosis in the emergency room that allows early source control, a clear commitment from the surgeon to proceed to surgery promptly when required as well as the

Table 24.2 Risk factors for IAH typically present in patients with abdominal sepsis (based on Holodinsky et al. [10])

Risk factor	Odds ratio (95% CI)
Presenting diagnosis	
Sepsis	2.38 (1.34–4.23)
Abdominal infection	2.49 (0.48–13.0)
Abdominal surgery	1.93 (1.30–2.85)
Ileus	2.05 (1.40–2.98)
Disease severity	
Acidosis	1.93 (1.12–3.45)
Shock/hypotension	
Vasopressor use	2.33 (1.02–5.35)
Shock	4.68 (1.93–6.44)
Hypotension	2.12 (1.05–4.50)
Crystalloid resuscitation	
Fluid balance	5.22 (2.03–7.45)
Non-crystalloid resuscitation	
Fluid resuscitation (>3.5 L crystalloid or colloid)	2.17 (1.30–3.63)

use of open-abdomen treatment in selected cases (see below). At all stages fluid resuscitation should be carefully considered; whilst this may be life-saving in many occasions, over resuscitation often ensues, and patients often suffer from the consequences of peripheral interstitial oedema that is difficult to treat.

24.7 Management

When IAH develops, several strategies are available to avoid deterioration or reduce IAP [1]. Fluid administration should be carefully considered, and parameters such as urinary output are not reliable to assess organ perfusion.

Adequate analgesia and removal of constrictive bandages can help to maximize abdominal wall compliance. Postoperative bleeding or fluid accumulation may add to IAH, and ultrasound may be helpful to identify these lesions and guide drainage. Postoperative ileus and gut distention are another common contributor to IAH for which nasogastric drainage and suctioning can be required. If these interventions are unsuccessful and ACS ensues, abdominal decompression with open-abdomen treatment may be necessary.

The updated 2013 WSACS IAH/ACS consensus management statements provide an overview of the current management of IAH/ACS in critically ill patients [1]. Medical and minimally invasive therapies have been proposed for patients with IAH, before one needs to resort to decompressive laparotomy. Admittedly high-quality evidence for these interventions is often lacking, but according to the latest WSACS guideline, there is enough data to suggest that less invasive methods be attempted before surgical management of IAH is considered. The WSACS IAH/ACS management algorithm (including the different levels of recommendation for each intervention when data are available) is shown in Fig. 24.2.

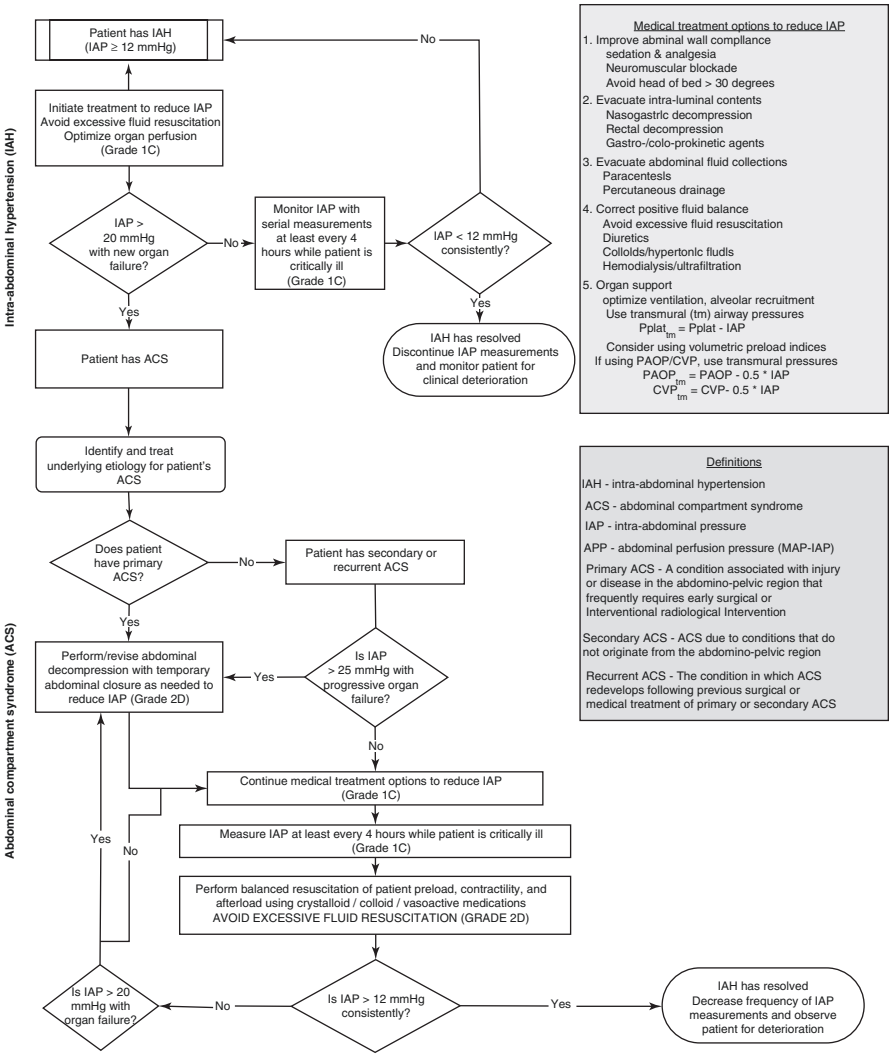

Fig. 24.2 IAH/ACS management algorithm

Medical management strategies have been classified based on their mechanism of action in three domains: (1) improvement of abdominal wall compliance (adequate sedation and analgesia, body positioning changes, neuromuscular blocking agents), (2) evacuation of intra-luminal contents (nasogastric or rectal decompression, use of prokinetic agents) and (3) drainage of intra-abdominal fluid collections (percutaneous catheter drainage of peritoneal fluid). Again, the expected benefit and potential harm should be individually considered, as risks associated with each of these treatment options may vary according to the clinical setting. Percutaneous catheter drainage of free fluid is probably the most easy and accessible treatment

option in several conditions that lead to free fluid accumulation with significant impact organ dysfunction. It can easily be performed at the bedside with or without ultrasound guidance, although we recommend the latter. Throughout the treatment, keeping an eye on the fluid balance is important and avoidance of excessive fluid resuscitation and correction of an all too positive patient fluid balance (through limited resuscitation volumes and maintenance fluid for most patients, diuretics in selected patients and haemodialysis or ultrafiltration in the rare patient). The WSACS IAH/ACS medical management algorithm summarizes the role of these interventions (Fig. 24.3).

When medical interventions fail as well as in hyperacute situations, surgical intervention may be necessary through a decompressive laparotomy. The

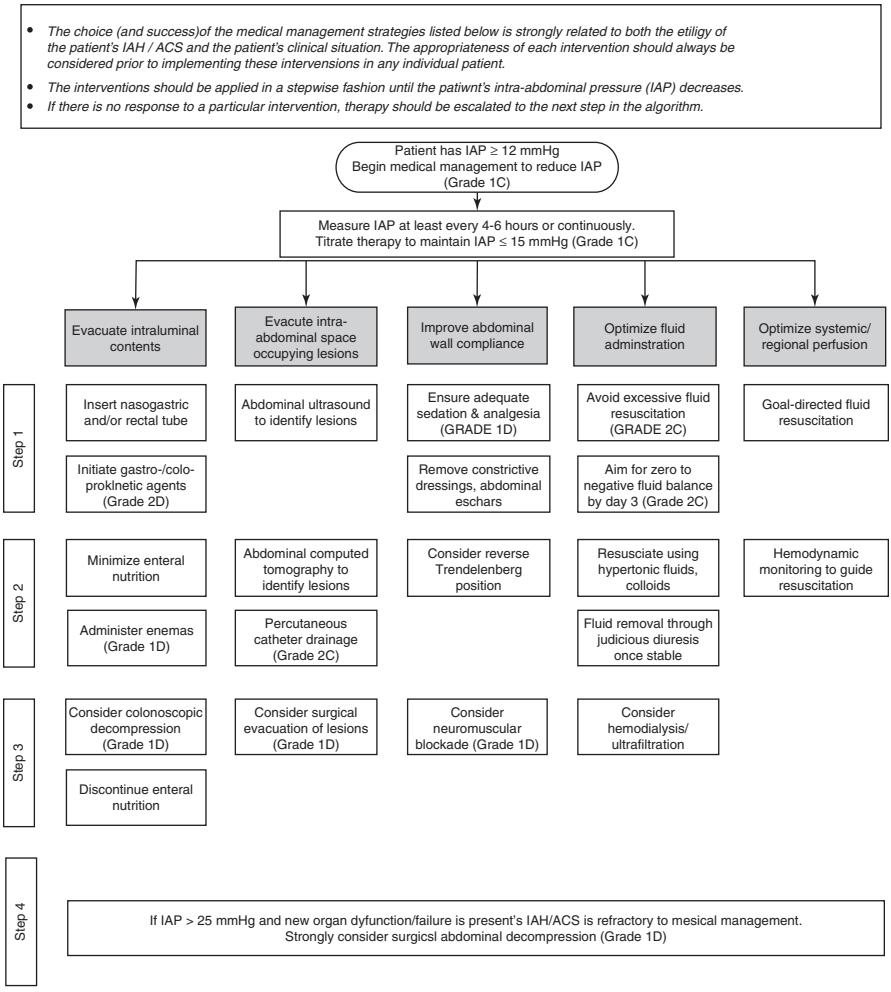

Fig. 24.3 WSACS IAH/ACS medical management algorithm

introduction of medical treatment options for IAH and ACS, however, has greatly reduced the need for surgery. Decompressive laparotomy is effective in reducing IAP and improves organ function when done in a timely fashion [13]. This implies that this intervention should be done early in the course of the disease. When prolonged ACS has led to irreversible organ damage (at least on a short-term basis), decompressive laparotomy may come too late. A midline full-length laparotomy is most often used, and a method for temporary abdominal closure (TAC) will be required in most patients (see below). The decision to decompress an abdomen may be less prone to discussion in patients who have had surgery for abdominal sepsis; often other persistent problems are detected during decompressive laparotomy such as intestinal ischaemia, perforation or suture leakage.

24.8 The Role of Open-Abdomen Management

As many of the contributors to IAH and ACS are not easy to treat (such as oedema of both bowel, retroperitoneum and abdominal wall as well as ileus among others), leaving the abdomen open as a preventive measure after surgery is an often employed strategy [14].

Open-abdomen therapy has been shown to effectively reduce IAP when patients are suffering from ACS, so it can be assumed that this is an effective preventive measure as well. Moreover, by preventing that the patient enters a vicious circle of organ dysfunction, more fluid administration and higher IAP, leaving the abdomen open—at least temporarily—is an attractive strategy that has been used for a long time in damage control surgery for trauma patients. Whereas it is clear that the concepts of damage control surgery cannot be blindly extrapolated to peritonitis, the contribution of IAH to organ dysfunction may have many similarities in both situations.

The exact role of open-abdomen treatment (OAT) in peritonitis however is still under debate. In a small study of 40 patients, Robledo et al. found an increased mortality rate in patients treated with OAT, which lead to early termination of the study [15]. It is not clear if the causes of death were related to the OAT, and it should also be noted that a home-made open-abdomen technique was used without the application of negative pressure. IAP was not monitored pre- or postoperatively, and it is not clear how often IAH and ACS ensued in these patients. This study demonstrates that this is not universally applicable in peritonitis and that only patients at risk for IAH should be considered.

Whereas OAT was often done using home-made appliances that had many disadvantages, the recent addition of negative-pressure therapy (NPT) to the armamentarium has revolutionized the care for these patients in the ICU. There is an increasing body of literature demonstrating that integrating NPT in OAT leads to higher fascial closure rates as well as shorter duration of OAT. Although most of the research has been done in trauma patients, several studies have included vascular surgery and peritonitis patients as well.

A recent systematic review of OAT and TAC systems that focused specifically on non-trauma patients, most of them suffering from peritonitis, found that TAC using

NPT and a mesh-mediated technique resulted in the highest fascial closure rates and the lowest risk of enterocutaneous fistula [16]. From this review, it is clear that not all TAC systems are created equal and the impact of leaving the abdomen open is also linked to the TAC that will be used afterwards.

Based on the currently available evidence, OAT treated with NPT and mesh-mediated traction has the best results in terms of closure rates and lowest complication rates with acceptable reported mortality rates.

One of the hypotheses for these results is the additional negative pressure that is more effective in removing fluid from the abdominal cavity. Indeed, several studies have shown that NPT is effective in removing postoperative fluid accumulation, but it may also be effective in reducing tissue oedema which facilitates abdominal closure and decreases the inflammatory response in this setting.

The research on this topic is ongoing; so far studies often mixed different causes leading to OAT, and the role of NPT in the specific setting of peritonitis may be difficult to estimate. Nevertheless, the results appear to be promising. In a non-randomized study comparing OAT with and without NPT, Mutafchiyski et al. report improved outcomes using NPT in patients with diffuse peritonitis, including shorter ICU stay (15 vs 26 days) and lower mortality rates (31% vs 53%) [17]. Kirkpatrick et al. randomized 45 patients (just over half of them suffering from peritonitis) to OAT using either NPT (KCI ABThera) or Barker's vacuum pack; not only outcomes but also inflammatory mediators in the plasma and locally were studied [18]. There was no difference in IL-6 (baseline vs 24 or 48 h) between the groups. Although severity scores were no different at baseline, 90-day mortality in the NPT group was significantly lower, which could not be explained by the differences in peritoneal fluid drainage, fascial closure rates or markers of systemic inflammation.

Conclusion

Patients with abdominal sepsis are at risk of IAH, both because of the primary condition and treatment they receive, both surgical and medical. The increased IAP may further impact intestinal perfusion and function, which may affect intestinal healing and contribute to systemic inflammation and lead to bacterial translocation. Proactive IAP monitoring, restrictive fluid resuscitation, avoiding fluid accumulation in the abdomen and selected use of open-abdomen treatment in patients with severe abdominal sepsis at risk will reduce the risk of ACS. Open-abdomen management with negative-pressure therapy currently is the preferred TAC method; the exact role of NPT in dampening systemic inflammation remains unclear.

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Thromboprophylaxis in Patients with Abdominal Sepsis

25

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25.1 Introduction

Venous thromboembolism (VTE), pulmonary embolism (PE), and deep venous thrombosis (DVT) are potentially severe complications in surgical patients. PE is considered the leading preventable cause of in-hospital death [1, 2]. Prevention of venous thromboembolism in critical surgical patients is a challenge because of the high risk of venous thromboembolism [3]. An analysis of a large registry of 175,665 critically ill adult medical-surgical patients from 134 intensive care units (ICU) in Australia and New Zealand was published in 2011. The study showed a significant association between omission of early thromboprophylaxis and hospital mortality in critically ill adult patients [4].

There have been no comprehensive studies that have compared the incidence of symptomatic VTE over a spectrum of different urgent or elective surgical procedures [5]. Moreover, there have been no comprehensive studies in the setting of patients affected by sepsis of abdominal origin (abdominal sepsis). Patients with abdominal sepsis may be at increased risk of VTE due to their premorbid

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conditions, surgical intervention, admitting diagnosis of sepsis, long-term intravascular catheter, invasive tests and procedures, prolonged immobility, or paralysis during ICU stay.

25.2 Risk Factors for VTE

25.2.1 General Risk Factors for VTE

The risk of VTE may be determined by patient-specific factors. It is well known that the incidence of venous thrombosis (VT) increases sharply with age. It is quite rare in young individuals with an incidence as low as 1 per 10,000 annually before the fourth decade of life, rising rapidly after 45 years of age, and approaching 5–6 per 1000 annually by age 80 [6]. Other risk factors include obesity, smoking status, prior VTE, malignancy, higher Charlson comorbidity score, hormone replacement therapy, and inflammatory bowel disease [7, 8].

Several scoring systems have been proposed to stratify patients according to their risk of developing VTE. For quick reference, the most widely used and the ones suggested by the American College of Chest Physicians are the Padua score [9] for the medical patients and the Caprini and Rogers score for the surgical patients [7, 10, 11]. In the setting of abdominal surgery, low-risk procedures include cholecystectomy and appendectomy [12]. On the contrary, extensive abdominal or pelvic surgery (i.e., small bowel or colonic resections due to bowel perforations) is associated with a higher risk of VTE [5]. VTE risk appears to be higher for patients undergoing abdominal or pelvic surgery for cancer [13] such colonic cancer perforations.

25.2.2 Risk Factors for VTE Associated with Sepsis

Sepsis triggers blood coagulation that contributes to localized VTE [14, 15]. A delicate balance exists between anticoagulant and procoagulant mechanisms. Normally, the coagulation system comprises the procoagulant mechanisms responsible for the initiation of coagulation and maintenance of normal hemostasis and the balancing anticoagulant mechanism that downregulates the procoagulant action and prevents widespread thrombosis. The key event underlying VTE is the overwhelming inflammatory host response to the pathogen. It leads to the overexpression of inflammatory mediators that causes an upregulation of procoagulant mechanisms and simultaneous downregulation of natural anticoagulants inducing platelet activation, production of tissue factor, and increased fibrin turnover, which can all lead to thrombotic complications [16].

A prospective cohort study using the National Surgical Quality Improvement Program database of the American College of Surgeons (ACS-NSQIP) was designed to evaluate the impact of preoperative sepsis on risk of postoperative arterial and venous thromboses. The study included 2,305,380 adults who

underwent a range of surgical procedures [17]. The systemic inflammatory response syndrome (SIRS) was defined by the presence of two or more between temperature >38 °C or <36 °C; heart rate >90 beats/min; respiratory rate >20 breaths/min or a $PaCO_2$ <32 mmHg (<4.3 kPa); white blood cell count >12,000 cell/mm^3, <4000 cells/mm^3, or >10% immature band forms; and anion gap acidosis (>12 mEq/L). Sepsis was defined as SIRS plus one between positive result on blood culture, clinical documentation of purulence, and positive result on culture from any site thought to be causative. Severe sepsis/septic shock was defined as the presence of sepsis associated with an organ and/or circulatory dysfunction (such as oliguria, acute alteration in mental status, acute respiratory distress/hypotension), and septic shock was defined by the requirement for inotropic or vasopressor agents [18]. Among all surgical procedures, patients with preoperative systemic inflammatory response syndrome or any sepsis had three times the odds of having an arterial or venous postoperative thrombosis (odds ratio 3.1, 95% confidence interval 3.0–3.1). The adjusted odds ratios were 2.7 (2.5–2.8) for arterial thrombosis and 3.3 (3.2–3.4) for venous thrombosis. The adjusted odds ratios for thrombosis were 2.5 (2.4–2.6) in patients with systemic inflammatory response syndrome, 3.3 (3.1–3.4) in patients with sepsis, and 5.7 (5.4–6.1) in patients with severe sepsis, compared with patients without any systemic inflammation. In patients with preoperative sepsis, both emergency and elective surgical procedures had a twofold increased odds of thrombosis. This prospective study clearly points out a positive correlation between the severity of infection and the risk of thrombosis. Moreover, emergent and elective surgery was an independent risk factor for thrombosis with an additive effect to sepsis.

Similar results were reported by a validated risk model to predict 90-day VTE events in postsurgical patients, in 2014. The aim of the study was to stratify patients prior to surgery according to their VTE risk [19]. They used data from a statewide surgical quality collaboration for surgical procedures between 2010 and 2012 with a total of 10,344 patients enrolled. Seven risk factors were incorporated into a weighted risk index: current cancer (five-point factor), family history of VTE (four-point factor), personal history of VTE and sepsis/septic shock/systemic inflammatory response syndrome (three-point factors), male sex (two-point factor), and age $\geq$ 60 years and BMI $\geq$ 40 kg/m^2 (one-point factors). An 18-fold increase in 90-day VTE among surgical patients was identified. Sepsis, septic shock, and SIRS had an odds ratio of 2.22 (1.25–3.95), when considered as an aggregate determinant.

Despite a widespread awareness of the risk of VTE in septic patient and the implementation of evidence-based guidelines, incidence of VTE itself and its impact on clinical outcome of the patient are still high; in 2015 Kaplan et al. [20] published a prospective study of 113 consecutively enrolled patients in the ICU with severe sepsis and septic shock. In patients receiving guideline-recommended thromboprophylaxis, the incidence of VTE was 37.2% (95% CI, 28.3–46.8). Most VTE events were clinically significant (defined as pulmonary embolism, proximal DVT, and/or symptomatic distal DVT) and associated with an increased length of stay (18.2 ± 9.9 days vs 13.4 ± 11.5 days, $P < .05$).

Abdominal compartment syndrome (ACS) may be a complication of abdominal sepsis. Patients with advanced abdominal sepsis commonly develop shock bowel resulting in excessive bowel edema. These changes and associated forced closure of the abdominal wall may result in increased intra-abdominal pressure (IAP) ultimately leading to intra-abdominal hypertension (IAH) [21]. An uncontrolled IAH, with an IAP exceeding 20 mmHg and a new organ failure onset, leads to ACS [22]. Although no study specifically addressed the relationship between ACS and VTE, their connection is sound from a pathophysiological and clinical point of view. The patient affected by ACS has multiple factors associated with VTE: he is septic, often in septic shock requiring vasopressor, paralyzed in order to control IAP and facilitate mechanical ventilation, has invasive monitoring such PA catheter and arterial catheter, and has central venous line in place for delivering drugs or parenteral nutrition. Moreover, ACS can lead to polycompartment syndrome. Polycompartment syndrome is defined as a pressure elevation in one of the four body compartments (i.e., head, thorax, abdomen, limb) secondary to an elevated pressure in another compartment or to the treatment for that [23]. It may have a great relevance in the practice of the care of critically ill patients, because of the effects of elevated pressure within the abdomen on multiple organ systems. Elevated IAP commonly results into decreased venous return secondary to direct compression of the inferior vena cava as well as from an increased thoracic pressure. Reduced caval venous flow impairs lower-extremity venous outflow and contributes to onset of DVT.

25.2.3 Risks Associated with Intensive Care Unit Admission

Additional, specific risk factors for the ICU population are vasopressor use, respiratory or cardiac failure, pharmacologic sedation, mechanical ventilation, and central venous catheter [24]. In 2000, Cook and colleagues [25] identified in a prospective observational study of 93 consecutive patients admitted to a mixed medical-surgical ICU the following risk factor for VTE: mechanical ventilation, immobility, femoral venous catheter, sedatives, and paralytic drugs. Another prospective cohort study of 261 consecutive adult patients expected to be in ICU for ≥72 h was published in 2005 [26]. Four independent risk factors for ICU-acquired DVT were found: personal or family history of VTE, end-stage renal failure, platelet transfusion, and vasopressor use. Patients with DVT had a longer duration of mechanical ventilation, ICU stay, and hospitalization than patients without DVT.

An interesting retrospective audit in 28 North American ICU, including 1935 medical-surgical patients, was published in 2011 [3]. Patients received thromboprophylaxis with unfractionated heparin (UH) (54.0%) or low-molecular-weight heparin (LMWH) (27.6%). Guideline concordance occurred for 95.5% patient-days and was more likely in patients who were sicker and heavier, had cancer and previous VTE, and received mechanical ventilation. Reasons for not receiving thromboprophylaxis were high risk of bleeding (44.5%), current bleeding (16.3%), no reason (12.9%), recent or upcoming invasive procedure (10.2%), nighttime admission or discharge (9.7%), and life-support limitation (6.9%).

25.3 Methods of Thromboprophylaxis

Early and frequent ambulation of hospitalized patients at risk for VTE is an important principle of patient care [27] and represents the first method of thromboprophylaxis. Mechanical methods of thromboprophylaxis include both graduated compression stockings (GCS) and intermittent pneumatic compression (IPC). Although mechanical methods of thromboprophylaxis are attractive options in patients who have a high risk of bleeding, they have not been studied as extensively as pharmacologic thromboprophylaxis [28] and are currently recommended only for low risk of VTE patient or for moderate risk with increased bleeding risk [18].

A systematic review reported a significant reduction in the rate of DVT with the use of GCS compared with no thromboprophylaxis [29]. Nineteen RCTs were identified involving 1681 individual patients and 1064 individual legs (2745 analytic units). Of these 19 trials, nine included patients undergoing general surgery, six included patients undergoing orthopedic surgery, and only one trial included medical patients. GCS were applied on the day before surgery or on the day of surgery and were worn up until discharge or until the patients were fully mobilized. In the treatment group (GCS) of 1391 units, 126 developed DVT (9%) in comparison with the control group (without GCS) of 1354 units where 282 (21%) developed DVT.

Also thromboprophylaxis with IPC has been studied to reduce the incidence of DVT in general surgical patients. Urbankova et al. [30] in 2005 published a meta-analysis on IPC and DVT prevention. The authors identified 15 trials, including five in orthopedics, four in general surgery, three in oncologic surgery, three in neurosurgery, and one in urology about the role of IPC devices in reducing DTV. A total of 2270 patients were included: 1125 and 1145 in the IPC and in non-prophylaxis groups, respectively. IPC devices reduced the risk of DVT by 60%.

LMWHs are now the pharmacologic agents of first choice for thromboembolism prophylaxis. LMWHs are generated from the chemical depolymerization of UH and have significantly great activity toward factor Xa than UHs [31].

Although UH is effective for the prevention of DVT and pulmonary embolism in surgical patients, heparin-induced thrombocytopenia (HIT) presents a serious safety concern. Advantages of LMWHs over UH also include a higher anti-Xa activity compared with antithrombin activity, better bioavailability at low doses, no monitoring required, and a longer half-life (4 h vs 0.5–2 h), allowing for once-daily dosing [32]. However, a long half-life can sometimes be a disadvantage in the case of bleeding. In addition, LMWHs are incompletely reversed by protamine sulfate. LMWH renal excretion may limit their use in patients with severe renal failure.

The efficacy and safety of heparin thromboprophylaxis in medical-surgical patients in the ICU was evaluated in a systematic review in 2013. Seven trials that involved 7226 patients were included [33]. Any heparin thromboprophylaxis compared with placebo reduced DVT rates and pulmonary embolism. Compared with UH, LMWH reduced rates of pulmonary embolism and symptomatic pulmonary embolism. Major bleeding and mortality rates do not appear to be significantly influenced by heparin thromboprophylaxis in the ICU setting.

Fondaparinux is a synthetic pentasaccharide that selectively inhibits coagulation factor Xa. It has been shown to be highly efficacious in the prevention of DVT among high-risk orthopedic patients [34, 35]. In the setting of general surgery, the efficacy and safety of postoperative fondaparinux (2.5 mg once/day) was compared with that of the LMWH dalteparin started preoperatively in high-risk abdominal surgical patients [36]. The study suggested that postoperative fondaparinux is at least as effective and as safe as preoperative dalteparin for the prevention of VTE after abdominal surgery.

Unlike UH and LMWH, it has not been associated with HIT. In addition, because fondaparinux does not interfere with thrombin binding, it has no negative effect on wound healing. Because of its long half-life (approximately 18 h), patients whose creatinine clearance is <30 mL/min may experience an accumulation of fondaparinux and thus may be at greater risk of bleeding.

25.4 Thromboprophylaxis in Patients with Abdominal Sepsis

There is evidence that primary prophylaxis substantially reduces the incidence of VTE without increasing the risk of major bleeding [10]. However, the use of pharmacological prophylaxis in low-risk patients and in patients with contraindications could be more risky than beneficial. Active bleeding, previous major bleeding episode, untreated bleeding disorder, severe renal or hepatic failure, thrombocytopenia, uncontrolled systemic hypertension, concomitant use of anticoagulants, antiplatelet therapy, or thrombolytic drugs may be considered risk factors for pharmacological prophylaxis. In these patients, a careful assessment of risks and benefits is mandatory. In the last decade, many guidelines have been published in order to increase compliance with prophylactic measures [27, 37]. Many of these guidelines do not stress risk factors related to clinical conditions in the setting of critical care surgery. Sepsis should be always considered an additional risk factor for VTE.

The American College of Chest Physicians (ACCP) recommendations for thromboprophylaxis in surgical patients are based on risk stratification [37]. However, among the suggested predictive models, the Rogers score [10] doesn't include sepsis as predictor of VTE, and in Caprini score [38], sepsis represents a low risk. This contrasts with the recent large cohort study by Donzé et al. [17] that demonstrated a higher risk of VTE (2.7%) for surgical patients with sepsis. However, the 2012 guidelines from the Surviving Sepsis Campaign [39] recommend that patients with severe sepsis receive daily pharmacoprophylaxis against VTE with daily subcutaneous LMWH, recognizing the higher risk.

The lack of certainty in the guidelines is related to our limited capacity to detect hypercoagulable states. Whole-blood coagulation test such as thromboelastography or platelet function test can detect a thrombotic tendency or a lack of efficacy of pharmacologic interventions. Transfusion protocol based on thromboelastographic parameters demonstrated in a recent meta-analysis the ability to decrease blood product transfusion [40]. Another recent meta-analysis suggested

the ability to reduce postoperative thromboembolic events at least in the cardiac surgery cohort of patients with an OR 0.44, 95% CI 0.28–0.70; $P = 0.0006$ [41]. Whole-blood, viscoelastic test is appealing when dealing with the jeopardizing scenario of administering a possible life-threatening therapy such as anticoagulation in a patient that has just undergone surgery or is scheduled for a "second look." The rationale is sound, and it is to administer anticoagulation to a patient that has an overt hypercoagulable state. Anyhow, no study addressed this specific treatment, so there's no defined cutoff for which we should start anticoagulation. Moreover, little is known about the relationship between a normal or even hypocoagulable state and the real local coagulable state in a vessel with a sluggish circulation due to an increased IAP.

In septic patients who have a contraindication to heparin, guidelines suggest other alternatives to pharmacoprophylaxis such as mechanical prophylactic treatment.

If creatinine clearance is <30 mL/min, the guidelines recommended the use of a form of LMWH that has a low degree of renal metabolism (such as dalteparin) or UH.

Conclusions

According to the existing literature, thromboprophylaxis in patients with abdominal sepsis is suggested as follows:

- In patients with sepsis who undergone a minor procedure such as laparoscopic appendectomy or cholecystectomy even with no risk factors, pharmacoprophylaxis up to complete mobilization is suggested.
- In all patients who undergone major operations, complete pharmacoprophylaxis is suggested.
- In patients with severe sepsis or septic shock, to continue pharmacoprophylaxis until resolution of severe sepsis is suggested.
- In high-risk septic patients who have a contraindication to receive pharmacoprophylaxis, mechanical prophylactic treatments, such as graduated compression stockings or intermittent compression devices, are suggested.
- In septic patients with multiple risk factors, to combine pharmacoprophylaxis with the use of mechanical thromboprophylaxis is suggested.
- If available and there's expertise in interpreting the data, a viscoelastic test should be performed and the results weighted when considering to initiate, or terminate, a thromboprophylaxis in a patient without a clear indication.

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Nutritional Support for Abdominal Sepsis

26

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26.1 Introduction

With early sepsis recognition, preoperative optimization, and damage control surgery, early hospital deaths from IAS have decreased substantially over the past decades. Yet, despite tremendous advances in care, intra-abdominal sepsis (IAS) remains a frequent and significant challenge for emergency surgeons. Many of those who survived initial treatment would develop early systemic inflammatory response syndrome (SIRS) which frequently causes multiple organ failure (MOF). With improved compliance with evidence-based ICU care, far fewer MOF patients are dying nowadays. Many IAS survivors require repeat operations, experience nosocomial infections, and have prolonged ICU stays. A substantial subset is now progressing into a new MOF phenotype of chronic critical illness (CCI) termed persistent inflammation immunosuppression catabolism syndrome (PICS). PICS patients are discharged to nonhome destinations, fail to rehabilitate, and frequently suffer an indolent death. PICS patients progressively lose lean body mass, which limits their rehabilitation. Early enteral nutrition (EEN) has been shown to be beneficial in MOF primarily in preventing nosocomial infections. However, EEN fails to prevent ongoing catabolism. Traditionally, this was presumed to be due to difficulties in placing patients in early positive caloric and nitrogen balance with EEN. However, attempts to optimize EEN with feeding protocols or by using supplemental parenteral nutrition (PN) have not prevented the progressive cachexia

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seen in IAS survivors. To better understand the implications of nutritional support in IAS, this chapter will review (a) the PICS paradigm, (b) the role of gut dysfunction in PICS, (c) the rationale for EEN, (d) adjuncts to protect the gut, (e) specific nutrients for PICS, (f) recommendations for parenteral nutrition (PN), and (g) adjunct therapies to promote anabolic nutrition.

26.2 The PICS Paradigm

The initial descriptions of MOF in the 1970s concluded that MOF was due to uncontrolled infection, and the majority of cases were due to IAS with an attendant mortality exceeding 80%. These reports focused on tremendous research efforts on the prevention and treatment of IAS. As a result, outcomes after IAS have progressively improved over the past 40 years. With these ongoing advances in care, the epidemiology of MOF after IAS has evolved from predominantly early fulminant death to more prolonged ICU stays prior to death. Most recently, with more effective early interventions and consistent implementation of evidence-based ICU care, far fewer IAS-induced MOF patients are dying in the ICU. Then they become an ever-growing population of CCI patients who fail to rehabilitate with very poor long-term outcomes. Based on recent laboratory and clinical research data, the PICS paradigm was recently proposed (Fig. 26.1) and is frequently seen after

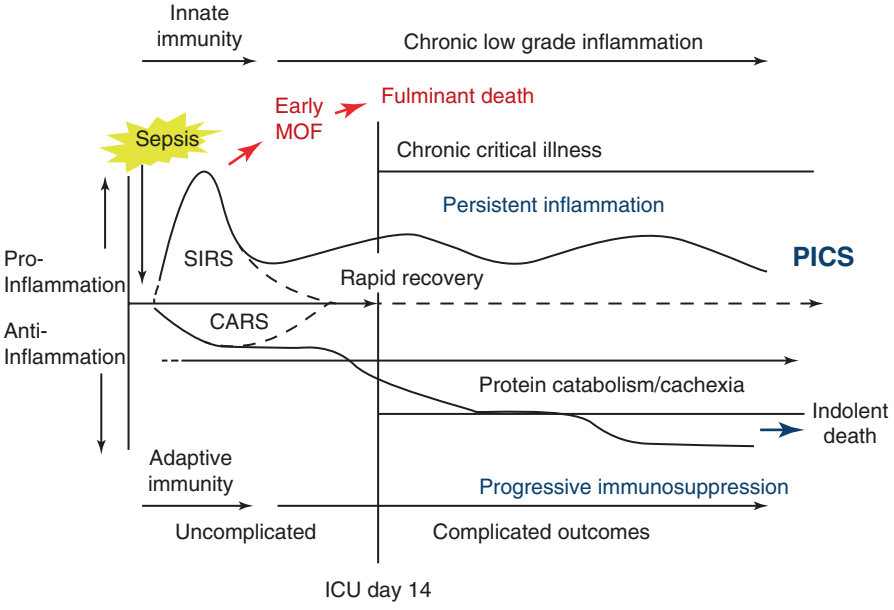

Fig. 26.1 The clinical representation of how PICS manifests. *MOF* multiple organ failure. *SIRS* systemic inflammatory response syndrome. *CARS* compensatory anti-inflammatory response syndrome. *PICS* persistent inflammation immunosuppression catabolism syndrome

IAS. Following severe sepsis, there are simultaneous pro-inflammation (called SIRS) and anti-inflammation (compensatory anti-inflammatory response syndrome called CARS) systemic responses. In some cases, SIRS can become overwhelming which leads to an early MOF and fulminant death trajectory. Fortunately, modern ICU care is directed at early detection and prevention of this trajectory's fatal expression. If severe sepsis patients survive early MOF, they either rapidly recover from their aberrant immunology (i.e., achieves homeostasis) or become persistently dysfunctional and enter into CCI phase (defined as >14 days in ICU with organ dysfunction). These CCI patients experience ongoing immunosuppression (e.g., lymphopenia) and inflammation (e.g., neutrophilia) that is associated with a persistent acute-phase response (e.g., high C-reactive protein) and ongoing protein catabolism. Despite aggressive nutritional intervention, there is a tremendous loss of lean body mass and proportional decrease in functional status and poor wound healing. An estimated 30–50% of these CCI patients progress into PICS. Clinically, PICS patients suffer from recurrent nosocomial infections and poor wound healing, require ventilator and pressure support, and develop decubitus ulcers. They are discharged to long-term acute care facilities (LTACFs) where they experience sepsis recidivism requiring rehospitalization, failure to rehabilitate, and ultimately an indolent death [1]. These PICS patients have a clinical phenotype that resembles patients experiencing cancer cachexia and comparatively have strikingly similar immunologic and metabolic profiles. [2].

Investigators have been describing the growing epidemic of CCI under a various descriptive terms (including the post-intensive care syndrome) and in a variety of patient populations [3, 4]; no unifying mechanistic etiology is identified. The PICS described here proposes a possible underlying mechanistic etiology that drives this new phenotype of multiple organ dysfunction. In murine models of chronic sepsis and trauma, Moldawer and colleagues have identified the expansion of myeloid-derived suppressor cells (MDSCs) as a possible explanation of the persistent immunosuppression, concurrent inflammation, and ongoing catabolism that are being observed in PICS patients (similar to that seen in the chronic phase of neoplastic disease) [5, 6].

Recently, a focused translational study of surgical patients with severe sepsis confirmed the clinical relevance of these laboratory observations in showing that MDSCs are persistently elevated up to 28 days after sepsis [7]. The MDSCs were shown to suppress T-lymphocyte proliferation and decrease the release of T_{H1} and T_{H2} cytokines. Moreover, MDSC proliferation can be correlated with adverse outcomes including the following: (a) early MDSC expansion was associated with early mortality, (b) persistent expansion was associated with prolonged ICU stays, and (c) persistent expansion was a strong independent predictor of nosocomial infections and poor post-discharge disposition [7, 8].

This MDSC expansion is a well-conserved response to a variety of insults called "emergency myelopoiesis" [9]. It is the bone marrow's (BM's) attempt to preserve innate immunity, and to accomplish this, the BM concurrently suppresses lymphopoiesis and erythropoiesis with resulting lymphopenia and anemia (commonly observed in CCI patients). Hemopoietic stem cells are preferentially directed down

the common myeloid progenitor cell line to produce MDSCs. These MDSCs are not allowed to mature into granulocytes, monocytes, and dendritic cells but are released early from the BM. While a primary role of MDSCs is to fight infections, they are poor phagocytes and do not present antigens effectively. Their immunosuppressive activity is attributed to a number of mechanisms including the upregulation of arginase-1 (ARG1), increased interleukin-10 production and cell-surface expression of programmed death ligands 1 (PD-L1), nitrosylation of major histocompatibility complex (MHC) molecules preventing their appropriate interaction with the T-cell receptors (TCRs) and co-receptors as well as promoting TCR dissociation, and promotion of regulatory T-cell expansion. While best known for their detrimental suppression of adaptive immunity in chronic cancer, MDSCs also produce inflammatory mediators (including nitric oxide, reactive oxygen species, tumor necrosis factor, etc.) that cause persistent low-grade inflammation that characterizes both cancer and PICS cachexia. In addition to MDSCs, sepsis and trauma patients suffer from significant tissue injury with release of damage-associated molecular patterns (DAMPs) [10]. While these endogenous alarmins are less well studied, they may also contribute to the persistent inflammation in PICS.

26.3 The Role of Gut Dysfunction in PICS

In brief, severe trauma and sepsis are two prime inciting events for MOF. Both cause disproportionate splanchnic hypoperfusion and gut injury. With resuscitation/reperfusion, there is a release of pro-inflammatory mediators that can amplify SIRS. This gut ischemia/reperfusion (I/R) injury also initiates a local inflammatory response that results in a variety of gut dysfunctions (e.g., gastroparesis, gastric alkalinization, ileus, duodenogastric reflux, impaired mucosal blood flow, epithelial apoptosis, increased permeability, impaired local gut immunity). Early isotonic crystalloid resuscitation can amplify inflammation, cause problematic edema, and worsen ileus. Early laparotomy with bowel manipulation also promotes gut inflammation, mucosal injury, and worsened ileus. Other standard ICU interventions that may contribute to worsening gut dysfunctions include vasopressor agents (decrease mucosal perfusion), stress gastritis prophylaxis (worsens gastric alkalinization), narcotics (worsen ileus), antibiotics (promote bacterial overgrowth), and PN (gut disuse). Over a short period of time, the normally sterile upper GI tract becomes heavily colonized with drug-resistant pathogens that are present in the ICU environment. Interestingly, stressful insults have recently been shown to stimulate a genomic response in quiescent gut bacteria such that they become more invasive and secretes more toxins. As a result, the gut becomes a reservoir for virulent bacteria and toxic products. These microorganisms escape the gut via aspiration or translocation to cause late nosocomial infections and ongoing sepsis that perpetuates the aberrant immunology that characterizes CCI and PICS. Thus, the gut can be both the victim and instigator of PICS.

26.4 The Rationale for Early Enteral Nutrition (EEN)

EEN has long been recognized to be beneficial in high-risk surgical ICU patients. In the 1970s, it was utilized to provide nutrients to prevent acute protein malnutrition that was induced by injury stress response. However, with the widespread availability of parenteral nutrition (PN) in the early 1980s, it became the preferred method of nutritional support. In the 1980s, PN was enthusiastically embraced as a panacea for surgical patients, and special "stress formula" PN fortified with branched-chain amino acids (BCCA) was designed to combat the "septic auto-cannibalism" that occurred after IAS. Unfortunately, by the early 1990s, numerous clinical trials failed to document improved outcomes in surgical patients receiving early PN, and several showed increased adverse outcomes (primarily increased nosocomial infections oftentimes due to overfeeding, poor glycemic control, and lack of catheter care bundles). Additionally, a series of clinical trials comparing EEN to early TPN consistently demonstrated reduced nosocomial infection with EEN [11]. While these trials spurred considerable debate over underlying explanation, the preponderance of evidence suggests this is due to beneficial effect of EEN rather than harmful effects of PN. Research efforts in the 1990s provided a plausible explanation for how EEN promotes vital gut functions that interrupt this sequence of events in MOF to prevent late nosocomial infections. In a variety of models (i.e., sepsis, hemorrhagic shock, and gut I/R), intraluminal nutrients have been shown to reverse shock-induced mucosal hypoperfusion. In laboratory, EEN has also been shown to reverse impaired intestinal transit when given after a gut I/R insult. Improved transit should decrease ileus-induced bacterial colonization. Moreover, EEN attenuates the gut permeability defect that is induced by critical illness. Finally, and most importantly, the gut is a very important immunologic organ, and the severity of systemic immunosuppression can be lessened by feeding the gut. Dr. Kudsk and others have performed a series of laboratory studies that have nicely elucidated a mechanistic explanation of how this occurs [12, 13]. Enteral nutrition supports the function of the mucosal-associated lymphoid tissue that produces 70% of the body's secretory immunoglobulin A. Naive T and B cells target and enter the gut-associated lymphoid tissue, where they are sensitized and stimulated by antigens sampled from the gut lumen and thereby become more responsive to potential pathogens in the external environment. These stimulated T and B cells then migrate via mesenteric lymph nodes and the thoracic duct into the vascular tree for distribution of gut-associated lymphoid tissue and extraintestinal sites of mucosal-associated lymphoid tissue. Lack of enteral stimulation (i.e., use of PN) causes a rapid and progressive decrease in T and B cells within gut-associated lymphoid tissue and simultaneous decrease in intestinal and respiratory immunoglobulin A levels. Previously resistant PN-fed laboratory animals, when challenged with pathogens via respiratory tree inoculation, succumb to overwhelming infections. These immunologic defects and susceptibility to infection are reversed within 3–5 days after initiating enteral nutrition [14–17].

26.5 Adjuncts to Protect the Gut

26.5.1 Probiotics, Prebiotics, and Synbiotics

Table 26.1 represents our recommendation based on current literature to protect the gut from further injury while caring for critically ill patients. As mentioned earlier, Alverdy et al. demonstrated that acidosis and electrolyte abnormalities (phosphate depletion) can promote ileus and render normally symbiotic bacteria virulent causing loss of microbial balance for our ICU patients [18–22]. In fact, the gut microbiome has recently become heavily researched in various pathologic states, and the role of pre-, pro-, and synbiotics has increasingly shown benefits such as protecting intestinal barrier and modulation of host inflammatory response [23–25].

A probiotic is defined as a live microorganism supplement that improves the host's intestinal microbial balance such as lactobacilli, bifidobacteria, and saccharomyces. A prebiotic is defined as a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of specific bacteria in the colon such as the nondigestible oligosaccharide fructooligosaccharides (FOS). It has been shown that the colon will ferment the supplemented FOS into short-chain fatty acids providing nutrition to clonocytes and promoting the growth of bifidobacteria, which reduces the colonization of virulent bacteria such as staphylococcus, clostridia, and fusobacteria [26–28]. Synbiotics are a combination of pro- and prebiotics, and the combination is postulated to improve the survival of the probiotic organism by having a specific substrate readily available for probiotic fermentation. Manipulation of the colonic microbiome can also reduce the incidence of enteral nutrition/antibiotic-associated diarrhea by suppressing enteropathogens and promoting water and electrolyte uptake [29]. Even a study of trauma patients who were provided symbiotic supplementation had decreased intestinal permeability and lower combined infection rates than those receiving other immunomodulating formulas. The authors postulated that the presence of synbiotics in the GI tract reduced pathogenic flora and thereby decreased the incidence of pneumonia [30]. A subsequence double-blind study confirmed this beneficial effect of prophylactic probiotics on reducing incidence of ventilator-associated

Table 26.1 Approach to maximizing gut function in critical illness

Correction of acidosis and electrolyte abnormality
• Prokinetic agents
• Glycemic control
• Maintain visceral perfusion
• Early nutritional support
– Enteral preferred <48 h (<24 h may be even better)
– Specific nutrients to attenuate metabolic response
• Minimize medications that alter GI function
– Anticholinergics, narcotics, pressors
• Supporting gut microbiome

pneumonia in mechanically ventilated patients [31]. Although pre-, pro-, and synbiotics are very intriguing and have some clear indications, further research is needed as a recent meta-analysis showed no difference between critically ill patients who were supplemented and those that were not [32].

26.6 Prokinetic Agents

Another strategy used to aid in gut protection can be prokinetic agents. Gastroparesis and ileus are common post-injury sepsis and postoperatively following resuscitation. Agents that promote or restore motility have long been sought after to aid in feeding tolerance. Prokinetic agents are aimed at blocking anti-motility mediators or overriding them by stimulating normal pathways. An example is erythromycin that acts on motilin (the endogenous hormone partly responsible for regulating normal GI motility) receptors. Erythromycin has been shown to enhance gastric emptying and intestinal transit in animal models and in some clinical trials, but its effectiveness in reducing postoperative ileus has been unsatisfactory [33]. Metoclopramide was also shown to be effective in improving gastric emptying and EN tolerance although it was associated with more side effects (tardive dyskinesia). Both agents have been associated with QT prolongation. Another promising agent, ghrelin, has been shown in a rodent model to not only accelerate gastric emptying and small intestinal transit but also reverse postoperative gastric ileus [34]. In fact, a recent trial by Heyland et al., the PEP uP trial, showed that an enteral nutrition feeding protocol utilizing early prokinetic agents could increase feeding tolerance and resulted in a 12% increase in calories the critically ill patient received [35].

26.7 High Protein

Provision of 1.3 g/kg protein and target calorie was associated with a 50% decrease in 28-day mortality in prospective study of mechanically ventilated patients, while no mortality benefit was achieved in only target calorie group (protein of 0.8 g/kg) [36]. Incremental decrease in mortality as protein dose increased was observed in another study: 27% in group 1 (0.79 g/kg protein) versus 24% in group 2 (1.06 g/kg protein) versus 16% in group 3 (1.46 g/kg protein) [37]. Historically, nutritional supplementation of MOF patients focused on early protein intake (>1.2 g/kg/day) [38, 39]. PICS patients qualify as a chronic phenotype of MOF. As such, high-protein supplementation could be relevant in promoting anabolism in PICS patients. While there is no specific data of the optimal protein dosing in PICS patients, a recent review article by Delano and Moldawer demonstrates that cancer cachexia patients experience remarkably similar alterations in metabolism as seen in PICS [6]. Theoretically, what works in cancer cachexia could be applied to PICS. Data support the recent guideline recommendation that cancer patients should consume at least 1.2–2.0 g protein/kg/day [40, 41]. Aging sarcopenia is another example where muscle wasting is linked to a chronically inflamed state inducing a

cachexia-like phenotype, and here the evidence-based recommendations are to provide 1.5 g protein/kg/day [42]. Historically, it has been well accepted that burn patients suffer from a hypercatabolic state with immense energy expenditure [43]. Here, Alexander et al. demonstrated improved survival and less bacteremia in burn children who received early aggressive high-protein nutritional support [44]. Furthermore, Herndon et al. make a strong recommendation that protein requirements for the burn patient double to 2.0 g/kg/day based on the observation that amino acid oxidation in burn patients is twice that of normal healthy controls [45]. Of note, both American Burn Association guidelines and the European Society of Parenteral and Enteral Nutrition recommended the provision of 1.5–2 g/kg of protein for patients with burn injury though higher doses have been used [46, 47].

26.8 Immunosuppression and Arginine

Arginine is a semi-essential amino acid with immunomodulating, phagocytic, and wound healing properties. Immune-enhancing enteral diets fortified with arginine have convincingly been shown to be beneficial in surgical patients undergoing major operations and in trauma patients at high risk for MOF [48–50]. It is a conditionally essential amino acid under stress or during illness that can be synthesized from three primary sources: (1) dietary intake contributing 25–30% of total daily arginine, (2) the remaining 70–75% of endogenous arginine is either synthesized in the urea cycle by conversion of citrulline in the kidney, or (3) protein turnover/breakdown.

Arginine serves as an intracellular substrate for NO production in macrophages to improve bactericidal activity, as well as improving T-cell function, proliferation, and maturation [51–57]. Arginine is a critical part of the zeta chain of the T-cell receptor (TCR), and arginine deficiency has been shown to render T cells incompetent [52, 58–64]. Arguably one of the most important ramifications of arginine depletion is the immunosuppressed state secondary to lack of T-lymphocyte expansion and, more importantly, circulating CD4 cells to help fight infection. Furthermore, decreased T-cell expansion and receptor function result in multifactorial immune incompetence contributing to an increased risk of nosocomial infections in critically ill and PICS patients [52, 65, 66].

Another contributor to immunologic disturbance after critical illness is the expansion of an immunosuppressive line of leukocytes known as myeloid-derived suppressor cells (MDSCs). These immature myeloid lineage cells are released from the bone marrow into the circulation during times of stress and elaborate pro-inflammatory cytokines, potentiate acute cachexia, serve relatively no immunologic function, and express high levels of arginase-1 [5, 8, 62, 67–72]. Arginase-1 is an enzyme that reduces the circulating arginine levels thus making severe stress and critical illness an arginine-deficient state [51, 62, 73–77]. As mentioned previously, without arginine, T cells become incompetent which is likely a key mechanism for immunosuppression after sepsis, trauma, burn, and other critical illness. Thus, arginine supplementation becomes an attractive therapeutic option in PICS patients.

While ASPEN/SCCM 2016 guidelines recommend against routine supplementation of arginine containing immune nutrition in septic patients, arginine along with fish oil has been shown to be beneficial in pre- and postsurgical patients [48, 78].

26.9 Can Leucine Help Fight Catabolism?

Leucine is a branched-chain amino acid that stimulates anabolism through the mammalian target of rapamycin (mTOR) signaling pathway in septic rat model. After sepsis, mTOR is downregulated and becomes relatively inactive to leucine [79, 80]. Currently, it is unknown whether this persists into the chronic phase of PICS and would be worthy of future study in PICS patients who have survived the acute septic event and are now profoundly catabolic. Thus, in this setting, leucine supplementation could potentially be used to help dampen, and even reverse, the catabolic state [81, 82].

Stimulating the mTOR pathway increases protein synthesis and inhibits proteosomal protein breakdown. Leucine stimulates multiple enzymes that ultimately increase either mRNA to induce anabolism (protein synthesis). These include ribosomal protein S6 kinase, S6K1, and eukaryotic initiation factor 4E-binding protein, 4E-BP1 [83, 84]. The end goal is that leucine simulates mTOR to promote hypertrophic muscle growth. It is well known that critically ill patients lose lean muscle mass at an accelerated rate [43, 85–89]. PICS patients persist in this catabolic state indefinitely, unable to rebuild muscle mass even with adequate caloric intake. In fact, this unique patient population suffers greatly for catabolism, and it is this pathologic state that leucine supplementation would provide the most benefit. Through mTOR signaling, PICS patient would hopefully reduce catabolism and enter an anabolic state to regain muscle mass, increase the possibility of rehab, and regain baseline function/independence once discharged from the ICU.

26.10 Recommendation for Parenteral Nutrition (PN)

Achieving caloric goals with EEN presents a challenge, as often critically ill patients present with concomitant comorbidities that make EEN prohibitive [90, 91]. Parenteral nutrition (PN) has shown benefit in providing supplemental calories in patients where IAS and gut dysfunction make it prohibitive to provide enteral nutrition, or enteral nutrition caloric needs would not be met within a reasonable period of time. PN does come with a price, and defining the time frame that is “reasonable” was a much-researched area. Marik et al. described the physiologic price of its use: PN causes hyperglycemia, hepatocellular injury, and immunosuppression [92]. When to start PN has long been a controversy between the European Society of Parenteral and Enteral Nutrition (ESPEN) and North American (ASPEN) nutritional societies, whereby ESPEN recommended early PN (after 2 days of not obtaining target nutrition) [93]. ASPEN, in contrast, recommended waiting for a longer duration and initiating PN after 7 days of not reaching target caloric goals. Casaer

compared the two guidelines and reported significant benefit in delaying PN nutrition as discussed below [94–97].

Casaer et al. performed a large multicenter PRCT (the EPaNIC trial), comparing early initiation of supplemental PN (ESPEN approach) with late initiation (ASPEN approach) in adults in the ICU to supplement insufficient EN. In 2312 patients, PN was initiated within 48 h after ICU admission (early-initiation group), whereas in 2328 patients, PN was not initiated before day 8 (late-initiation group). The overall outcome was that the patients who received late PN were more likely to be discharged alive from the ICU and hospital, without evidence of decrease functional status, lower infection rates, lower incidences of cholestasis, and a modest cost saving [95].

Thus, the ASPEN guidelines on PN, even on the revised 2016 version, suggest waiting 7–10 days prior to starting PN for patients with low nutrition risk, though for patients who are PN dependent or patients with underlying severe malnutrition who are unable to meet nutrition goal enterally within 48–72 h, PN should be considered as soon as possible following ICU admission [39]. It is thought that the risks of PN outweigh the benefits in the first week. After the first week to a week and a half, the decline of nutritional status increases, and the risk-to-benefit ratio shifts to favor PN. Once initiating PN, lipids are not indicated for the first week. Lipids with only long-chain triglycerides (18 carbon chains) are pro-inflammatory and cause immunosuppression [98].

26.11 Anabolic Nutritional Supplements

Five anabolic strategies and their effects on morbidity and mortality in pediatric burn patients were studied, including (a) growth hormone, (b) intensive insulin therapy, (c) oxandrolone, (d) propranolol, and (e) in-patient active exercise programs. Hart demonstrated that growth hormone can be a "potent anabolic agent and salutary modulator of posttraumatic metabolic responses" at 12 months' follow-up [43, 99–101].

Herndon has also demonstrated that intense glucose control (80–160 mg/dl) in >30% total body surface area pediatric burn patients significantly increased bone mineralization and muscle strength in this population ($p = 0.05$) [102]. In another studies, Porro demonstrated that oxandrolone substantially decreased resting energy expenditure, increased insulin-like growth factor 1 secretion during the first year after burn injury, and, in combination with exercise, increased lean body mass and muscle strength considerably [103], while Herndon showed a reduction in burn-induced proteolysis with an increase in muscle anabolism following propranolol administration [100].

26.12 Adjuncts to Promote an Anabolic Response

The loss of lean body mass in patients with prolonged ICU stay is dramatic. In a classic study, Graham Hill and colleagues performed serial body composition by bioimpedance studies in critically injured over 25 days in the ICU. They demonstrated that despite optimal nutritional support, there was an obligatory 16% loss of

lean body mass and that excessive administration of substrates was converted into fat (It is the authors' feeling that this indicates simply giving macronutrients is not going to reserve the loss of lean body mass and that interventions are needed to promote anabolism). This tremendous loss of lean body mass was recently confirmed by Puthucheary et al. who performed serial ultrasound of the rectus femoris over the first 10 days of ICU stay and demonstrated a 20% decrease in cross-sectional area (CSA), and the subset of MOF patient lost 30% [69]. Interestingly, at 7 days, protein synthesis was variably increased, but breakdown was consistently low in all patients with negative protein balance despite all patients being fed. Muscle biopsies looking at intracellular regulators of protein homeostasis revealed decreased anabolic and increased catabolic signaling. These indicate that simply giving macronutrients is not going to reserve the loss of lean body mass and that interventions are needed to promote anabolism.

26.13 Specific Nutrition for PICS: Specialized Pro-resolving Mediators

Specialized pro-resolving mediators (SPMs) are lipid mediators that can not only decrease inflammation by cessation of leukocyte infiltration and activation but also "pro-resolve" inflammation by stimulating macrophages to clear debris, bacteria, and apoptotic cells [104, 105]. First described by Dr. Serhan, SPMs attenuate efferocytosis (clearing of cellular debris) of macrophages to eliminate the source of inflammation. Simplified for this discussion, SPMs are purified extracts from omega-3 polyunsaturated fatty acids [105].

SPMs could be an advanced therapeutic agent for the PICS population to promote resolution of the irregular inflammatory cascade, as well as possibly prevent patients with chronic critical illness from progressing to the PICS phenotype. Hypothetically, by resolving the persistent inflammation, SPMs will also decrease the amount of energy diverted to sustain this catabolic state, decrease hepatic re-prioritization of proteins that could be used for anabolism, and allow the patient to return to physiologic homoeostasis. However, further research is needed to delineate the novel role of SPMs in PICS nutrition, as these lipid mediators are likely to be only one agent in the armamentarium of a multimodality therapeutic approach for PICS.

Conclusion

The gut in the setting of abdominal sepsis can serve as both the instigator and the victim in the pathogenesis of MOF. The role of supplemental nutrition in these critically ill patients can drastically alter clinical courses and have lasting ramifications. Through both nutritional and nonnutritional value, EN provides substantial benefit. Providing PN can be beneficial if provided to the high-risk patient that can't be fed enterally. The horizon of critical care nutrition is ever changing, and in the near future, modulation through microbiome manipulation could prove to be a great tool in the armamentarium of preventing gut dysfunction and treating those that are critically ill.

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