Clinical Management of Endotoxemia: Source Control

10

Silvia Pierantozzi, Tiziana Principi, and Salomone Di Saverio

10.1 Introduction

In recent years, the issue of source control in septic patients has been debated and discussed both in guidelines and randomized trials. The term "source control" encompasses all those physical measures used to control a focus of invasive infection and to restore the optimal function of the affected area [1]. Appropriate source control is a key principle in the management of sepsis and septic shock [2]. Intra-abdominal infections and soft tissues infections are the sites where a source control is more feasible and more impactful. Source control may include drainage of an abscess, debriding infected necrotic tissue, removal of a potentially infected device, or definitive control of a source of ongoing microbial contamination [3]. Foci of infection readily amenable to source control include intra-abdominal abscesses, gastrointestinal perforation, ischemic bowel or volvulus, cholangitis, cholecystitis, pyelonephritis associated with obstruction or abscess, necrotizing soft tissue infection, other deep space infection (e.g., empyema or septic arthritis), and implanted device infections [3].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/978-3-031-18591-5_10.

S. Pierantozzi · T. Principi (✉)
Anaesthesia and Intensive Care, Saint Mary of the Rescue, San Benedetto del Tronto, Italy
e-mail: tiziana.principi@sanita.marche.it

S. Di Saverio
Department of General Surgery, Saint Mary of the Rescue, San Benedetto del Tronto, Italy

S. De Rosa, G. Villa (eds.), *Endotoxin Induced-Shock: a Multidisciplinary Approach in Critical Care*, https://doi.org/10.1007/978-3-031-18591-5_10

10.2 Timing

Source control of infectious foci was associated with improved survival in recent observational and cluster randomized studies [4]. Source control should be achieved as soon as possible following initial resuscitation in septic shock [5, 6]. While there are limited data to conclusively issue a recommendation regarding the timeframe in which source control should be obtained, smaller studies suggest that source control within 6–12 h is advantageous [5–8]. Studies generally show reduced survival beyond that point.

Kim et al. [8, 9] found lower 28-day mortality in septic shock patients who underwent source control, but no association between the time to source control and 28-day mortality. Surviving Sepsis Campaign (SSC) in 2021 recommended that the target time (no more than 6–12 h after the establishment of the diagnosis) of performance of source control was sufficient for most cases [2]. However, studies considered by SSC guidelines included only single disease entities and the definition of rapid source control was different in each study considered [7, 9, 10].

A prospective, observational study including 1011 critically ill patients with severe sepsis or septic shock found that performance of source control within the first 6 h was associated with 16% lower 28-day mortality [6]. Another prospective observational study [11] found significantly lower mortality, even after adjustment for confounding factors (patients undergoing source control were older, and a higher proportion had shock). However, the authors could not demonstrate that source control was time dependent. Patients who received early source control also received better early resuscitation, suggesting that these patients might have been sicker; however, they found no significant differences in baseline characteristics between patients who received early source control and those who received late source control. Yet, despite better early management, the mortality for patients receiving early source control was similar to those receiving late source control. The most likely explanation is that the clinical team considered source control more urgent in patients who underwent earlier source control and that the multivariate analysis failed to measure this confounder.

There are at least three reasons for delaying source control in severely septic patients:

1. Small foci of infection might not be clinically evident at first.
2. Physicians aware of the need for source control might delay intervention in apparently stable patients to enable nonemergency source control.
3. Surgical intervention might be deferred to allow necrosis to define itself anatomically to optimize intervention (e.g., in necrotizing pancreatitis) [12].

Determining the impact of early versus late source control would require formal randomization and prospective trials in more homogenous populations of patients and specific sources of infection [13, 14]. Clinical experience suggests that without adequate source control, many severe presentations will not stabilize or improve despite rapid resuscitation and provision of appropriate antimicrobials. Tellor et al.

[10] showed that inadequate source control and administration of inappropriate antibiotics were independent predictors of mortality. Lack of adequate source control was the strongest predictor of mortality, which is consistent with other analyses of complicated intra-abdominal infections [14].

However, what actually represents "adequate" source control is controversial. In general, the authors considered the goal of source control to be drainage of infected fluid collections, debridement of infected tissue, and definitive measures to avoid further contamination, as outlined by Marshall [15]. However, it has been increasingly recognized in recent years that less invasive techniques can constitute adequate source control. For instance, percutaneous drainage of an infected fluid collection is well accepted as a means of source control, as long as the goal of elimination of a substantial amount of the microbial inoculum and prevention of ongoing contamination can be achieved [14].

10.3 Intra-abdominal Infections

The timing and adequacy of source control are important in the management of intra-abdominal infections (IAIs); late and/or incomplete procedures may have severely adverse consequences on outcome especially in critically ill patients.

IAIs include several different pathological conditions and are usually classified into uncomplicated and complicated [16]. In uncomplicated IAIs, the infectious process only involves a single organ and does not proceed to the peritoneum. Patients with such infections can be managed with either surgical source control or with antibiotics alone. In complicated IAIs (cIAIs), the infectious process extends beyond the organ and causes either localized peritonitis or diffuse peritonitis. The treatment of patients with complicated intra-abdominal infections involves both source control and antibiotic therapy. Peritonitis is classified into primary, secondary, or tertiary peritonitis [16]. Primary peritonitis is a diffuse bacterial infection without loss of integrity of the gastrointestinal tract in absence of an identifiable source of infection during surgical exploration; this is rare and mainly occurs in infancy and early childhood as well as in cirrhotic patients. Secondary peritonitis, the most common form of peritonitis, is an acute peritoneal infection resulting from loss of integrity of the gastrointestinal tract or from infected viscera. It is caused by perforation of the gastrointestinal tract by direct invasion from infected intra-abdominal viscera. Anastomotic dehiscences are common causes of secondary peritonitis in the postoperative period. Tertiary peritonitis is a recurrent infection of the peritoneal cavity that follows either primary or secondary peritonitis. It is a complication of a secondary peritonitis and may be termed also "ongoing peritonitis" or "persistent" peritonitis [17]. The primary objectives of intervention include (a) determining the cause of peritonitis, (b) draining fluid collections, and (c) controlling the origin of the abdominal sepsis.

Diagnosis of IAIs is primarily clinical. Patients with IAIs typically present with rapid-onset abdominal pain and signs of local and systemic inflammation. Hypotension and signs of hypoperfusion such as oliguria, acute alteration of mental

status, and lactic acidosis are indicative of ongoing organ failure. Physical evaluation may limit the differential diagnoses to better direct decisions regarding a proper management plan including the selection of appropriate diagnostic testing, the need for initiation of antibiotic therapy, and whether emergent intervention is required. Inflammatory markers such as C-reactive protein (CRP) and procalcitonin (PCT) have been evaluated in the diagnosis of bacterial infection. CRP is an acute phase protein promptly released during an inflammation. Since systemic bacterial infection is often associated with an inflammatory reaction, it represents an indirect marker of infection and inflammation [18]. Conversely, PCT rapidly increases in the presence of bacterial and fungal infections but not viral infections or noninfectious inflammation [19]. Ultrasound (US) and computed tomography (CT) have been used over the last two decades to complete the clinical assessment of patients with IAIs.

10.3.1 Appendicitis

Acute appendicitis is one of the most common general surgical emergencies worldwide and the most common cause of intra-abdominal sepsis. Although several infectious agents are known to trigger or be associated with appendicitis [20] the full range of specific causes remains unknown [6]. Recent theories focus on genetic factors, environmental influences, and infections. The rate of perforation varies from 16 to 40%, with a higher frequency occurring in younger age groups (40–57%) and in patients older than 50 years (55–70%) [21]. Appendiceal perforation is associated with increased morbidity and mortality compared with non-perforating AA. The mortality risk of acute but not gangrenous AA is less than 0.1%, but the risk rises to 0.6% in gangrenous AA. On the other hand, perforated AA carries a higher mortality rate of around 5%. In the nineteenth century, surgeons started performing appendicectomie do surgery became the most widely accepted treatment.

Current evidence shows laparoscopic appendectomy (LA) to be the most effective surgical treatment, being associated with a lower incidence of wound infection and post-intervention morbidity, shorter hospital stay, and better quality of life scores when compared to open appendectomy (OA) [22].

Recent systematic reviews and meta-analyses of RCTs have concluded that the majority of patients with uncomplicated AA can be treated with an antibiotic-first approach [23]. The success of the non-operative approach requires careful patient selection and exclusion of patients with gangrenous AA, abscesses, and diffuse peritonitis.

The antibiotic-first strategy can be considered safe and effective in selected patients with uncomplicated acute appendicitis. Patients who wish to avoid surgery must be aware of a risk of recurrence of up to 39% after 5 years.

In-hospital surgical delay up to 24 h is safe in uncomplicated acute appendicitis and does not increase complications and/or perforation rate in adults. Surgery for uncomplicated acute appendicitis can be planned for the next available list

minimizing delay wherever possible (better patient comfort, etc.). Several systematic reviews of RCTs comparing laparoscopic appendectomy (LA) versus open appendectomy (OA) have reported that the laparoscopic approach for AA is often associated with longer operative times and higher operative costs, but it leads to less postoperative pain, shorter length of stay, and earlier return to work and physical activity [24].

10.3.2 Cholecystitis

The estimated overall prevalence of gallstones is 10–15% in the general population. Between 20 and 40% of patients with gallstones will develop gallstone-related complications, with an incidence of 1–3% annually; acute calculus cholecystitis (ACC) is the first clinical presentation in 10–15% of the cases [25]. Cholecystectomy is the most common therapeutic approach for ACC and is considered the standard of care for gallstone disease for the majority of patients. Conservative management with fluids, analgesia, and antibiotics is an option for people with mildly symptomatic acute cholecystitis (i.e., people without peritonitis or those who have worsening clinical conditions). In patients with moderate or severely symptomatic cholecystitis or in those with mildly symptomatic acute cholecystitis who prefer surgery, laparoscopic cholecystectomy is preferred over open cholecystectomy [26]. The optimal timing of uncomplicated cholecystectomy is within 7 days from hospital admission and within 10 days from the onset of symptoms.

Acute cholangitis is associated with significant mortality [27]. The mortality rates in acute cholangitis have been declining (88 to <10%) with the advent of readily available biliary decompression via endoscopic retrograde cholangiopancreatography (ERCP). In cases where ERCP is unsuccessful, alternative therapies include percutaneous transhepatic biliary drainage and/or surgical decompression, although these modalities carry significant morbidity [28]. Lee et al. [29] demonstrated that acute bacteremic cholangitis with organ failure is associated with worse outcomes, specifically acute kidney injury and septic shock. Studies have suggested that early ERCP reduces mortality resulting from cholangitis, including inpatients with co-existent gallstone pancreatitis [30]. Khashab et al. [18] report that delaying source control with ERCP beyond 72 h in patients with acute cholangitis was significantly associated with a worsening composite endpoint of death, persistent organ failure, and length of ICU stay. Jang et al. [31] have shown that ERCP performed within 24 h in patients with mild to moderate cholangitis associated with choledocholithiasis have shorter lengths of hospital stays. Karvellas et al. [32] showed that, in patients with septic shock, endoscopic biliary decompression >12 h after the onset of shock and delayed receipt of appropriate antimicrobial therapy were both significantly associated with adverse hospital outcome. This might suggest that early initiation of antimicrobial therapy and urgent biliary decompression (within 12 h) could potentially improve outcomes in this high-risk patient population.

10.3.3 Perforation

Gastrointestinal perforation complicated by septic shock is associated with high mortality and morbidity. The best time to initiate surgery is difficult to determine. It is common to stabilize circulatory dynamics before surgery [3]; however taking a long time to initiate surgery may result in death from sepsis [14]. Perforated peptic ulcer (PPU) is a complication of peptic ulcer disease. The incidence has been estimated at six to seven per 100,000 inhabitants [33]. Mortality rates as high as 25–30% have been reported [34, 35]. Surgical delay in PPU is a well-established negative prognostic factor. However, the evidence derives from studies with a high risk of bias [36], and no study has assessed the association between hourly surgical delay and adverse outcome. Buck et al. [37] showed that every hour of delay from admission to surgery was associated with an adjusted 2.4% decreased probability of survival compared with the previous hour.

Duodenal perforation represents a rare but potentially life-threatening condition. The mortality rate ranges from 8 to 25% [38]. The incidence of peptic ulcer disease has decreased in recent years. This can partly be explained by the use of proton pump inhibitors (PPIs) and eradication treatment for Helicobacter pylori. Management of duodenal perforations includes conservative, endoscopic, and surgical strategies. The type of treatment should be individualized and depends on the mechanism of injury, the timing, location and extent of the injury and the clinical state of the patient.

Acute left-sided colonic diverticulosis (ALCD) is common in Western countries with its prevalence increasing throughout the world, which is likely due to changes in lifestyle [39]. ALCD ranges in severity from uncomplicated phlegmonous diverticulitis to complicated diverticulitis including abscess and/or perforation. In patients with suspected ALCD, diagnosis is based on clinical history and signs (acute pain or tenderness in the left lower quadrant), laboratorial inflammation markers (C-reactive protein (CRP) and white blood cell count (WBC)), and radiological findings (contrast-enhanced CT scan). Immunocompromised patients may fail standard, non-operative source control. As such, most of these patients require urgent surgical intervention, and this is associated with a significantly higher mortality rate [40].

In patients with CT findings of pericolic extraluminal gas, guidelines suggest a trial of non-operative source control with antibiotic therapy; however, high mortality associated with sepsis requires maintaining a high index of clinical suspicion for deterioration and more aggressive management. WSES expert panel recommends antibiotic therapy in patients with pericolic extraluminal gas [41]. Approximately 15–20% of patients admitted with acute diverticulitis have an abscess on CT scan. The treatment of abscess always requires antibiotic therapy. If the abscess is limited in size, systemic antibiotic therapy alone is considered safe and effective in removing the abscess and solving acute inflammation with a pooled failure rate of 20% and a mortality rate of 0.6% [42]. When abscess diameter is larger, antibiotics could fail to reach the adequate concentration inside the abscess leading to an increased failure rate. The size of 4–5 cm may be a reasonable limit between antibiotic

treatment alone, versus percutaneous drainage combined with antibiotic treatment in the management of diverticular abscesses [43]. When the patient's clinical conditions allow it and percutaneous drainage is not feasible, antibiotic therapy alone can be considered. However, careful clinical monitoring is mandatory. In patients with generalized peritonitis, the authors suggest performing laparoscopic peritoneal lavage and drainage only in very selected patients. 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. Finally, they suggest Hartmann's procedure (HP) for managing diffuse peritonitis in critically ill patients and in selected patients with multiple comorbidities and damage control surgery (DCS) with staged laparotomies in selected unstable patients with diffuse peritonitis due to diverticular perforation.

Azuhata et al. [5] hypothesized that the outcomes of patients with GI perforation with associated septic shock could be improved by initiating surgery immediately after admission in order to control the infectious lesions entirely (early source control) with the support of early hemodynamic stabilization by initial resuscitation in accordance with EGDT. Therefore, they developed a protocol including early source control and EGDT for GI perforation with septic shock. Among the patients in which surgery was started within the first 2 h, the 60-day survival rate was 98%. As the time to initiation of surgery increased, the survival rate decreased and was 0% for the group that waited more than 6 h.

10.3.4 Soft Tissues and Skin Infection

These kinds of infections represent the third most frequent cause of severe sepsis and septic shock following pneumonia and intra-abdominal infections in some series [44], but one of those that source control measures can be more evident.

Skin and soft tissue infections (SSTIs) encompass a variety of pathological conditions that involve the skin and underlying subcutaneous tissue, fascia, or muscle, ranging from simple superficial infections to severe necrotizing infections.

The spectrum of diseases that are included in this group can present differently, according to causative microorganism, or extension or clinical symptoms. A clinical categorization depending on the presence of septic shock and the urgency of requirement for surgical procedures in order to achieve source control has been described [45] with worst outcomes in those with inadequate therapy and sepsis. Source control in these infections comprises topical actions, incision and drainage, debridement, up to amputation (Fig. 10.1).

Necrotizing soft tissue infections can be caused by polymicrobial (Type I) or monomicrobial organisms (Type II). Monomicrobial infections account for 10% of NSTI and are most commonly caused by Group A β-hemolytic streptococci, especially the toxin producing strains of S. pyogenes. Other less common organisms include Vibrio vulnificus (Type III NSTI) which is found in marine environments, Aeromonas hydrophila, found in fresh or brackish water; and Clostridium perfringens. Polymicrobial infections account for the majority of infections and involve a

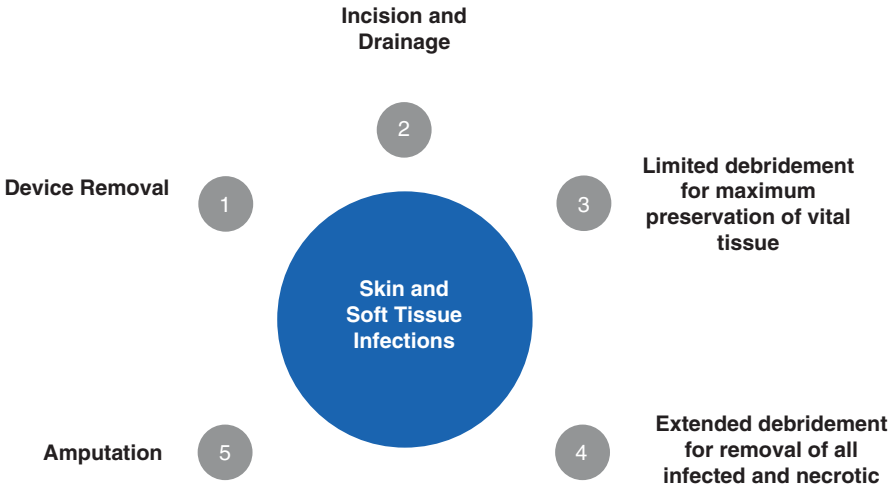

Fig. 10.1 Skin and soft tissue infections

combination of bacteria, including Staphylococcal, Streptococcal species, Escherichia coli, Bacteroides fragilis, or Clostridium species.

Broad-spectrum antibiotics that include gram-negative, gram-positive, and anaerobic coverage should also be initiated immediately after the diagnosis is suspected and continued until adequate source control is achieved.

Early surgical debridement with complete removal of necrotic tissue is essential to decrease mortality and other complications in patients with NSTIs. It is the most important determinant of outcome in necrotizing infections. This was well described in a study by Bilton et al. [46] in which patients with NSTIs, who had adequate surgical debridement (early and complete), were compared to those with either delayed or incomplete debridements. The mortality in the latter group was 38% compared to 4.2% in the group receiving early adequate surgical treatment. Delay in source control in patients with NSTIs has been repeatedly associated with a greater mortality.

In a retrospective study [47] of 121 patients with Vibrio vulnificus-related necrotizing infection, it was found that a substantial reduction in mortality risk was achieved by initiating surgical treatment within 12 h after admission compared with delaying either 12–24 h or more than 24 h after admission to initiate surgical treatment. Another review including both adults and pediatric patients supports [48] early (<12 h) initial debridement for NSTI to decrease mortality.

Guidelines suggest to plan the first re-exploration within 12–24 h and to repeat re-exploining outcomes in necrotizing infections when surgical re-debridements are performed in early versus delayed intervals. Scheduled re-explorations should be done at least every 12–24 h after the initial operation or sooner if clinical local or systemic signs of worsening infection become evident, as well as with worsening laboratory parameters.

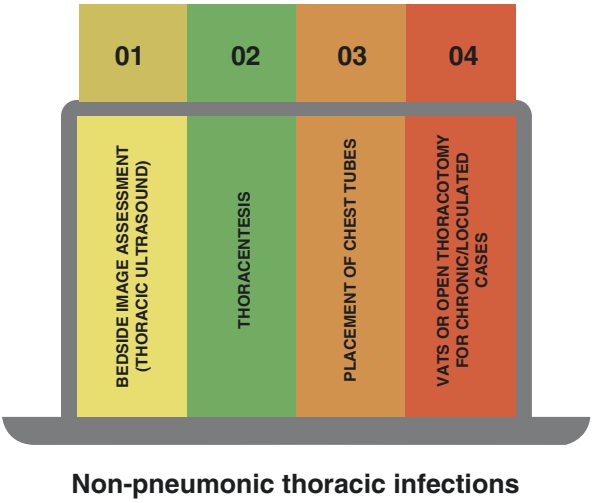

Fig. 10.2 Non-pneumonic thoracic infections

10.4 Non-pneumonic Thoracic Infections

Pleural infection is a non-rare complication for pneumonia with an approximate annual incidence of up to 80,000 cases in the UK and the USA combined. The associated mortality and morbidity is high; in the UK 20% of patients with empyema die; almost 20% of these empyema episodes require surgical intervention as source control measure [49]. In recent years, the use of thoracic ultrasound at the bedside to determine the presence of effusions especially in septic shock patients at the ICU has increased. Recent recommendations on this matter [50] suggested as first approach the use of thoracic ecography, following diagnostic sampling thoracocentesis, and if necessary the placement of a chest tube. The role of video assisted thoracoscopy and open thoracotomy can be reserved for those chronic or loculated cases (Fig. 10.2).

10.5 Conclusion

Septic shock is a time-dependent emergency that requires a multidisciplinary approach to improve outcome and reduce mortality and morbidity. All possible strategies should be implemented to control the source of infection in the first hours after diagnosis.

References

1. Marshall JC, al Naqbi A. Principles of source control in the management of sepsis. Crit Care Clin. 2009;25(4):753–68, viii–ix.
2. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Crit Care Med. 2021;49(11):e1063–e143.
3. Jimenez MF, Marshall JC, International Sepsis Forum. Source control in the management of sepsis. Intensive Care Med. 2001;27(Suppl 1):S49–62.
4. Bloos F, Ruddel H, Thomas-Ruddel D, Schwarzkopf D, Pausch C, Harbarth S, et al. Effect of a multifaceted educational intervention for anti-infectious measures on sepsis mortality: a cluster randomized trial. Intensive Care Med. 2017;43(11):1602–12.
5. Azuhata T, Kinoshita K, Kawano D, Komatsu T, Sakurai A, Chiba Y, et al. Time from admission to initiation of surgery for source control is a critical determinant of survival in patients with gastrointestinal perforation with associated septic shock. Crit Care. 2014;18(3):R87.
6. Bloos F, Thomas-Ruddel D, Ruddel H, Engel C, Schwarzkopf D, Marshall JC, et al. Impact of compliance with infection management guidelines on outcome in patients with severe sepsis: a prospective observational multi-center study. Crit Care. 2014;18(2):R42.
7. Moss RL, Musemeche CA, Kosloske AM. Necrotizing fasciitis in children: prompt recognition and aggressive therapy improve survival. J Pediatr Surg. 1996;31(8):1142–6.
8. Wong CH, Chang HC, Pasupathy S, Khin LW, Tan JL, Low CO. Necrotizing fasciitis: clinical presentation, microbiology, and determinants of mortality. J Bone Joint Surg Am. 2003;85(8):1454–60.
9. Kim H, Chung SP, Choi SH, Kang GH, Shin TG, Kim K, et al. Impact of timing to source control in patients with septic shock: a prospective multi-center observational study. J Crit Care. 2019;53:176–82.
10. Tellor B, Skrupky LP, Symons W, High E, Micek ST, Mazuski JE. inadequate source control and inappropriate antibiotics are key determinants of mortality in patients with intra-abdominal sepsis and associated bacteremia. Surg Infect. 2015;16(6):785–93.
11. Martinez ML, Ferrer R, Torrents E, Guillamat-Prats R, Goma G, Suarez D, et al. Impact of source control in patients with severe sepsis and septic shock. Crit Care Med. 2017;45(1):11–9.
12. Hartwig W, Maksan SM, Foitzik T, Schmidt J, Herfarth C, Klar E. Reduction in mortality with delayed surgical therapy of severe pancreatitis. J Gastrointest Surg. 2002;6(3):481–7.
13. Opal SM, Dellinger RP, Vincent JL, Masur H, Angus DC. The next generation of sepsis clinical trial designs: what is next after the demise of recombinant human activated protein C?*. Crit Care Med. 2014;42(7):1714–21.
14. Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Surg Infect. 2010;11(1):79–109.
15. Marshall JC. Intra-abdominal infections. Microbes Infect. 2004;6(11):1015–25.
16. Sartelli M. A focus on intra-abdominal infections. World J Emerg Surg. 2010;5:9.
17. Montravers P, Dufour G, Guglielminotti J, Desmard M, Muller C, Houissa H, et al. Dynamic changes of microbial flora and therapeutic consequences in persistent peritonitis. Crit Care. 2015;19:70.
18. Khashab MA, Tariq A, Tariq U, Kim K, Ponor L, Lennon AM, et al. Delayed and unsuccessful endoscopic retrograde cholangiopancreatography are associated with worse outcomes in patients with acute cholangitis. Clin Gastroenterol Hepatol. 2012;10(10):1157–61.
19. Spoto S, Valeriani E, Caputo D, Cella E, Fogolari M, Pesce E, et al. The role of procalcitonin in the diagnosis of bacterial infection after major abdominal surgery: advantage from daily measurement. Medicine (Baltimore). 2018;97(3):e9496.
20. Lamps LW. Infectious causes of appendicitis. Infect Dis Clin N Am. 2010;24(4):995–1018, ix–x.

21. Livingston EH, Woodward WA, Sarosi GA, Haley RW. Disconnect between incidence of nonperforated and perforated appendicitis: implications for pathophysiology and management. Ann Surg. 2007;245(6):886–92.
22. Jaschinski T, Mosch C, Eikermann M, Neugebauer EA. Laparoscopic versus open appendectomy in patients with suspected appendicitis: a systematic review of meta-analyses of randomised controlled trials. BMC Gastroenterol. 2015;15:48.
23. Podda M, Gerardi C, Cillara N, Fearnhead N, Gomes CA, Birindelli A, et al. Antibiotic treatment and appendectomy for uncomplicated acute appendicitis in adults and children: a systematic review and meta-analysis. Ann Surg. 2019;270(6):1028–40.
24. Li X, Zhang J, Sang L, Zhang W, Chu Z, Li X, et al. Laparoscopic versus conventional appendectomy—a meta-analysis of randomized controlled trials. BMC Gastroenterol. 2010;10:129.
25. Montravers P, Dupont H, Gauzit R, Veber B, Auboyer C, Blin P, et al. Candida as a risk factor for mortality in peritonitis. Crit Care Med. 2006;34(3):646–52.
26. Lagunes L, Rey-Perez A, Martin-Gomez MT, Vena A, de Egea V, Munoz P, et al. Association between source control and mortality in 258 patients with intra-abdominal candidiasis: a retrospective multi-centric analysis comparing intensive care versus surgical wards in Spain. Eur J Clin Microbiol Infect Dis. 2017;36(1):95–104.
27. Mosler P. Diagnosis and management of acute cholangitis. Curr Gastroenterol Rep. 2011;13(2):166–72.
28. Sugiyama M, Atomi Y. Treatment of acute cholangitis due to choledocholithiasis in elderly and younger patients. Arch Surg. 1997;132(10):1129–33.
29. Lee CC, Chang IJ, Lai YC, Chen SY, Chen SC. Epidemiology and prognostic determinants of patients with bacteremic cholecystitis or cholangitis. Am J Gastroenterol. 2007;102(3):563–9.
30. James PD, Kaplan GG, Myers RP, Hubbard J, Shaheen AA, Tinmouth J, et al. Decreasing mortality from acute biliary diseases that require endoscopic retrograde cholangiopancreatography: a nationwide cohort study. Clin Gastroenterol Hepatol. 2014;12(7):1151–9 e6.
31. Jang SE, Park SW, Lee BS, Shin CM, Lee SH, Kim JW, et al. Management for CBD stone-related mild to moderate acute cholangitis: urgent versus elective ERCP. Dig Dis Sci. 2013;58(7):2082–7.
32. Karvellas CJ, Abraldes JG, Zepeda-Gomez S, Moffat DC, Mirzanejad Y, Vazquez-Grande G, et al. The impact of delayed biliary decompression and anti-microbial therapy in 260 patients with cholangitis-associated septic shock. Aliment Pharmacol Ther. 2016;44(7):755–66.
33. Moller MH, Adamsen S, Thomsen RW, Moller AM, Peptic Ulcer Perforation Trial Group. Multicentre trial of a perioperative protocol to reduce mortality in patients with peptic ulcer perforation. Br J Surg. 2011;98(6):802–10.
34. Moller MH, Larsson HJ, Rosenstock S, Jorgensen H, Johnsen SP, Madsen AH, et al. Quality-of-care initiative in patients treated surgically for perforated peptic ulcer. Br J Surg. 2013;100(4):543–52.
35. Blomgren LG. Perforated peptic ulcer: long-term results after simple closure in the elderly. World J Surg. 1997;21(4):412–4. discussion 4–5.
36. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). J Clin Epidemiol. 2011;64(4):407–15.
37. Buck DL, Vester-Andersen M, Moller MH, Danish Clinical Register of Emergency Surgery. Surgical delay is a critical determinant of survival in perforated peptic ulcer. Br J Surg. 2013;100(8):1045–9.
38. Machado NO. Management of duodenal perforation post-endoscopic retrograde cholangiopancreatography. When and whom to operate and what factors determine the outcome? A review article. JOP. 2012;13(1):18–25.
39. Dalla Valle R, Capocasale E, Mazzoni MP, Busi N, Benozzi L, Sivelli R, et al. Acute diverticulitis with colon perforation in renal transplantation. Transplant Proc. 2005;37(6):2507–10.
40. Bordeianou L, Hodin R. Controversies in the surgical management of sigmoid diverticulitis. J Gastrointest Surg. 2007;11(4):542–8.

41. Sartelli M, Moore FA, Ansaloni L, Di Saverio S, Coccolini F, Griffiths EA, et al. A proposal for a CT driven classification of left colon acute diverticulitis. World J Emerg Surg. 2015;10:3.
42. Gregersen R, Mortensen LQ, Burcharth J, Pommergaard HC, Rosenberg J. Treatment of patients with acute colonic diverticulitis complicated by abscess formation: a systematic review. Int J Surg. 2016;35:201–8.
43. Brandt D, Gervaz P, Durmishi Y, Platon A, Morel P, Poletti PA. Percutaneous CT scan-guided drainage vs. antibiotherapy alone for Hinchey II diverticulitis: a case-control study. Dis Colon Rectum. 2006;49(10):1533–8.
44. Shen HN, Lu CL. Skin and soft tissue infections in hospitalized and critically ill patients: a nationwide population-based study. BMC Infect Dis. 2010;10:151.
45. Marwick C, Broomhall J, McCowan C, Phillips G, Gonzalez-McQuire S, Akhras K, et al. Severity assessment of skin and soft tissue infections: cohort study of management and outcomes for hospitalized patients. J Antimicrob Chemother. 2011;66(2):387–97.
46. Bilton BD, Zibari GB, McMillan RW, Aultman DF, Dunn G, McDonald JC. Aggressive surgical management of necrotizing fasciitis serves to decrease mortality: a retrospective study. Am Surg. 1998;64(5):397–400. discussion-1.
47. Chao WN, Tsai CF, Chang HR, Chan KS, Su CH, Lee YT, et al. Impact of timing of surgery on outcome of Vibrio vulnificus-related necrotizing fasciitis. Am J Surg. 2013;206(1):32–9.
48. Gelbard RB, Ferrada P, Yeh DD, Williams BH, Loor M, Yon J, et al. Optimal timing of initial debridement for necrotizing soft tissue infection: a Practice Management Guideline from the Eastern Association for the Surgery of Trauma. J Trauma Acute Care Surg. 2018;85(1):208–14.
49. Finley C, Clifton J, Fitzgerald JM, Yee J. Empyema: an increasing concern in Canada. Can Respir J. 2008;15(2):85–9.
50. Scarci M, Abah U, Solli P, Page A, Waller D, van Schil P, et al. EACTS expert consensus statement for surgical management of pleural empyema. Eur J Cardiothorac Surg. 2015;48(5):642–53.