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GUIDELINE

The Bucharest ESTES consensus statement on peritonitis

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Abstract

Introduction Peritonitis is still an important health problem associated with high morbidity and mortality. A multidisciplinary approach to the management of patients with peritonitis may be an important factor to reduce the risks for patients and improve efficiency, outcome, and the cost of care.

Methods Expert panel discussion on Peritonitis was held in Bucharest on May 2017, during the 17th ECTES Congress, involving surgeons, infectious disease specialists, radiologists and intensivists with the goal of defining recommendations for the optimal management of peritonitis.

Conclusion This document is an updated presentation of management of peritonitis and represents the summary of the final recommendations approved by a panel of experts.

Keywords Peritonitis · Sepsis · Antibiotics

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Peritonitis definition, classifications and severity scores

- ✓ Peritonitis is a form of complicated intra-abdominal infection but is not synonymous with it
- ✓ Abdominal sepsis refers to sepsis caused by an intra-abdominal infection
- ✓ Peritonitis can be classified as primary, secondary or tertiary peritonitis, and as localized or diffuse
- ✓ Physiologic scores and the Mannheim peritonitis index (MPI) should be used to predict short-term risk of morbidity and mortality

According to the Merriam-Webster medical dictionary, peritonitis is defined as inflammation of the peritoneum, the serous membrane lining the abdominal cavity and organs contained within. The cause of inflammation can be infectious (bacteria or fungus) or non-infectious, related to chemical irritants such as gastro-intestinal contents, pancreatic enzymes, bile or foreign substances such as barium from radiological investigations.

There are many related terms found in the literature, sometimes used synonymously, including intra-abdominal infection (IAI), intra-abdominal sepsis, or more commonly peritoneal contamination, infection or sepsis, terminology that is sometimes used for grading of intra-abdominal infection.

In fact, IAI is not synonymous with peritonitis [1]. Peritonitis might be a form of IAI and/or might be caused by IAI. Both terms should not be used interchangeably [1, 2]. Abdominal sepsis refers to a systemic inflammatory response to infection, caused by an IAI. Sepsis with acute dysfunction of at least one organ was called severe sepsis and when accompanied by hemodynamic instability refractive to fluid administration and/or requiring vasopressor support was called septic shock [3]. However, Singer et al. and the recently convened European Society of Intensive Care Medicine and the Society of Critical Care Medicine task force redefined sepsis as life-threatening organ dysfunction caused by a deregulated host response to infection [4]. Organ dysfunction is present when there is an increase in the Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score of two points or more. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater and serum lactate level greater than 2 mmol/L (> 18 mg/dL) in the absence of hypovolemia. The bedside clinical score termed quickSOFA (qSOFA) consists of respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100 mmHg or less. The task force concluded the term severe sepsis was redundant and should be abandoned [4].

One of the first classifications of IAI was described in 1982 by Meakins et al. [5] based on ten possible anatomic locations of IAI. It was later combined with the Acute Physiology Score and then coined Surgical Stratification System [6]. Based on the anatomy of the source and severity measured by physiological compromise, this classification was far from satisfactory as it only took into account secondary bacterial peritonitis, and in further studies outcome was similar irrespective of the category [7]. For these reasons, the classification was rapidly surpassed and the APACHE II severity score became commonplace. The APACHE II severity score, however, is not strictly speaking a classification, nor specific for peritonitis, although it is correlated with morbidity and mortality.

The so-called Hamburg classification [1] divides peritonitis into three types: primary, secondary and tertiary, to which one can add a fourth type, called peritoneal dialysis-related peritonitis.

Primary bacterial peritonitis refers to spontaneous bacterial invasion of the peritoneal cavity, occurring mainly in infancy and early childhood, in patients with cirrhosis or who are immuno-compromised.

Secondary bacterial peritonitis refers to those infections due to intra-abdominal perforation (traumatic, iatrogenic or disease-related), anastomotic dehiscence, translocation of bacteria, gastro-intestinal inflammation or necrosis (the latter including pancreatic necrosis), or sometimes, non-bacterial peritonitis or penetrating infectious processes.

Tertiary peritonitis refers to persistent or recurrent infections, sometimes described being related to organisms of low intrinsic virulence or the immune-compromised patient, usually following unsuccessful operative attempts to treat secondary peritonitis.

Clinically, peritonitis is often classified either as local or as diffuse. Local peritonitis refers to loculi of infection, usually walled-off or contained by adjacent organs, whereas diffuse is synonymous with generalized peritonitis, that is spread to the entire cavity.

Several scoring systems have been developed to stratify disease and predict outcome.

These include, among others, the Acute physiology and chronic health evaluation (APACHE) II score, the Simplified Acute Physiology Score (SAPS), the Sepsis Severity Score (SSS) and the Mannheim Peritonitis Index (MPI) [8, 9]. The Hinchey score is specific to complicated diverticular disease [10].

Age, once used as a "score" has not lived up to expectations and has been abandoned.

There are also organ dysfunction scores, originally developed for use in the critically ill, that have a place in severe peritonitis [11–15]. The most commonly used organ

dysfunction scores include the Multiple Organ Dysfunction Score (MODS) [12] and the Sequential Organ Failure Assessment (SOFA) scores [11]. As mentioned above the SOFA score has been integrated into the new definition of sepsis [4].

The Mannheim peritonitis index (MPI) was developed by Wacha and colleagues in 1983 [16], based on the retrospective analysis of data from 1253 patients with peritonitis; 20 possible risk factors were considered. Of these only eight proved to be of prognostic relevance and were retained for the MPI, classified according to their predictive power. These included fecal exudate (12 points), diffuse generalized peritonitis (6 points), purulent exudate (6 points), organ failure (kidney, lung, shock, or intestinal obstruction) (7 points), age > 50 years (5 points), female sex (5 points), preoperative duration of peritonitis > 24 h (4 points), malignancy (4 points), non-colonic sepsis (4 points). Patients with a score exceeding 26 were associated with high mortality [17].

Prospective studies have confirmed that the MPI was not only as efficient as APACHE II in predicting the short-term risk of mortality of a patient with peritonitis [18, 19], but it is one of the easiest scoring systems to apply. It can be calculated at the time of surgery whereas the APACHE II score requires assessment over a 24-h period and it is more or less organ specific. The MPI has been found to be highly predictive of morbidity and mortality [19, 20]. Moreover, the latter group was the only team to perform a true sensitivity analysis with a Receiver-Operator-Characteristic curve [20].

Yet, the MPI has not yet gained wide acceptance. However, no score can predict the outcome of peritonitis with certainty in an individual patient.

Other factors affecting prognosis are age, fecal peritonitis, metabolic acidosis, blood pressure, pre-operative organ failure, serum albumin, cardiac function, malnutrition, malignancy, cause of infection, site of origin of peritonitis and number of organs involved in multi-organ-failure (MOF).

Management (techniques and indications)

Initial fluid resuscitation strategy

- ✓ Resuscitation in sepsis is initially based on goal-directed fluid therapy
- ✓ Colloids remain a viable therapeutic option based on their superior hemodynamic properties and plasma volume expanding capacity
- ✓ The initial target mean arterial pressure (MAP) in patients with septic shock should be at least 65 mmHg

Intravenous fluids are an integral component of the multimodal resuscitation strategy. In widespread use for years, uncertainty hovers over their relative safety and efficacy. Fluid resuscitation is the mainstay in the initial treatment of sepsis, but the choice of fluid is unclear. The ideal resuscitative fluid should restore intravascular volume while minimizing edema. However, edema and edema-related complications are common consequences of current resuscitation strategies [21]. Interest in the comparative effectiveness of different intravenous solutions continues and international debates still flourish [22].

The previous definitions of severe sepsis and septic shock, stated in 1991 and updated in 2001 were: severe sepsis (defined as acute organ dysfunction secondary to infection) and septic shock (defined as severe sepsis plus hypotension not reversed with fluid resuscitation) originate in the systemic inflammatory response following infection and lead to cardiovascular and organ dysfunction. Initial infection can be located anywhere in the body including skin and soft tissues, pulmonary, urinary, or digestive tract as in the case of peritonitis. As new guidelines were being developed, new definitions for sepsis and septic shock (Sepsis-3) were published. Sepsis is now defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality [23]. The Sepsis-3 definition also proposed clinical criteria to operationalize the new definitions.

Resuscitation in sepsis is initially based on goal-directed fluid therapy. The timing, rather than the type, of fluid therapy has been proposed as being crucial [24]. The relative proportion of the different fluids used for initial resuscitation varies between countries [20]. Cost is invariably included as a factor in guidelines on the choice of fluids, with the higher cost of colloids, particularly albumin, being emphasized. Colloids are more expensive than crystalloids, but remain a viable therapeutic option based on their superior hemodynamic properties and plasma volume expanding capacity, despite a lack of survival benefit in systematic reviews of heterogenous patient populations [25, 26].

A consensus committee of 55 international experts recently proposed the new guidelines for management of sepsis [27]. They recommend that, in the initial resuscitation from sepsis-induced hypoperfusion, at least 30 mL/kg of intravenous crystalloid fluid be given within the first 3 h (strong recommendation, low quality of evidence). They also recommend that, following initial fluid resuscitation, additional fluids be guided by frequent reassessment of hemodynamic status (clinical examination, as well as other noninvasive or invasive monitoring, as available). Where available, dynamic over static variables should be used to

predict fluid responsiveness. The initial target should be a minimum mean arterial pressure (MAP) of 65 mmHg in patients with septic shock requiring vasopressors and all efforts should be made to normalize serum lactate levels as a marker of tissue hypoperfusion.

Avoiding fluid overload by choosing the appropriate amount of fluids in patients who are fluid-responsive on one hand, and treating intravenous fluids like other medications, on the other hand, are the major changes. Whenever clinicians decide to prescribe intravenous fluids, they need to weigh the risks and benefits of giving fluid and also the advantages and side effects of each fluid type in order to optimize patient outcomes [28].

Supportive and antibiotic management in peritonitis

- ✓ Antimicrobial therapy should start no later than 1 h after the recognition of peritonitis
- ✓ Early administration of enteral nutrition (EN) is recommended against early parenteral nutrition in hemodynamically stable patients
- ✓ High protein intake is recommended (1.2–3 g/kg/day)

Peritonitis is the second cause of Intensive Care Unit (ICU) admission after complicated pneumonia and recent studies have reported increasing rates of healthcare-associated peritonitis remaining a leading cause of death and morbidity in ICU patients [29]. Management of peritonitis is becoming increasingly complex mostly because of growing prevalence of multidrug-resistant (MDR) bacteria.

Antibiotics

The cornerstone of appropriate antimicrobial therapy is the timing, spectrum and dosing of antibiotics [30]. Microbiologic cultures must be obtained before starting any antibiotic treatment but should not delay administration of antimicrobials (maximum 1 h after the recognition of peritonitis) because failure to initiate appropriate empiric therapy is associated with a considerable increase in morbidity and mortality. Empiric broad spectrum antimicrobial therapy is recommended to cover all likely pathogens (bacteria and fungi). Antibiotic doses must be optimized according to their pharmacokinetic and pharmacodynamic properties in order to improve outcome and avoid side effects. Furthermore, once pathogen identification and sensitivities are available empiric antibiotic therapy must be narrowed to avoid resistance. As soon as patients improve clinically and inflammatory signs decrease, antibiotics must be stopped promptly to minimize toxic side effects and to reduce infections from multi-resistant pathogens [31–33]. Antibiotic therapy can be suspended after 4 days in the absence of fever, elevated white count or temperature for 48 h, but it should be adapted to the pathology that produced the peritonitis.

In primary peritonitis, which represents a minority of cases (1%), infection is mainly sustained by Streptococci, Pneumococci and Haemophilus influenzae and antibiotics currently employed are ceftriaxone, cefotaxime, ceftazidime as well as acylaminopenicillins. In continuous ambulatory peritoneal dialysis (CAPD) peritonitis agents more frequently involved are coagulase-negative Staphylococci and Staphylococcus aureus and empirical therapy is based on vancomycin plus gentamicin or a group 2 cephalosporin with or without ciprofloxacin [34].

Community acquired secondary peritonitis is sustained most frequently by *E. coli*, *Bacteroides fragilis* and other anaerobes and enterococci [35]. In peritoneal contamination of less than 6 h duration the usual antibiotics employed are aminopenicillin/BLI (beta-lactamase inhibitor), acylaminopenicillin/BLI, ertapenem or group 2 cephalosporin in combination with metronidazole or ceftriaxone. In prolonged, diffuse and fecal peritonitis empirical therapy includes acylaminopenicillin/BLI, or group 1 (ertapenem) or group 2 (imipenem/cilastatin, meropenem) carbapenems or combinations of metronidazole with group 2, 3a or 4 cephalosporins, ciprofloxacin, levofloxacin or a monotherapy with moxifloxacin [33, 36].

Tertiary peritonitis shows a bacterial spectrum similar to that of postoperative secondary peritonitis. Group 1 or 2 carbapenems, tigecycline, acylaminopenicillin/BLI or group 3a cephalosporins in combination with metronidazole are recommended [37].

Tigecycline fails to cover Proteus, Providentia and Pseudomonas, so it should be combined with antipseudomonal therapy in tertiary peritonitis (ciprofloxacin, ceftazidime, amikacin, imipenem/meropenem and piperacillin-tazobactam).

In IAI with MRSA (multi resistant Staphylococcus aureus) colonization has been seen in abdomens left open and Tigecycline represents a good therapeutic option [33, 38].

Peritonitis sustained by vancomycin-resistant enterococci (VRE) is treated with the same antibiotics used against MRSA except for vancomycin. Carbapenems, fluoroquinolones, tobramycin and tigecycline are the antibiotics of choice for pathogens producing extended spectrum beta lactamases (ESBL). In the case of pan drug resistance (PDR) Pseudomonas, colistin remains the unique effective treatment [39].

New antimicrobial agents have been developed against resistant pathogens: Ceftolozane/Tazobactam, Ceftazidime/Avibactam, Aztreonam/Avibactam, Imipenem/Relebactam and S-649266 are all novel antibiotics targeted against extended spectrum beta lactamase pathogens. Two other new antibiotics, Eravacycline and Plazomicin, represent a good therapeutic option against carbapenemase producing *Klebsiella pneumoniae*, carbapenem-resistant Acinetobacter baumanii and ESBL producers. New lipoglycopeptides and oxazolidinones play a role against resistant Gram-positive pathogens.

Of note, in recent years prevalence of Candida infections in ICU patients with peritonitis has increased; in general, high dose Fluconazole is sufficient but resistance of Candida against Fluconazole is increasing and Echinocandin or Amphotericin B are viable options. [40]. Risk factors for invasive fungal infections include immunocompromised states, including, neutropenia; intravascular or other catheters (especially if parenteral nutrition is involved); prostheses and broad-spectrum antimicrobial usage.

Nutrition

Early administration of enteral nutrition (EN) is recommended rather than parenteral nutrition (PN) in hemodynamically stable patients because of its potential physiologic advantages related to the maintenance of gut integrity, modulation of the inflammatory response and reduction of insulin resistance in the first 7 days of ICU stay. PN can be added to EN to provide the recommended caloric and protein intake (1.2 and 3 g/kg/day to improve nitrogen balance) [41].

Despite the risk of gastroparesis and feeding intolerance in critically ill patients, post-pyloric placed feeding tubes and routine monitoring of gastric residual volumes are justified only in patients at high risk of aspiration. Prokinetics are weakly recommended in treating feeding intolerance and their use must be assessed daily and stopped as soon as possible.

Omega 3 fatty acids, carnitine, arginine and glutamine are not recommended as supplements in critically ill patients with peritonitis because of the absence of evidence of outcome improvement [42].

Sedation and analgesia

Minimizing sedation in critically ill patients with peritonitis reduces the duration of mechanical ventilation, allows early mobilization and decreases length of ICU and hospital stay. Several strategies have been adopted including intermittent sedation, daily sedation interruption and avoidance of sedatives. Pain management depends on the extent of tissue damage. Multimodal analgesia is preferred in order to decrease the adverse events of a single agent at high dose: non-opioid analgesics, alone or combined with opioids, are the drugs most commonly used [43].

Damage control and open abdomen

- ✓ Damage control laparotomy and open abdomen treatment are viable solutions in the treatment of secondary peritonitis with severe physiological derangement
- ✓ The principles of damage control surgery (DCS) are based on abbreviated surgery with control of bleeding and contamination, leaving the abdomen open (OA), restoration of physiology in an intensive care unit, planned re-operation and definitive repair with delayed fascial closure
- ✓ Negative pressure therapy (NPT) strategy has improved bowel protection and prevented fascial retraction allowing a reduction in terms of complication and higher rates of fascial closure

Damage control laparotomy and open abdomen treatment are viable solutions in the treatment of secondary peritonitis with severe physiological derangement, but accurate patient selection is essential.

Damage control surgery (DCS) also known as abbreviated laparotomy and planned re-operation or staged abdominal repair surgery is a concept of abbreviated laparotomy designed to prioritize physiological recovery over anatomical reconstruction in the severely injured patient. The principles of DCS are based on abbreviated surgery with bleeding and contamination control, leaving the abdomen open (OA), restoration of physiology in an intensive care unit, planned re-operation and definitive repair with delayed fascial closure. This staged approach leads to prevention of patient's physiological exhaustion caused by shock and permits a definitive treatment after restoration of physiological parameters. DCS, especially if combined with damage control resuscitation (DCR) is associated with improved outcomes in trauma patients [44]. Immediate definitive repair of severe injuries in patients with deranged physiology is well known to be detrimental to outcome [45].

Due to similarities in impaired physiology between trauma surgery and non-trauma surgical emergencies (or the need to plan a second look laparotomy in secondary or post-operative peritonitis, bowel ischemia or severe acute

pancreatitis) some centers have extended the DCS principles to treat non-trauma acute conditions [46].

In secondary or tertiary peritonitis DCS consists of postponing restoration of intestinal continuity to a subsequent operation and leaving the abdomen open with a temporary abdominal closure (TAC) [47]. This approach is indicated essentially in cases where it has not been possible to obtain source control at the first operation or in patients with significantly impaired physiology. The basic concept of an OA strategy in peritonitis instead of either abdominal closure with planned re-laparotomy or re-laparotomy on demand is that the contaminated peritoneal cavity is treated as an open abscess. The temporary abdominal closure facilitates repeated peritoneal lavage. OA is also indicated in cases with, or at high risk of, abdominal compartment syndrome (ACS) and where it is impossible to obtain a primary direct fascial closure due to visceral edema.

At the present time, only level III and IV data support the benefits of a DCS approach with OA and TAC in patients with non-traumatic surgical emergencies such as peritonitis. The retrospective nature of these studies with no standard definition of damage control techniques and heterogeneous assessment of physiology impairment and lack of prospective randomized trials suggest only a cautious advocacy for DCS in non-trauma setting [2].

An OA strategy following DCS is associated with high complication rates including enteroatmospheric fistula (EAF) and fascial retraction with difficult/impossible delayed fascial closure [48]. Patient selection is therefore essential in order to avoid over-treatment. As in trauma surgery several authors have estimated that a small proportion of non-traumatic abdominal emergencies would benefit from this strategy [49–51] since most of these abdominal emergencies never reach a critical level of physiological derangements at which DCS is indicated.

Further research will need to focus on correct selection of patients that might clearly benefit from a DCS approach.

TAC with NPT and mesh-mediated fascial traction seems to provide best results in terms of fewer complications and better primary delayed fascial closure rates.

Choice of TAC is a key element in the OA management. Static TAC methods used at the beginning of the era of DCS, such as simple skin closure, towel-clips closure or Bogotá bag, were used to contain abdominal viscera, but did not prevent lateral fascial retraction hindering definitive fascial closure. Furthermore, mortality was close to 40% [47] and severe complications such as EAF, especially in the septic abdomen, were frequently associated [52, 53].

At the present time, the most commonly used NPT techniques are commercial devices and the so-called "Barker" vacuum-pack, a limited cost system where viscera are protected by a plastic sheet and sterile surgical towels are sealed and connected through a drain with continuous negative pressure [54].

Introduction of NPT devices and a more comprehensive understanding of pathophysiology of OA has improved the outcome of this population of patients. NPT strategy has improved bowel protection and prevented fascial retraction allowing a reduction in terms of complications and higher rates of delayed fascial closure, especially if abdomen closure is obtained within 8 days [48]. Benefits in terms of reduction of systemic effects through cytokine removal by negative pressure have been demonstrated in porcine models [55] and improved outcomes have also been documented in a prospective observational study [56]. A recent randomized controlled study could not find any statistically significant difference in the reduction of systemic inflammatory markers between NPT and the Vacuum-pack technique [57].

At the present time, the most promising results in terms of primary delayed fascial closure have been reported when a combined technique using NPT with a polypropylene mesh sutured to the fascial margins. The fascial margins are progressively approximated by increased tension via the mesh until a direct suture can be performed [58]. The results of this technique, although mostly reported in single centers with limited number of cases seem to be promising.

Further prospective studies are needed in order to evaluate the efficacy of NPT on the reduction of inflammatory mediators and its potential relation to prevention of multiorgan failure. Larger prospective series to determine the best treatment for primary delayed fascial closure are also needed.

Particularities according to disease and organ

Upper GI anastomosis leakage and perforated gastroduodenal ulcer

Post-surgical upper gastro-intestinal anastomotic leaks are the most common and feared complications for any anastomoses. For this short review we will address post-operative leaks following esophagectomy and sleeve gastrectomy, the most frequent bariatric procedure today. The factors and causes responsible for upper gastro-intestinal anastomotic leaks (patient, surgeon or technique related) as well as the diagnosis and current management will be examined.

Anastomotic leaks following esophagectomy

- ✓ The risk factors are cervical and hiatal location of the anastomosis, positive margins for malignancy, local ischemia and technical errors
- ✓ The diagnosis is usually made clinically and/or by contrast esophagogram/flexible endoscopy or CT scan
- ✓ The management depends on clinical presentation and location of the anastomosis and extent of anastomotic disruption, and grading of the leak
- ✓ Nonoperative, conservative management such as delayed initiation of oral feeding and antibiotics may suffice for occult (Grade I) leaks
- ✓ General principles of management include systemic antibiotics, closure or occlusion of the defect as soon as possible which can either be done by stents or surgically
- ✓ In more serious situations, if sepsis is poorly controlled with more conservative measures, esophageal diversion or resection can be entertained
- ✓ After bariatric surgery, the chances are higher that the leak will close using a stent and providing enteral nutrition support

The prevalence of anastomotic leakage following esophagectomy ranges from 0 to 35%, with cervical anastomotic leaks being more frequent. The main risk factors for anastomotic leakage are cervical and hiatal location of the anastomosis, positive margins for malignancy, local ischemia and technical errors. Other factors for anastomotic leak are higher ASA score, malnutrition, diabetes, renal failure, steroids, obesity, smoking, surgeon's experience (and frequency with which the operation is performed by individual surgeon as well as institutional overall experience). Moreover, whether the anastomosis is performed hand sewn or stapler influences the frequency of leaks. Recent evidence favors use of stapling in preventing an anastomotic leak. In the meta-analysis by Liu et al. [59] of 15 RCTs (n = 2337) comparing stapling vs. hand-sewn anastomosis use of stapler reduced the risk of leak by 34%. In another recent study by Ryan et al. [60] of 21 RCTs combining prospective/retrospective cohort studies (n = 7167) of transthoracic vs transhiatal approaches (TTE vs THE) there was no difference between TTE and THE. Use of an omentoplasty to reduce the leak rate was reported as favorable by Schaheen et al. [61]. Interestingly, Zhou et al. [62] reported no differences in leak according to whether esophagectomy was done minimally invasively or via an open approach.

Clinical presentation of the leak varies according to the location of the anastomosis and other factors, such as degree of spillage, whether the leak is early (mechanical failure) or late (ischemia), patient defense mechanisms, and patient status (fully awake, under respiratory assistance, vasopressive support, associated sepsis). The diagnosis is usually made clinically and/or via contrast esophagogram/flexible endoscopy or CT scan. The management depends on clinical presentation and location of the anastomosis and extent of anastomotic disruption, i.e., grading of the leak that may be without clinical signs (Grade 1) to major leak (Grade 3) or Grade 4, with entire gastric conduit necrosis. Nonoperative, conservative management such as delayed initiation of oral feeding and antibiotics may suffice for occult (Grade I) leaks. The general principles of management include systemic antibiotics and closure or occlusion of the defect as soon as possible, which could be done by stents or surgically. Drain associated fluid collections, prevent distal obstruction and minimize factors that are keeping the perforation open (e.g., tumor, foreign body, persistent infection). If sepsis is poorly controlled with conservative measures esophageal diversion or resection should be entertained. In recent years laser-assisted fluorescent-dye angiography (LAA) has been used to assess perfusion in the gastric graft and to correlate perfusion with subsequent anastomotic leak. In a study of 150 patients undergoing esophagectomy with planned gastric pull up reconstruction a leak was found in 24 patients (16.7%) and was significantly less likely when the anastomosis was placed in an area of good perfusion [63]. Use of stents has been recently reported in 267 patients by van Boeckel et al. [64] with success a rate of 81–94%. The commonest complication, stent migration, occurred more often with self-expanding plastic stents [n = 47 (31%)].

Leaks following laparoscopic sleeve gastrectomy for morbid obesity

- ✓ The definitive management of these leaks depends on the patient's condition and the ability to provide enteral nutritional support
- ✓ Using a stent and providing enteral nutritional support increase the chances that the leak will close

Morbid obesity has risen to true world-wide epidemic proportion. Laparoscopic and robotically assisted sleeve gastrectomy has become one of the most common bariatric procedures world-wide. In large published case series of open and laparoscopic cases, the leak rate varies between 1 and 8.3% after gastric bypass [65]. However, although post-operative complications are not common in all these procedures, they must be recognized and addressed promptly in order to minimize possible mortality and significant morbidity.

The etiology of GI leaks is multiple but generally falls into mechanical/tissue causes or ischemic causes, both of which involve intraluminal pressure that exceeds the strength of the tissue and/or staple line [66].

Identifying the best technique with lowest complication such as reinforcement of the stapled resection of the stomach after gastric bypass has been studied extensively. A systematic review by Gagner and Buchwald [67] of 88 RCTs, retrospective or prospective studies (n = 8920) of laparoscopic sleeve gastrectomy (LSG) compared 4 staple-line reinforcement methods. The study compared LSG staple-line leak rates of 4 prevalent surgical options: no reinforcement, over sewing, nonabsorbable bovine pericardial strips (BPS), and absorbable polymer membrane (APM). There were 191 leaks in 8920 patients; an overall leak rate of 2.1%. Leak rates ranged from 1.09% (APM) to 3.3% (BPS). APM leak rate was significantly lower than other groups ($p < 0.05$). The percentage of leak was the lowest with absorbable membrane 1.09 (N/A); Over sewing 2.04 ($p = 0.02$); No reinforcement 2.60 ($p = 0.001$); while the highest leak rate was using bovine pericardium 3.30 ($p = 0.0006$). A meta-analysis by Parikh et al. [3] of 112 studies (n = 9991) of LSG found that use of a Bougie ≥ 40 Fr significantly (47%) reduced the odds of a leak [OR 0.53 (0.37, 0.77)] while there were no significant effects for distance to pylorus or use of buttressing.

Recognizing the leak early and addressing it promptly is necessary if complications are to be minimized. Traditionally, any leak from the gastric anastomosis or any form of bariatric surgery would have meant re-operating, wide drainage or a combination of both. The definitive management of these leaks depends on the patient's condition, and the ability to provide nutritional support enterally. Using a stent, and providing enteral nutritional support the chances are higher that the leak will close. Recently, the American Society for Metabolic and Bariatric Surgery issued a position statement and recommendations on prevention, detection, and treatment of gastrointestinal leak after gastric bypass and sleeve gastrectomy, including the roles of imaging, surgical exploration, and nonoperative management [65]. While meticulous tissue handling, use of proper tissue thickness, and avoidance of inadvertent narrowing, undue tension, and twisting or kinking of the mesentery and tissues are most important, other elements in this statement should be examined by every surgeon doing a GI anastomosis.

Biliary peritonitis

- ✓ The standard for acute cholecystitis is surgical treatment and laparoscopic cholecystectomy is a safe and effective treatment
- ✓ The optimal time for this approach is as soon as possible after diagnosis, better in the first 3 days after the presentation of symptoms
- ✓ For critically ill patients with biliary sepsis percutaneous cholecystostomy is an alternative for patients at high risk for surgery
- ✓ For patients with severe inflammation partial cholecystectomy, it is also a safe option but it should be associated with the closure of the cystic duct or suture of the infundibulum and drainage
- ✓ For acute cholangitis, endoscopic drainage is the preferable option for management because serious complications are very rare

Biliary peritonitis is in important cause of morbidity and mortality and now is the second commonest cause of peritonitis after appendicitis according to the CIAO study, a multicenter investigation performed in 68 medical centers in Europe during a 6-month observational period in 2012 [68].

Cholecystectomy is gold standard treatment for patients with acute cholecystitis but percutaneous cholecystostomy could be an alternative for patients at high risk for surgery in elderly or critically ill patients with biliary sepsis [69–71]. In a systematic review of severely ill patients with comorbidities treated by percutaneous cholecystostomy, 40% of patients were later cholecystectomized, with a mortality rate of 1.96%. Procedure mortality was 0.36%, but 30-day mortality rates were 15.4% in patients treated with percutaneous cholecystectomy and 4.5% in those treated with acute cholecystectomy ($p < 0.001$) [72].

Early diagnosis and emergency surgical treatment of gallbladder perforation are the key points for reducing morbidity and mortality rates associated with this condition, but unfortunately gallbladder perforation is rarely diagnosed pre-operatively. Delayed surgical intervention is associated with elevated morbidity and mortality rates, increased likelihood of ICU admission, and prolonged post-operative hospitalization [2, 74].

Biliary leaks are an iatrogenic injury to the biliary canals and can develop after laparoscopic cholecystectomy in

0.4–0.7% of cases. Bile leakage has been defined as the bilirubin concentration in the drainage at least 3 times the serum bilirubin concentration on or after postoperative day 3, or as the need for radiologic or operative intervention resulting from biliary collections or biliary peritonitis in patients who underwent hepato-biliary or pancreatic operations [74]. Endoscopic treatment of biliary leaks in the form of sphincterotomy and stent placement is associated with a high rate of success. Closure of the leak has been reported in 91.0% of cases [75].

Acute cholangitis differs in severity, from a mild form, which can be managed with parenteral antibiotics alone, to severe or suppurative cholangitis requiring early biliary drainage [76]. Treatment of acute cholangitis requires treatment of the underlying cause in addition to administration of antimicrobial agents and biliary drainage [77].

In 2001, Hui et al. reported on a prospective study of 142 consecutive patients with acute cholangitis. Emergency ERCP was performed in patients who did not respond to medical therapy. Thirty-one patients (21.8%) required emergency ERCP. A maximum heart rate of more than 100/min, albumin of less than 30 g/L, bilirubin of more than 50 micromole/L and prothrombin time of more than 14 s on admission were associated with failure of medical treatment and the need for emergency ERCP ($p = 0.001, < 0.001, 0.006$ and 0.004, respectively) [78].

Biliary drainage can be performed by an endoscopic or percutaneous transhepatic approach. For critically ill patients with acute cholangitis, endoscopic biliary drainage is equally effective for malignant or benign biliary disease [79]. To date no RCTs have been published comparing the safety and effectiveness of endoscopic and percutaneous transhepatic biliary drainage in the treatment of acute cholangitis. Endoscopic drainage is preferable to open drainage due to the shortened length of hospitalization and because significant complications are rare [80].

Patients with biliary peritonitis should be operated on without delay and the surgery should include drainage of the abdomen and repair of the underlying cause. However, in certain circumstances the operative findings may dictate that drainage is the only option. After surgery for generalized postoperative peritonitis, a strategy of planned relaparotomy is suggested when source control is uncertain. An on demanded relaparotomy approach is adequate for purulent and biliary peritonitis if the septic source has been controlled [81].

Small bowel perforation

- ✓ Surgery is the first choice of treatment for small bowel perforation
- ✓ Primary repair of perforated bowel is preferable to resection in the absence of gross fecal peritonitis and during the first 6 h after perforation
- ✓ Primary anastomosis should be avoided in the presence of gross or fecal peritonitis because it is associated with a high risk of complications

Surgery is the first choice of treatment for small bowel perforations. The surgeon has several options including simple suture and wedge or segmental resections. Primary repair is preferred over resection whenever possible because of lower complication rates. Better outcomes could also reflect the limited tissue injury in these patients [82, 83].

The technique of anastomosis (whether stapled or hand-sewn) in small bowel resection appears to have little influence on the anastomotic complication rate. If an enterectomy is required, the entire unhealthy segment is resected, leaving fit and well-perfused ends for anastomosis. For patients with malignant lesions, perforations associated with mesenteric vascular injuries, necrotic bowel, or multiple adjacent perforations primary repair should not be performed [31, 82, 84].

A laparoscopic approach may be performed if the patient's overall health status and the surgeon's experience are appropriate [84]. There is no RCT comparing laparoscopic with open surgery despite the management of small bowel perforation being well represented in the literature [85].

Primary anastomosis should be considered carefully in the presence of gross or fecal peritonitis because it is associated with a high risk of complications [31]. In delayed presentations, a protective ileostomy may be prudent to address fecal peritonitis in order to reduce mortality rates [86, 87]. Thorough systematic abdominal lavage is essential in cases of serious abdominal suppuration [86, 87].

Patients with duodenal perforation post-Endoscopic Retrograde Cholangiopancreatography (ERCP) require early detection and prompt treatment. The development of

abdominal pain, pyrexia or signs of critical illness should prompt consideration of urgent surgical exploration for repair or drainage. Successful non-operative management of sphincterotomy-related retroperitoneal perforations is possible in stable patients even if there is extensive retroperitoneal gas observed on CT. A high number of pancreaticobiliary and duodenal perforations (70%) secondary to periampullary endoscopic interventions can be treated non-operatively by nasogastric drainage, antibiotic coverage and nutritional support [86, 88].

Appendicitis

- ✓ Complicated appendicitis is represented by perforation, abscess or localized/generalized peritonitis
- ✓ The laparoscopic approach in complicated appendicitis is still a subject of discussion

Complicated appendicitis is represented by perforation, abscess or localized/generalized peritonitis. Clearly, some prefer open appendectomy in this setting [89, 90], but it is of note that most uncomplicated cases of acute appendicitis can be treated through a single 15–20 mm incision in the right iliac fossa [91]. The laparoscopic approach in complicated appendicitis is still a subject of discussion, essentially as concerns the postoperative complications. Special attention should be paid to the complexity of adhesiolysis and peritoneal lavage: in the pouch of Douglas, peri-cecal space, hepato-phrenic space and infrahepatic space. One potential advantage of laparoscopy is that it allows a better view of the entire peritoneal cavity and of all the spaces without the necessity to make a large incision, or enlarge a smaller one if a complication is found or an anatomic variation (ectopic appendix) is discovered [91–93]. In cases with difficult access to an ectopic appendix (retrocecal, subhepatic or mesoceliac) or limited mobility of the cecum or discovery of peritonitis, conversion to laparoscopy (coined "reversed conversion" by Schrenk et al. [94] and developed by Navez et al. [95] with three to five 5–10 mm incisions is an excellent solution to explore the entire abdomen and treat the disease instead of enlarging the right iliac fossa oblique incision or deciding to perform a large midline incision, both of which can lead to postoperative parietal co-morbidity (surgical site infection or incisional hernia) [91]. However, there are reports stating that laparoscopic appendicectomy (LA) has been associated with higher rates of organ space infections, especially in complicated cases [96]. Thereaux et al. recently published an article with 141 patients operated for diffuse appendicular peritonitis. The most important point in this paper is that all the patients were operated by the same experienced team with a conversion rate of 3.5% and 7.1% (10 cases) intraabdominal abscesses [97]. In a very recent RCT on complicated appendicitis, Thomson et al. stated that for 114 patients and 7% conversion rate, also operated by the same team of senior laparoscopic surgeons, LA is at least as safe as the open approach for complicated appendicitis [98]. The conclusions are controversial, but recent studies with experienced laparoscopic surgeons have not been able to find any statistically significant differences in terms of postoperative abscesses [99, 100]. Surgeons who have better and extensive experience in laparoscopic surgery can obtain better results with LA than with open surgery [91]. The best surgical approach should be the approach that best suits the surgeon's experience.

For perforation during endoscopy, endoscopic treatment with placement of a clip is possible when the perforation site is recognized during or within 6 h of the procedure and the bowel preparation is adequate. The decision for endoscopic treatment depends on the size and the cause of perforation as well as the endoscopist's experience and access to endoscopic devices. Clips are suitable for closure of small therapeutic perforations less than 1 cm.

Colorectal perforations

- ✓ Perforation from colorectal malignancy is a surgical emergency and source control and aggressive supportive care for sepsis physiology must be the primary goal
- ✓ Perforation is a pathological condition in which saving life is prioritized, and some aspects such as the extent of lymph node dissection may be compromised
- ✓ Primary anastomosis should be avoided in the presence of gross or fecal peritonitis because it is associated with a high risk of complications

Perforation from colorectal malignancy is a surgical emergency characterized by numerous challenges for the surgical team as well as for the anesthetic one [101]. The surgeon is faced with a multitude of unfavorable factors including septic shock, poorly defined tissue planes and the technical demands of an oncologic resection without the leisure of time or adequate oncologic work-up. [102] How aggressive the treating surgeon should be in these unstable patients is still an ongoing controversy. In addition, advances in critical

care and adjuvant therapy have improved outcomes in septic shock and metastatic colon cancer. The incidence of malignant perforation from colorectal cancer ranges from 1.2 to 9%, total mortality can reach 12–48% [103] and large series analyzing the perioperative and long-term outcome in these patients are lacking [103]. There are two types of perforation associated with colon cancer: direct perforation from tumor necrosis and perforation of the proximal colon due to obstruction by the tumor [103]. Source control and aggressive supportive care for sepsis physiology must be the primary goal. This approach is supported by the substantial risk of peri-operative mortality faced by these patients [102]. Tan et al. reported a series of 45 patients with colonic perforation [101]. Sigmoid colon (37.8%) and cecum (28.9%) were the most common sites of perforation. Hartmann's procedure and right hemicolectomy were performed most frequently in 17 (37.8%) and 15 (33.4%) patients, respectively. 17.8% patients died in the perioperative period. Independent variables predicting worse peri-operative complications (Clavien/Dindo grades III to V) [106] were ASA score ≥ 3 and worse peritoneal contamination (MPI > 26). Left-sided perforation was the only independent factor predicting stoma creation. The only factor predicting long-term survival was the stage of malignancy ($p < 0.001$). The overall mean survival time for stage II, III, and IV disease were 63.7, 38.1, and 13.8 months, respectively. 41.7% patients had disease recurrence. The median time to recurrence was 13 months (6–48 months).

Zielinski et al. reported eighty-six patients with colonic perforations associated with primary colon cancer in whom the overall survival (OS) was significantly worse in those with diffuse peritonitis compared to those with contained perforations, with 5-year estimated OS at 24% vs. 62% ($p = 0.003$). Post-operative mortality was significantly higher for the diffuse peritonitis patients (19% vs. 0% in contained perforations group) and only 5% in a case matched control group of patients undergoing resection for colon cancer who did not have colonic perforations. Perioperative mortality is the main reason for inferior OS in the unadjusted analysis when compared to non-perforated controls. R0 resection could be achieved in 62–68% of patients with perforated colon cancer. Ping Song et al. [103] reported a series of twenty-six consecutive patients with an overall mortality rate during hospitalization of 15.4%. All deaths occurred in patients with perforation proximal to the tumor. Perforation proximal to the tumor occurred more commonly in patients with advanced age (> 70), higher American Society of Anesthesiologists (ASA) score and higher preoperative lactate. Hiroshi Asano et al. [105] reported a review of 44 colorectal cancer perforation patients. In-hospital mortality was 25.0% (8 of 32 patients) for proximal site perforation but 8.3% (1 of 12 patients) in the cancer site perforation patients. There was no significant difference in recurrence rates between the two groups. The recurrence rates in the patients who underwent surgery with R0 resection were 18.2% in those at stage II and 54.5% in those at stage III.

In terms of conclusions, the patient has two possible elevated risk sources: from the malignancy and from the septic complications secondary to perforation. Perforated colorectal malignancy is associated with high morbidity and mortality rates. However, perforation is a pathological condition in which saving life is prioritized, and some aspects such as the extent of lymph node dissection may be compromised. Short-term outcome is determined by ASA score and severity of peritonitis while long-term outcome by the stage of the cancer. Perforated colorectal cancer is a high-risk factor for recurrence, and the application of postoperative adjuvant chemotherapy is expected to contribute to improvement of prognosis.

Primary anastomosis should be avoided in the presence of gross or fecal peritonitis because it is associated with a high risk of complications.

Anastomotic leakage

- ✓ There is no consensus on the management of anastomotic leaks
- ✓ The diagnostic methods commonly used when a leakage is suspected are CT scan, contrast enema, endoscopic examination, and reoperation
- ✓ Nonoperative management can be performed successfully in both diverted (at the initial operation) and nondiverted patients
- ✓ Patients with overt sepsis requiring surgical intervention almost always require a diverting stoma as part of their treatment, which might well become permanent

Anastomotic leak continues to be a feared surgical complication, leading to significant patient morbidity and mortality. Leak rates described in the literature are significant, ranging from 3 to 21% [106] with mortality rates of 3–22%. There is no consensus on the management of anastomotic leaks. Although operative intervention has traditionally been preferred, selected patients with anastomotic leaks have been managed nonoperatively with or without percutaneous intervention. Varying definitions of anastomotic leak may lead to some confusion as to the best treatment. Risk factors for leakage have been extensively studied, and the most frequent

factors mentioned are male sex, high age, a low anastomosis, malignant disease, high (ASA) score, long operation time, emergency operation, preoperative radiotherapy and perioperative blood loss or transfusion. [107]. The anastomotic leak definition proposed by Rahbari et al. is often used: grade A requires no therapeutic intervention; grade B includes active intervention without laparotomy, and if laparotomy is required, the leakage is classified as grade C [108]. The diagnostic methods commonly used when a leakage is suspected are CT scan, contrast enema, endoscopic examination, and reoperation [109]. Bodil and al. proved that almost one quarter of all CT scans were negative in patients who later were diagnosed with anastomotic leakage. It took a mean of 8.5 days before leakage was confirmed, compared to 4.3 days in patients who were diagnosed during a reoperation [107]. Blumetti et al. showed that median time to diagnosis of nonoperative leaks was 27 days (range 3–1400 days), and the median time to diagnosis of operative leaks was 6 days (range 2–660 days) [110]. Treatment of an anastomotic leakage differs with the severity and the location of the anastomosis. Often, there is a high frequency of permanent stoma after a reoperation and anastomotic take down. Salvage of the anastomosis is more common in grade A and B leakages with the treatment consisting of drainage and/or antibiotics [111]. Novel procedures to preserve the leaking anastomosis have also been described, including laparoscopic diverting ileostomy combined with an endoscopically placed polyurethane vacuum sponge at the site of the leak or endoluminal stenting combined with diverting stoma [112]. Chen and other several authors have highlighted the possibility of treating low-lying anastomotic leaks via a hybrid approach in which the anastomosis is managed endoluminally, while the peritoneal cavity is explored and treated via laparoscopy (a hydrid approach) [113]. The use of a protecting stoma should theoretically attenuate the severity of an anastomotic leak and allow wider use of nonoperative therapies. Studies have shown no difference in the number of symptomatic leaks in patients with a stoma, although the rate of reoperation for leak was significantly lower [114]. This demonstrates that the absence of fecal diversion should not affect the choice of management of anastomotic leak (operative vs. nonoperative). Rather, treatment should be based on the patient's overall clinical status [110].

Conclusion: Anastomotic leak in colon and rectal surgery continues to be an ongoing source of patient morbidity and mortality. Diverse presentation of leaks mandates that clinicians tailor the management of this condition to the individual patient. For a grade C low anastomotic leakage the recommendation is colostomy. For a right hemicolectomy anastomotic leak a new anastomoses is recommended for patients in good condition, without evidence of a severe inflammatory response and in the absence of gross fecal contamination. Nonoperative management can be performed successfully in both diverted (at the initial operation) and nondiverted patients. For an accessible and small abscess of less than 4 cm percutaneous drainage is the best option if it is available. Patients with overt sepsis requiring surgical intervention almost always require a diverting stoma as part of their treatment, which might well become permanent.

Complicated diverticular disease

- ✓ Patients with overt sepsis requiring surgical intervention almost always require a diverting stoma as part of their treatment, which might well become permanent
- ✓ Laparoscopic peritoneal lavage (LPL) has failed to demonstrate significant benefits

More than 80% of the patients with acute colonic diverticulitis heal without complications. Current studies have shown that in many patients without immunosuppressive medication or other factors associated with poor healing even antibiotics are not needed [115–117].

Complicated diverticulitis is characterized with perforation that can be either contained or uncontained. Based on the surgical findings of abscesses and peritonitis, Hinchey et al. classified the severity of acute diverticulitis into four grades [10]: Stage 1. Pericolic abscess; Stage 2. Pelvic, intra-abdominal, or retroperitoneal abscess; Stage 3. Generalized purulent peritonitis; Stage 4. Generalized fecal peritonitis.

Recently, Sallinen et al. published a new classification that takes into account organ dysfunction as one of the determinants [118]. Based on a retrospective analysis it sets the stage for the treatment of acute diverticulitis based on clinical, radiologic and physiologic parameters: Stage 1. Uncomplicated diverticulitis; Stage 2. Complicated diverticulitis with small abscess (<6 cm); Stage 3. Complicated diverticulitis with large abscess (≥6 cm) or distant intraperitoneal or retroperitoneal air; Stage 4. Generalized peritonitis without organ dysfunction; Stage 5. Generalized peritonitis with organ dysfunction. In their series, patients with Stages 1 or 2, only 1% and 5% needed surgery, none needed intensive care and the mortality rates were 0% and 1%, respectively. About half of the patients with Stage 3 disease needed surgery, 8% needed intensive care and the mortality rate was 3%. Surgery was required in nearly all (98%) of the patients with generalized peritonitis but no organ dysfunction (Stage

4), only 11% needed intensive care and the mortality rate was 4%. In contrast, of patients with peritonitis and organ dysfunction (Stage 5), all needed surgery and 50% needed intensive care resulting in a mortality rate of 32% emphasizing the importance of the physiological state of the patient in determining outcome.

The major current controversy in the management of acute colonic diverticulitis evolves around the management of patients with purulent peritonitis (Hinchey stage 3). Based on three randomized studies and a meta-analysis [118–122], it seems that while laparoscopic peritoneal lavage (LPL) is comparable to sigmoid resection in terms of mortality, it is associated with higher rate of reoperations and higher rate of intra-abdominal abscesses.

In colonic perforation or perforated diverticulitis initial lavage with or without simple suture and drainage was introduced in the late nineteenth century, then replaced progressively by the three-stage Mayo Clinic or the two-stage Mickulicz procedures. The technique of lavage and drainage regained popularity during the 1990s. This procedure can also be performed laparoscopically with the advantage of faster recovery and shorter hospital stay. In a prospective multi-center study of 100 patients, the authors concluded that LPL for perforated diverticulitis with generalized peritonitis is feasible, with short-term results showing a low recurrence risk [123].

Three recent randomized controlled trials, the DILALA trial, SCANDIV trial and LADIES trial with a total of 343 patients (178 in the lavage group versus 175 in the resection group) showed inconsistent outcomes when LPL alone was compared with resection. These three randomized trials all had serious deficiencies regarding the risk of bias and imprecision; their quality of evidence was low. Statistically the laparoscopic lavage group had a significantly higher rate of postoperative intra-abdominal abscess (RR 2.54, 95% CI 1.34–4.83), lower rate of postoperative wound infection (RR 0.10, 95% CI 0.02–0.51) and shorter length of postsurgical hospital stay (weighted mean difference = − 2.03, 95% CI − 2.59 to − 1.47). There was no statistically significant difference in postoperative mortality after index admission or within 30 days of intervention in all Hinchey stages. In Hinchey stage III there was no significant difference in postoperative mortality at 12 months, surgical reintervention at index admission or within 30-90 days from index intervention, stoma rate at 12 months, or adverse events within 90 days of any Clavien-Dindo grade between groups.

The authors found a significantly higher rate of postoperative intra-abdominal abscess in patients who underwent LPL than in those who underwent surgical resection. Since the aim of surgery was to treat the sepsis, and if this technique was associated with more postoperative abscesses, then this technique should be considered ineffective [124].

In conclusion laparoscopic peritoneal lavage (LPL) has failed to demonstrate significant benefits. Overall, the quality of evidence was low and there were serious concerns regarding the risk of bias and lack of precision. There was a significantly increased rate of intra-abdominal abscess formation with this approach. All in all, however, LPL does not appear inferior to traditional surgical resection and may achieve reasonable outcomes while consuming fewer hospital resources.

Tertiary peritonitis

At least 20% of patients treated for secondary peritonitis have a complicated outcome including anastomotic leaks and abscesses. While these are well known and defined, tertiary peritonitis is a rarer complication that is characterized by organ dysfunction and prolonged systemic inflammation associated with recurrent peritoneal infection by organisms of low intrinsic pathogenicity [38]. It can also be defined as persistence or recurrence of IAI after apparently adequate therapy for primary or secondary peritonitis.

In a study by Nathens and co-workers from 1998 including 59 patients with secondary peritonitis, tertiary peritonitis was defined as culture-proved IAI persisting or recurring at least 48 h after apparently adequate treatment of secondary bacterial peritonitis, and was observed in 44 patients (74%) [38]. *Enterococcus*, *Candida*, *Staphylococcus epidermidis*, and *Enterobacter* were the most common pathogens identified. Infectious foci were usually not amenable to percutaneous drainage and were poorly localized at laparotomy. Compared with patients with uncomplicated secondary peritonitis, tertiary peritonitis was associated with higher ICU mortality (64% vs. 33%), higher organ dysfunction scores and ICU length of stay.

More recently, the term "complicated intra-abdominal infections" has been introduced, and newer studies have grouped tertiary peritonitis among this group defined as persisting peritonitis despite adequate surgical and initial antimicrobial therapy [125]. In addition, other characterizations have been used, such as "persistent and tertiary chronic" peritonitis with distinct changes in immuno-responsiveness [126], and showing the microbiological shift from aerobic gram-negative bacteria towards gram-positive bacteria over time when the condition persists [127].

A study of 69 patients with secondary peritonitis identified 15 patients (22%) who developed tertiary peritonitis [128]. The transition to tertiary peritonitis was associated with higher Mannheim Peritonitis Index at initial operation, higher SAPS II score and C-reactive protein level on the second postoperative day, higher relaparotomy rate and mortality (60% vs. 9%), and longer ICU length of stay.

It seems that specifically Candidal peritonitis is increasing in incidence and continuing to be associated with high

mortality. Factors that have been identified with increasing risk of development of Candidal peritonitis include hollow viscus perforation, abdominal and thoracic surgery, surgical drains in situ, intravenous and urinary catheters, total parenteral nutrition, sepsis, antibiotic therapy more than 48 h before peritonitis, immunosuppression, diabetes mellitus and extensive Candidal colonization [129].

The true nature and exact characterization of tertiary peritonitis is still somewhat obscure. Is it a true entity and if so, what are the definitive clinical, microbiological and biochemical markers that help to identify it? Once this is elucidated, perhaps more relevant guidelines for the diagnosis and management can then be formulated.

What can estes add?

During the course of this conference peritonitis has been classified into four types: primary, secondary, tertiary [1] and peritoneal dialysis (PD) related. The literature is awash with guidelines for the management of primary and PD related peritonitis which are generally the preserves of the hepatologist and nephrologist respectively. There is uncertainty as to the true nature of tertiary peritonitis. Is it the result of inadequate treatment of secondary peritonitis, or is it a separate entity? Even if future research clearly proves the latter, it is likely that many cases considered to be tertiary peritonitis under current definitions may not fulfil the new diagnostic criteria. It therefore follows that the focus of the surgical community should be on the optimal management of secondary peritonitis.

The management of secondary peritonitis requires a combination of source control, supportive therapy to overcome organ dysfunction and antimicrobial therapy.

Secondary peritonitis is polymicrobial and the rapid initiation of antimicrobial therapy essential for the effective management of sepsis will require combination therapy determined on an empirical basis until the results of appropriate cultures with microbiological sensitivities are available. This should include antimicrobials with efficacy against bacteria and fungi. There are numerous national and international guidelines to help inform this process, but the most effective selection will be based on local surveillance of antimicrobial resistance and adapted for clinical risk factors for resistance on an individual patient basis [130].

Secondary peritonitis is often classified as either community acquired or healthcare acquired. This may affect the efficacy of antimicrobial agents in terms of both spectrum adequacy and microbial susceptibility [131] resulting in fewer healthcare acquired cases of peritonitis being as susceptible to a standard antimicrobial regimen as cases acquired in the community. In these cases, the choice of antimicrobial therapy may need to be modified, but unless this is done empirically at the outset, the distinction is of no practical value as far as antibiotic selection is concerned. Moreover, the prognosis in terms of morbidity and mortality is determined by the severity of the peritonitis rather than the geographical location within which it originated [132]. Community acquired fecal peritonitis resulting from a diverticular perforation might be expected to have more in common with fecal peritonitis due to the dehiscence of a colonic anastomosis than it would with a localized peritonitis resulting from a grade 2 cholecystitis [133]. The recent classification of acute diverticulitis that includes organ dysfunction suggests that this is also a better discriminator of outcome than the nature of the peritoneal contaminant [118].

We have sought to define the principles of management: optimizing the physiology with appropriate fluid resuscitation and organ support, effective use of antibiotics and interventional procedures. We have described the current state of knowledge regarding damage control surgery and the role of the open abdomen. We have looked in detail at specific organ systems and pathology.

Unlike the trauma patient, where control of exsanguinating hemorrhage mandates immediate intervention, the optimum timing for surgery in the septic patient with secondary peritonitis has yet to be determined and remains controversial. A balance has to be struck between ensuring adequate pre-operative resuscitation in terms of improving circulating volume and tissue perfusion whilst at the same time limiting the relentless progression of sepsis and organ dysfunction that follows in the absence of adequate source control. The use of goal-directed fluid therapy, ensuring a mean arterial pressure of at least 65 mmHg and normalizing serum lactate levels are worthy targets, but are they the best, and should they be modified in light of other factors?

The review of damage control surgery highlighted both the importance of patient selection in non-trauma emergency surgery and the paucity of strong evidence supporting the use of this therapeutic modality in this group of patients. The small-scale studies of the technique of combining negative pressure wound therapy with a polypropylene mesh are encouraging, but again, larger studies are required to subject this to appropriate scientific rigor.

These areas of immense uncertainty can be summarized succinctly as being when to open and when and how to close the abdomen in secondary peritonitis. That should remain the preserve of the surgeon and is an area where ESTES, with its extensive networks and wealth of individual experience can help.

As with most academic activity, this conference has raised more questions for the surgical body. When is the best time to obtain surgical source control in secondary peritonitis? How can that moment be determined? Which patients should be selected for damage control surgery and how should this be done? Finally, is the combined use of negative pressure

therapy and polypropylene mesh really the best method for achieving ultimate closure of the fascia in these patients?

Compliance with ethical standards

Conflict of interest Ideclare that Bogdan Diaconescu, Selman Uranues, Abe Fingerhut, Mihaela Vartic, Mauro Zago, Hayato Kurihara, Rifat Latifi, Dorin Popa, Ari Leppäniemi, Jonathan Tilsed, Matei Bratu, Mircea Beuran have no conflict of interest.

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