Langenbeck's Archives of Surgery (2019) 404:257–271
https://doi.org/10.1007/s00423-019-01752-7

REVIEW ARTICLE

# Intra-abdominal sepsis: new definitions and current clinical standards

A. Hecker[1] · M. Reichert[1] · C. J. Reuß[2] · T. Schmoch[2] · J. G. Riedel[1] · E. Schneck[3] · W. Padberg[1] · M. A. Weigand[2] · M. Hecker[4]

Received: 27 November 2018 / Accepted: 8 January 2019 / Published online: 26 January 2019


## Abstract

**Purpose** The abdomen is the second most common source of sepsis and is associated with unacceptably high morbidity and mortality. Recently, the essential definitions of sepsis and septic shock were updated (Third International Consensus Definitions for Sepsis and Septic Shock, Sepsis-3) and modified. The purpose of this review is to provide an overview of the changes introduced by Sepsis-3 and the current state of the art regarding the treatment of abdominal sepsis.

**Results** While Sepsis-1/2 focused on detecting systemic inflammation as a response to infection, Sepsis-3 defines sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection. The Surviving Sepsis Campaign (SSC) guideline, which was updated in 2016, recommends rapid diagnosis and initiating standardized therapy. New diagnostic tools, the establishment of antibiotic stewardship programs, and a host of new-generation antibiotics are new landmark changes in the sepsis literature of the last few years. Although the "old" surgical source control consisting of debridement, removal of infected devices, drainage of purulent cavities, and decompression of the abdominal cavity is the gold standard of surgical care, the timing of gastrointestinal reconstruction and closure of the abdominal cavity ("damage control surgery") are discussed intensively in the literature. The SSC guidelines provide evidence-based sepsis therapy. Nevertheless, treating critically ill intensive care patients requires individualized, continuous daily re-evaluation and flexible therapeutic strategies, which can be best discussed in the interdisciplinary rounds of experienced surgeons and intensive care medicals.

**Keywords** Sepsis-3 · Surviving Sepsis Campaign · SOFA · qSOFA

**Abbreviations**

| | |
|---|---|
| SSC | Surviving Sepsis Campaign |
| SOFA | Sequential Organ Failure Assessment |
| qSOFA | quick Sequential Organ Failure Assessment |
| WSES | World Society of Emergency Surgeons |
| SIRS | Systemic Inflammatory Response Syndrome |
| WHO | World Health Organization |
| PCT | Procalcitonin |
| CRP | C-reactive protein |
| MAP | Mean Arterial Pressure |
| POD | Postoperative Day |
| EGT | Early Goal–directed Therapy |
| ACS | Abdominal Compartment Syndrome |
| AGORA | Antimicrobials: A global alliance for optimizing their rational use in intra-abdominal infections |
| MEDUSA | Medical Education for Sepsis Source Control and Antibiotics |
| ESCMID | European Society for Clinical Microbiology and Infectious Diseases |
| ICU | Intensive Care Unit |
| CVP | Central Venous Pressure |
| $SaO_2$ | Oxygen Saturation |
| ARDS | Acute Respiratory Distress Syndrome |

A. Hecker and M. Reichert contributed equally to this work.

✉ A. Hecker
Andreas.Hecker@chiru.med.uni-giessen.de

[1] Department of General and Thoracic Surgery, University Hospital of Giessen, Rudolf-Buchheim-Street 7, 35392 Gießen, Germany

[2] Department of Anesthesiology, University Hospital of Heidelberg, Heidelberg, Germany

[3] Department of Anesthesiology, University Hospital of Giessen, Giessen, Germany

[4] Medical Clinic II, University Hospital of Giessen, Giessen, Germany

## Introduction

In 2017, the World Health Organization (WHO) and the World Health Assembly adopted a resolution that emphasizes the importance of sepsis diagnosis, treatment, and prevention worldwide. As a complex disorder of global priority, sepsis has now moved further into the spotlight of medicine and medical research [1].

Disproportionately, most literature on the incidence, prevalence, and evidence of sepsis comes from developed countries, where up to 2.8 million deaths were attributable to sepsis in 2010 [2, 3]. Due to a suspected high number of unreported cases, the estimated incidence of sepsis is even higher [4, 5]. Recently published epidemiologic data suggest that sepsis causes one third to half of in-hospital mortality in the USA. While the available literature is mainly from high-income countries, the incidence of sepsis and sepsis-associated death is assumed to be even higher worldwide. Data on chest infections reveal that 90% of the associated worldwide mortality is from the developing countries [3, 4]. Estimates suggest that about 1400 patients die from septic diseases worldwide per day [6].

In 66% of all surgical patients with sepsis, an intra-abdominal infectious focus could be detected. In 85% of such patients, this localization of a septic source is even higher after elective surgical intervention and the development of sepsis in the postoperative clinical course [7, 8].

## The new sepsis definitions

The primary sepsis definitions dating back to 1991 [9] defined sepsis as a systemic inflammatory response syndrome (SIRS) to an infection. The consecutive development of organ failure was termed "severe sepsis," and SIRS complicated by cardiocirculatory failure was called "septic shock." Due to its poor specificity, this Sepsis-1 definition was challenged ever since, resulting in its revision in 2001 [10]. However, although the International Sepsis Definitions Conference acknowledged its weaknesses, it confirmed the principal construct of the first definitions due to a lack of suitable alternatives. Nevertheless, it was recognized that SIRS criteria (Table 1) are unsatisfactory for describing the manifold appearance of sepsis, which is why the definitions were complemented by a list of possible symptoms, including the recognition of the fact that organ dysfunction can be the first detectable symptom. These extensions further reduced the specificity of the sepsis definitions, resulting in significant variance concerning estimated incidence and mortality [11]. Consequently, the sepsis definitions were revised again in 2014 and 2015, resulting in the publication of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) in February 2016 [2]. Sepsis-3 no longer focus on the signs and symptoms of inflammation, which can reflect a reasonable healthy response to a systemic infection. Instead, Sepsis-3

**Table 1** Diagnostic criteria of sepsis (from International Guidelines for the Management of Severe Sepsis and Septic Shock 2012)

| | |
|---|---|
| **Clinical criteria** | |
| *Temperature* | ≥ 38.0 °C<br>or<br>≤ 36.0 °C |
| *Heart rate* | ≥ 90/min |
| *Respiration* | Frequency ≥ 20/min<br>or<br>$PaCO_2$ ≤ 33 mmHg/4.3 kPa |
| Signs of a septic encephalopathy | Mental disorder |
| Deranged homeostasis | Edema,<br>fluid balance ≥ 20 ml/kg/24 h |
| Hyperglycemia | Blood glucose ≥ 140 mg/dl (7.7 mmol/l)<br>(without pre-existing diabetes mellitus) |
| **Criteria of inflammation** | |
| *Leukocytes* | ≥ 12,000/$mm^3$<br>or<br>≤ 4000/$mm^3$<br>or<br>≥ 10% immature neutrophils |
| CRP | Serum CRP more than two standard deviations above normal |
| PCT | Serum PCT more than two standard deviations above normal |
| **Hemodynamic parameters** | |
| Arterial hypotension | Systolic blood pressure ≤ 90 mmHg<br>or<br>Mean arterial pressure ≤ 70 mmHg<br>or<br>Decrease of systolic blood pressure ≥ 40 mmHg<br>or<br>Decrease of the systolic blood pressure more than two standard deviations |
| **Types and definitions of acute organ dysfunction** | |
| Neurologic | Glasgow Coma Scale (GCS) < 13 |
| Pulmonary | Horowitz Index ($PaO_2/FiO_2$) ≤ 250 (≤ 200, if the lung is the inflammatory focus)<br>+ pulmonary capillary wedge pressure (PCWP) without signs of fluid overload |
| Renal | Urine output ≤ 0.5 ml/kg/h for 1 h despite adequate resuscitation<br>Increase of serum creatinine ≥ 0.5 mg/dl (44.2 μmol/l) |
| Coagulation | INR ≥ 1.5<br>or<br>Platelet count < 80,000 or more than 50% decreased compared to 24 h before |
| Gastrointestinal | Intestinal paralysis<br>Hyperbilirubinemia (total bilirubin ≥ 4 mg/dl (70 μmol/l)) |
| Hypoperfusion | Lactate ≥ 4 mmol/l<br>Dispaired recapillarization |

The four SIRS criteria are in italics

CRP, C-reactive protein; PCT, procalcitonin; INR, international normalized ratio; aPTT, activated partial thromboplastin time

emphasize that, in sepsis, the host response is not healthy, but dysregulated, resulting in organ dysfunction of sufficient severity to be life threatening. Concrete sepsis is defined as "*life-threatening organ dysfunction caused by a dysregulated host response to infection*" [2]. Organ dysfunction is measured by the Sequential Organ Failure Assessment (SOFA) score and is deemed "life-threatening" if the score is increased by ≥2 points [12] (Table 2). Thus, "abdominal sepsis" is now defined as an increase of the SOFA score of ≥ 2 points due to intra-abdominal infection [13]**.** If the patient requires the application of vasopressors to maintain a mean arterial pressure (MAP) of ≥65 mmHg (despite adequate volume resuscitation) and the serum lactate is ≥ 2 mmol/l, the clinical situation is defined as *septic shock* [13]. The term "severe sepsis" has been abolished and should no longer be used.

The key consequences from the Sepsis-3 definition [13] are:

1. The formal diagnosis of sepsis relies on the detection of organ dysfunction based on the SOFA score.
2. The continuum of infection, sepsis, severe sepsis, and septic shock has been abolished in favor of the reduction to infection, sepsis, and septic shock only.
3. The concept of SIRS can still be used to describe a systemic response to a sterile hit (pancreatitis, trauma, etc.) or an infection, and its appearance should trigger a screening for infectious foci.
4. Sepsis is more than inflammation; it is a complex, life-threatening organ dysfunction resulting from dysregulated host response.

As the SOFA score is not always comprehensively available outside of intensive care units (e.g., in the emergency room or on surgical wards), the authors of Sepsis-3 suggested the quick (q) SOFA as a screening tool for sepsis. Resulting from a retrospective analysis of large databanks, the qSOFA consists of three easy-to-evaluate criteria:

1. Alteration in mental state (Glasgow Coma Scale < 15).
2. Respiratory rate ≥ 22 breaths/min.
3. Systolic blood pressure ≤ 100 mmHg.

The literature reveals that patients who meet these criteria have prolonged hospital stay and increased risk of death [4, 11]. If the patient fulfills two criteria, admission to intensive care is obligatory. Since its introduction in clinical medicine, several trials have underlined the specificity of the new stratification scores SOFA (intensive care) and qSOFA (emergency department, normal wards, outpatient department, emergency medical service) for predicting the mortality of the septic patient. Compared to qSOFA and the former Sepsis-2 criteria ("the SIRS criteria"), the SOFA score has the highest predictive values for intensive care unit (ICU) mortality, which Raith et al. recently analyzed in an impressive collective of 180,000 patients [14]. Despite the advantages of SOFA and qSOFA for risk stratification of patients with organ dysfunction (and sepsis!), the "old" SIRS criteria remain an important tool for surgeons and intensivists for everyday rounds. Compared to SOFA and qSOFA scores, the SIRS criteria have the highest sensitivity for

**Table 2** The SOFA score reflects organ dysfunction, which now defines the term "sepsis" according to the new Sepsis-3 definition [13] (in contrast to the complex SOFA score, the qSOFA score is an everyday tool for clinicians to categorize patients rapidly, e.g., in the emergency room)

| Organ system | Score | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 |
| Respiration | | | | | |
| $PaO_2/FiO_2$ (mmHg) | > 400 | < 400 | < 300 | < 200 | < 100 |
| Coagulation | | | | | |
| Platelets (per μl) | > 150,000 | < 150,000 | < 100,000 | < 50,000 | < 20,000 |
| Liver | | | | | |
| Bilirubin (mg/dl) | < 1.2 | 1.2–1.9 | 2.0–5.9 | 6.0–11.9 | > 12.0 |
| Cardiovascular | | | | | |
| (dosages in μg/kg/min) | MAP > 70 mmHg | MAP < 70 mmHg | Dopamine < 5 or dobutamine (any dose) | Dopamine 5.1–15<br>Epinephrine <0.1<br>Norepinephrine <0.1 | Dopamine > 15<br>Epinephrine > 0.1<br>Norepinephrine > 0.1 |
| Cerebral | | | | | |
| GCS | 15 | 13–14 | 10–12 | 6–9 | <6 |
| Renal | | | | | |
| Creatinine (mg/dl) | < 1.2 | 1.2–1.9 | 2.0–3.4 | 3.5–4.9 | > 5.0 |
| Urinary output | | | | < 500 ml | < 200 ml |

early detection of inflammation and infection, which is of major surgical importance both in the emergency setting and in the postoperative phase [14].

The SIRS criteria (Sepsis-2) help detect inflammation/inflammatory/infectious complications; qSOFA (emergency department) and SOFA (ICU) scores identify the septic patient, defining the need for intensive care.

As a consequence of the Sepsis-3 definition, the number of patients with sepsis has decreased in retrospective analyses, as organ failure does not result from sepsis, but defines it.

Donnelly et al. applied the new Sepsis-3 criteria to a cohort of > 30,000 patients from the REGARDS (REasons for Geographic and Racial Differences in Stroke) Study [15]. While 1526 patients fulfilled the SIRS criteria (in-hospital mortality, 9%), only 1080 were septic according to the SOFA score (13%), and only 378 patients had a positive qSOFA score (23%!) [15]. Last year, Shankar-Hari analyzed the influence of the new sepsis criteria on the epidemiology of sepsis in detail. While Sepsis-3 identifies a similar population of severe septic patients according to Sepsis-2, the identification of the population of patients with septic shock is more specific when the new criteria are applied [16]. While the qSOFA score has the highest predictive value for the critically ill septic patient, we still have to treat patients with infection (SIRS criteria) and the risk of sepsis development according to the sepsis guidelines.

**For surgeons, the SIRS criteria remain the most important tool for detecting inflammation, infection, and complications! The new definition of sepsis must NOT lead to any delay in diagnostic or therapeutic approaches!**

## Pathogenesis and risk factors

Figure 1 summarizes the general and independent risk factors for infections and sepsis. Additional to these "general" risk factors for sepsis, the surgical patient is permanently threatened by surgical complications caused by impaired healing of anastomoses or sutures for abdominal closure. Several trials have analyzed patient-related risk factors that lead to impaired healing, resulting in increased anastomotic leakage, surgical-site infections, and intra-abdominal sepsis. These factors, in part, overlap with the general risk factors, but are of major importance for abdominal surgery. Besides intraoperative complications and episodes of intraoperative hypotension, patient-related factors such as male gender, age, smoking, and diabetes mellitus correlate with increased anastomotic leakage rate. The same holds true for medication (corticosteroids, chemotherapeutics, immunosuppressants) and radiation (Fig. 1 and 2).

## Diagnosis

### Early identification of the septic patient

The clinical presentation depends on the site of infection. While general symptoms such as fever (or hypothermia), tachycardia, and tachypnea reflect the SIRS criteria, additional signs such as altered mental status, oliguria, change in the skin with elongated capillary refill time, elevated liver enzymes, pathologic coagulation, etc., should be recognized on

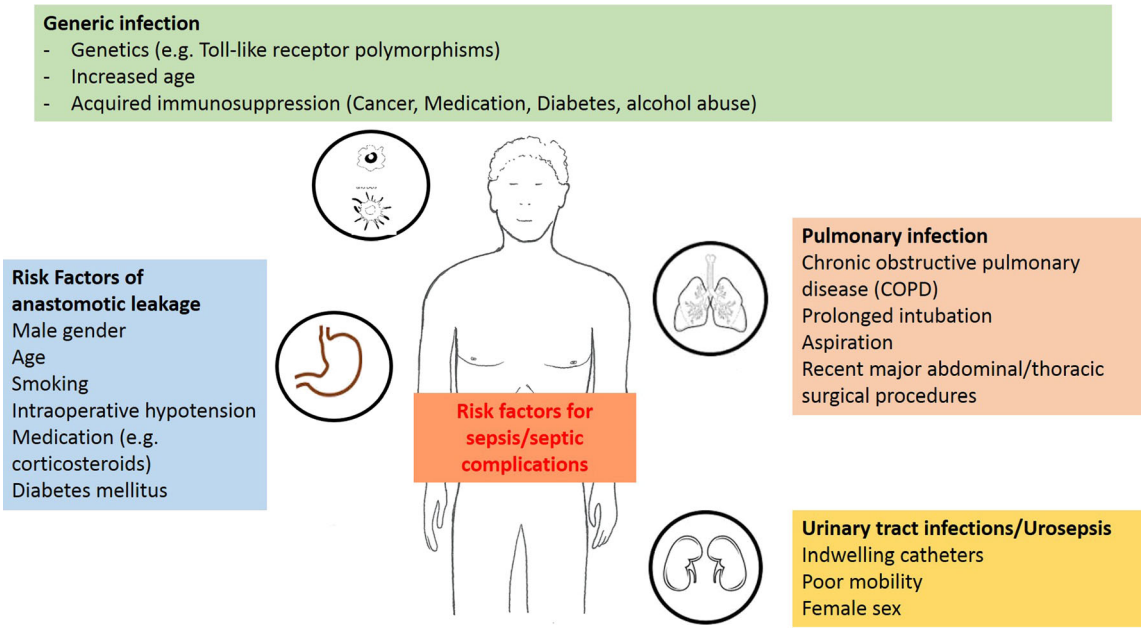


**Fig. 1** Simplified summary of risk factors for sepsis development [4]. In contrast to other medical specialties, the amount of risk factors is increased in visceral surgery due to the fact that impaired postoperative healing with failure of complex surgical reconstructions leads to anastomotic leakage and dramatically increased sepsis rates

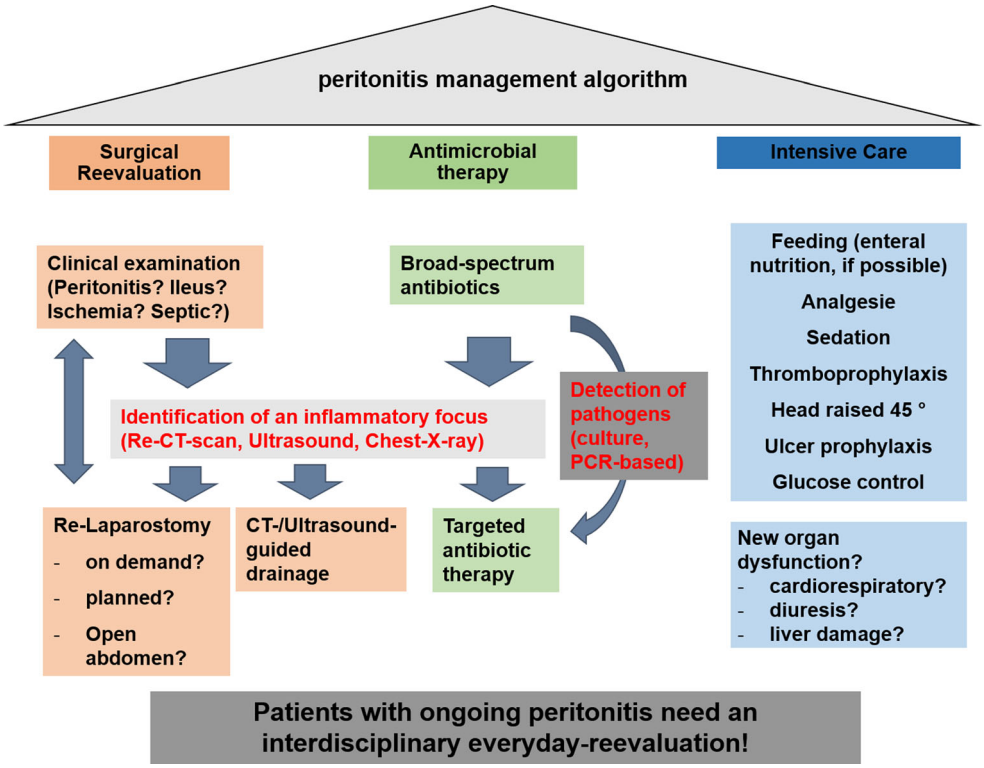


**Fig. 2** Schematic workflow for the interdisciplinary intensive care treatment of surgical patients with intra-abdominal sepsis. Therapy is based on the three columns: surgery, antimicrobial therapy, and intensive care treatment

everyday rounds, but especially should lead to further diagnostics (Table 1). Early diagnosis of any postoperative complication is life-saving, but can be masked by "normal" postoperative symptoms such as abdominal pain or gastrointestinal paralysis with nausea. Compared to community-acquired secondary peritonitis, abdominal pain, tenderness, and fever occur less often in postoperative or ongoing peritonitis [17]. Improving the time to diagnosis requires not only an experienced surgeon but also the establishment of interacting interdisciplinary rounds on intensive and intermediate care additionally consisting of anesthesiologists, pain therapists, antibiotic stewards, etc.

As early markers of infectious complications after surgery, the specificity of several molecular markers has been tested. More than 30 studies have evaluated the predictive value of C-reactive protein (CRP) for surgical complications in the postoperative phase. Typically, CRP peaks between postoperative day (POD) 2 and POD 3 (about 12–24 h after interleukin (IL)-6 peaks) and declines to baseline level on POD 5. Persistent elevation of CRP can indicate septic complications in the postoperative phase [18]. For colorectal resection (about 100 mg/l on POD 5) and pancreatic surgery (140 mg/l on POD 4), cut-off values have been suggested, which must lead to further diagnostics. The role of procalcitonin (PCT) has been controversially discussed in the literature. In contrast to single cut-off values, the PCT clearance kinetics appear to be a better indicator for diagnosing septic complications or for predicting clinical outcome: persistently increased plasma PCT levels are associated with infection or septic surgical complications. While systemic infections are in line with up to 5000-fold increase within 4 h, the located sources of infection can be PCT negative. To date, it remains nebulous whether PCT can distinguish between ("sterile") SIRS and sepsis. The CAPTAIN trial [19] revealed that none of the circulating biomarkers (including PCT) discriminated better between sepsis and SIRS than CRP alone. In contrast, PCT is a helpful tool for monitoring a patient with intra-abdominal infection [20]. Reith et al. published a trial on 246 patients with abdominal sepsis after surgery. A PCT reduction from POD 1 to POD 4 was a good predictor of clinical improvement.

As a marker of when to end antimicrobial therapy, PCT guidance can reduce treatment duration and even reduces mortality [21]. In the trial by de Jong et al., a PCT reduction of 80% of the initial value or serum PCT < 0.5 μg/dl were the cut-off values for ending antibiotic treatment [21].

Modern immunological research has identified a panel of markers such as IL-6, IL-1α, tumor necrosis factor alpha (TNFα), high mobility group box 1 (HMGB)-1, matrix metalloproteinase 9 (MMP-9), vascular endothelial growth factor (VEGF), intercellular adhesion molecule 1 (ICAM-1), myeloperoxidase (MPO), methylglyoxal, and caspase-3 as sensitive indicators of sepsis development [22, 23]. As patients who have undergone major surgery are in a phase of hyperinflammation (SIRS), it remains unclear if these markers can help to detect complications in the postoperative phase. As an example, the cut-off values of IL-6 in the current literature vary widely between 12 pg/ml and 2760 pg/ml [24].

Using ultrasound, surgeons have a bedside tool to obtain a rapid overview of potential peritoneal pathological conditions. Ultrasound-guided diagnostic drainage of suspicious fluid collections, combined with therapeutic tube insertion on demand, help to diagnose conditions such as intra-abdominal abscesses, hematoma, and pancreatic fistula. As a modern diagnostic approach, the measurement of intraperitoneal cytokines might be another promising tool for determining and monitoring the inflammatory reaction in patients [25]. Several studies have shown up to 1000-fold higher local concentration of cytokines compared to plasma levels [24]. Once suspected, computed tomography (CT) scan is the diagnostic gold standard for both secondary and ongoing peritonitis, with diagnostic sensitivity of 97.2% [17, 23]. For secondary peritonitis, the peritoneal CT attenuation values can even predict hospital survival. In hospital non-survivors, the values are significantly lower than that in survivors [26]. Alternatively, positron emission tomography (PET)-CT scan could play an important role in further diagnosis of intra-abdominal sepsis, but is mainly restricted to septic foci of unknown origin [27] or spreading multifocal bacteremia (e.g., *Staphylococcus aureus*) [28].

## Therapy

### Early goal–directed therapy and volume resuscitation

The therapeutic principle of early goal–directed therapy (EGT), which was first introduced by Rivers in 2001, postulated a protocol-based approach for treating patients with septic shock [29]. Targets for therapeutic resuscitation were central venous pressure (CVP, 8–12 mmHg), MAP (>65 mmHg), urinary output (>0.5 ml/kg body weight), and central venous oxygen saturation ($SaO_2$, >70 mmHg). In contrast to the single-center study by Rivers et al., three large multicenter randomized controlled trials (ProCESS [30], ARISE [31], ProMISe [32]) showed no benefit for a protocol-based sepsis therapy in the early resuscitation phase. Compared to the standard therapy, EGT showed no 90-day survival benefit, no improved 1-year survival, but longer duration of ICU stay and increased vasopressors.

In cases of hemodynamic instability (systolic blood pressure < 90 mmHg, MAP <70 mmHg, or systolic blood pressure decrease of >40 mmHg) or serum lactate >4 mmol/l, the SSC guidelines recommend the rapid application of crystalloids (30 ml/kg) within the first 3 h after hospital admission (3-h bundle, Table 3). Many trials on fluid resuscitation compared crystalloids versus colloids and could not show any benefit for the (expensive) colloid solutions [33]. Instead, colloids may be nephrotoxic (except albumin). Whether balanced crystalloid solutions (Ringer lactate) or "simple" saline solution should be used is still being discussed. Compared with saline, a buffered crystalloid solution could not reduce the risk of acute kidney injury in critically ill patients [34]. As reported previously [35], a chloride-restrictive balanced solution is in line with decreased rate of dialysis and renal insufficiency. This is being analyzed by two ongoing trials (BaSICS [36], PLUS trial protocol [37]).

However, how is volume application monitored? Over the years, a protocol-based, highly standardized resuscitation strategy has been postulated. In contrast, the new guidelines only recommend patient-oriented, individualized volume substitution according to the patient's fluid responsiveness, which can be examined by the passive leg raising test, for example. The predictors of inadequate fluid responsiveness are [38] heart insufficiency, hypothermia, deteriorated gas exchange, increased serum lactate (>4 mmol/l), immunodeficiency, and coagulopathy. In 2017, Marik et al. wrote about volume overload in the early phase of sepsis (>5000 ml) presenting the risk of increased mortality [39]. To date, how fluid can be substituted in sepsis remains a matter of debate. While the guidelines postulate substitution as long as the patient shows circulatory response/increased cardiac output ("fluid challenge"), Takala suggests that maintaining tissue perfusion should be the target parameter of modern, individualized fluid resuscitation [40].

### Source control

Source control in intra-abdominal sepsis is based on four important elements: debridement, removal of infected devices, drainage of purulent cavities, and decompression of the abdominal cavity. Inadequate initial source control increases the 28-day mortality rate from 26.7% to 42.9% [4, 41, 42]. While the importance of rapid surgical source control is clear, evidence for the effectiveness of so-called damage-control surgery is lacking until today. According to the modern concept of damage-control surgery, which was first established for

**Table 3** The newest version of the SSC guidelines recommend certain diagnostic and therapeutic measures within a 3- and 6-h timespan after hospital admission (these easy and rapid steps of sepsis therapy are essential for surgeons' education)

| 3-h bundle | 6-h bundle |
|---|---|
| Blood cultures prior to first administration of antibiotics | 30 ml/kg body weight fluid substitution in patients with shock |
| Serum lactate measurement | Vasopressors in cases of hypotension resistant to volume therapy |
| Broad-spectrum antibiotic | Second serum lactate measurement |

heavily injured victims in combat/military surgery, the first operation should be performed as short as possible, followed by secondary reconstruction of the gastrointestinal continuity or the abdominal wall. Ceresoli et al. [43] suggested that further studies are required to define the indications, timing, and techniques of damage-control surgery for patients with non-traumatic abdominal sepsis.

What is the rationale of damage-control surgery in the non-traumatic patient? In both trauma and intra-abdominal septic shock/severe intra-abdominal sepsis, the patient is threatened by a pathophysiological triad of coagulopathy, inflammation, and cardiovascular instability ("lethal triad"). As published recently by Lyons et al., hospital mortality increased progressively from 25.4% to 56.1% in patients without and with severe sepsis–associated coagulopathy, respectively [44]. Furthermore, cardiovascular instability with concomitant high levels of circulating catecholamines is associated with poor outcomes and severe side effects such as myocardial injury and peripheral ischemia [45–47]. From trauma surgery, the principle of an abbreviated initial surgical approach for controlling abdominal blood loss and contamination could lead to accelerated resuscitation of physiology within this critical early phase after damage. A retrospective case series showed that this approach resulted in improved survival of shocked patients.

Table 4 provides an overview of the five steps of an escalating approach in damage-control surgery. Only evidence level III and IV data exist to transfer the traumatic damage control concept to abdominal sepsis [48].

While evidence is low due to retrospective studies only, acceptance in several reviews and editorials has promulgated the concept widely. Regardless of the limitations of the studies, there is a general trend toward the adoption of damage control strategies for abdominal sepsis comparable to the experiences in trauma surgery in the early 1990s. In contrast to damage control for trauma or intra-abdominal hemorrhage, the concept has to be modified for intra-abdominal sepsis, especially in the presurgical phase (Table 4). There is growing evidence that patients with secondary peritonitis benefit from a damage control resuscitation phase prior to surgical intervention, which is strongly recommended by the SSC Guidelines 2016 (see 3-h bundle) [49] (Table 5).

In the case of ongoing, persisting peritonitis after initial surgery, three different surgical strategies have been established:

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

In contrast to relaparotomy on demand, which is performed in cases of clinical deterioration of the critically ill patient, the approach of a planned relaparotomy is based on the a priori decision for re-do surgery independent of its necessity. In a landmark study, Ruler et al. reported no difference between "on demand" ($n = 116$) and "planned" ($n = 116$) laparotomy in terms of patient mortality (on demand, 29%; planned, 36%), but the on-demand group had significantly lower intervention rates and hospital costs [57]. Nevertheless, a scheduled relaparotomy might still be indicated in cases of mesenteric ischemia requiring planned reassessment of the intestinal viability. The alternative approach in these cases would be an on-demand decision. The latter requires an experienced surgeon and an interdisciplinary everyday relook of the patient's clinical course. Neither the initial source of intra-abdominal infection nor the findings during the primary surgical source control could predict the demand for reintervention in 219 cases [58]. Any recurrence or persistence of organ failure should lead to rapid surgical intervention. Koperna et al. reported that ($n = 105$) mortality was significantly lower if a

**Table 4** The impact of the damage control concept is increasingly being evaluated for intra-abdominal source control

| Phase | Location | Trauma surgery | Septic shock |
|---|---|---|---|
| 0 | ER, ICU | Initiation of hemostatic resuscitation | Preoperative resuscitation<br>Warming<br>Antimicrobial therapy (3-h bundle) |
| 1 | ER,ICU,OR | Identification of the injury pattern, physiology | Identification of the patient's pathology and physiology |
| 2 | OR | Control hemorrhage and contamination | Decontamination, source control |
| 3 | OR | Reassessment during surgery | |
| 4 | ICU | Physiological restore on ICU, hemodynamic stabilization, correction of acidosis, hypothermia, coagulopathy, organ support (dialysis, ECMO) | Physiological restore on ICU, hemodynamic stabilization, correction of acidosis, hypothermia, coagulopathy, organ support (dialysis, ECMO etc.), specific, individualized antibiotic treatment |
| 5 | OR | Definitive repair, abdominal wall closure | |

An increasing number of trials have been published, showing the potential benefit of rapid source control without complex surgical reconstruction. Nevertheless, the current level of evidence remains low

**Table 5** Comparison of damage control surgery concepts for trauma versus intra-abdominal sepsis

| Author | Study design | Year | Number of patients with secondary peritonitis | Number of patients | Reference |
|---|---|---|---|---|---|
| Finlay et al. | Prospective | 2004 | Intra-abdominal sepsis ($n = 9$) | 14 | [50] |
| Bnieghbal et al. | prospective | 2004 | Neonatal generalized necrotizing enterocolitis | 25 | [51] |
| Tamijmarane et al. | Retrospective | 2006 | Complications after elective pancreatic surgery | 25 | [52] |
| Person et al. | Retrospective | 2009 | Peritonitis ($n = 15$), mesenteric ischemia ($n = 10$) | 31 | [53] |
| Kafka-Ritsch et al. | Prospective | 2012 | Perforated diverticulitis | 51 | [54] |
| Goussous et al. | retrospective | 2013 | Mesenteric ischemia ($n = 25$), bowel perforation ($n = 21$), anastomotic leakage ($n = 10$), necrotizing pancreatitis ($n = 2$) | 99 | [55] |
| Girard | Prospective | 2018 | Mesenteric ischemia ($n = 68$), peritonitis ($n = 44$), pancreatitis ($n = 28$) | 164 | [56] |

In both scenarios, the principle of rapid initial surgical control of the intra-abdominal situation is followed by a phase of physiological restoration in the ICU. Any definitive reconstruction of the gastrointestinal passage (anastomoses) or of abdominal wall defects is secondary to survival of the "lethal triad" of trauma/sepsis

relook on demand was performed within 48 h after initial emergency surgery, if necessary [59]. Both on-demand and planned relaparotomy present the risk of acute abdominal compartment syndrome (ACS) development: peritonitis itself on the one hand (primary ACS) and capillary leakage and fluid resuscitation (secondary ACS) on the other can lead to sustained intra-abdominal pressure > 20 mmHg with concomitant organ dysfunction [60]. As the diagnostic of choice, intra-abdominal pressure is typically measured indirectly through the bladder. Surveys revealed that, despite its hazardousness, ACS is often diagnosed too late. Only 47% of physicians could define ACS in that trial. Once suspected, the guidelines recommend monitoring the intra-abdominal pressure every 6 h in such cases [60].

Although it is one potential element of damage-control surgery, the current clinical guidelines do not recommend routine use of the open abdomen technique for secondary peritonitis [61, 62]. While open-abdomen surgery prevents ACS development and allows a rapid and easy second look, it presents the risk of enteroatmospheric fistulas or fascial deviation [63]. The increased morbidity is furthermore based on physiologic changes, which are in line with persistent opening of the peritoneal cavity: hypothermia, impaired immune function, fluid loss, and increased muscle proteolysis must lead to the modification and adaptation of intensive care therapy (passive rewarming/air warmers, pain control, tailored ventilator support, monitoring of pH and lactate, etc.). This complicated pathophysiological condition can result in increased mortality, which was reported recently [64]. Nevertheless, the open-abdomen approach is indicated for patients with secondary/persisting peritonitis, who face the risk of ACS development or in whom a second-look operation is expected. The prospective COOL trial (Closed or Open after Source Control Laparotomy for Severe Complicated Intra-abdominal Sepsis) is recruiting patients with severe intra-abdominal sepsis (defined as septic shock or a Predisposition, Infection, Response, Organ Dysfunction score > 3 or a World Society of Emergency Surgeons (WSES) sepsis severity score > 8) to analyze the influence of open versus fascial closure on mortality after source control [65].

## Antibiotic therapy

Blood cultures should be collected prior to any antimicrobial treatment. Two to three pairs (aerobic and anaerobic) of blood culture samples should be collected from both the peripheral blood and from central venous catheters. Any antibiotic therapy dramatically reduces the detection rate of the blood culture technique [66].

The 2016 SSC recommendations [49] postulate that:

1. Initial administration of intravenous antimicrobials should be performed within 1 h after admission.
2. The first choice is a broad-spectrum antibiotic (or a combination of antibiotics).
3. The antibiotic spectrum should be narrowed after the microbes have been isolated.
4. Based on the clinical situation, de-escalation of antimicrobial pharmacotherapy should be considered as soon as possible.

As outlined in the International Guidelines for Management of Sepsis and Septic Shock: 2016, the initial administration of antibiotics is a key step in the early management of sepsis and septic shock (3-hour bundle, Fig. 3, Table 3) [49]. In hypotensive patients, every hour of delayed initiation of antimicrobial therapy leads to an increase in mortality [67]. These beneficial effects of rapid empirical antibiotics within the "golden hour of sepsis" could also be confirmed for patients with sepsis (with organ dysfunction!) [68]. The German Medical Education for Sepsis Source Control and Antibiotics (MEDUSA) showed an increase in mortality of 2% per hour of delayed antimicrobial therapy (1%/hour of delayed source control) [69].

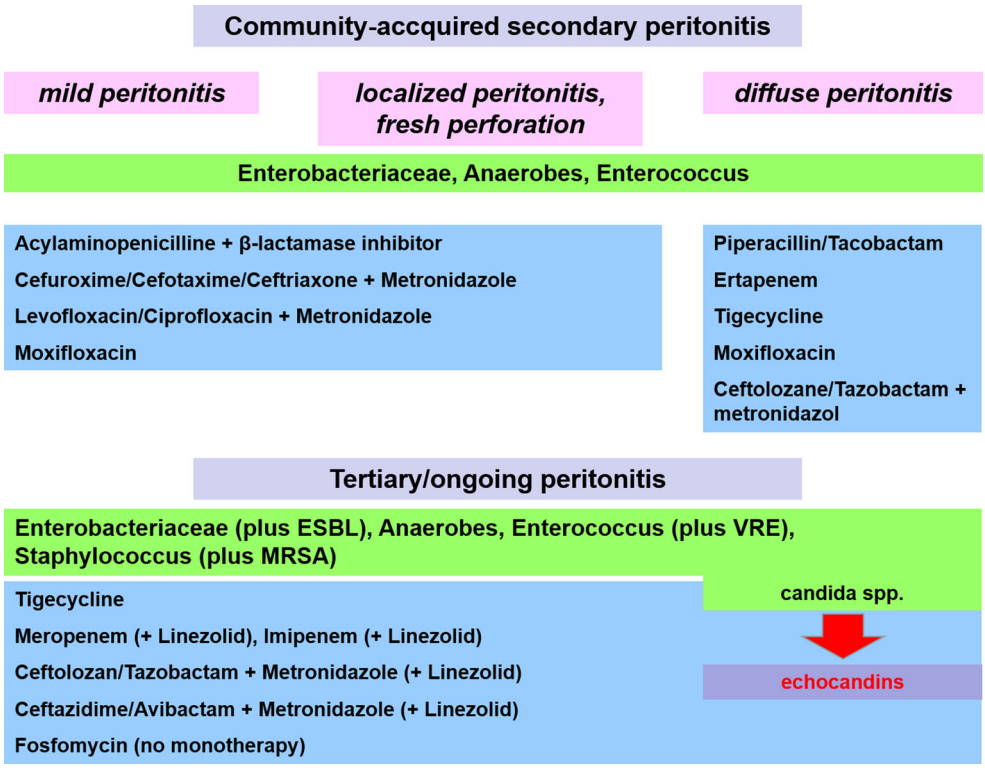


**Fig. 3** Schematic overview of the antimicrobial therapy for patients with secondary and/or ongoing peritonitis according to the guidelines of the Paul-Ehrlich Society. The SSC guideline postulates the administration of a broad-spectrum antibiotic as soon as possible. Modern antibiotic stewardship programs involve the interdisciplinary, everyday re-evaluation of the critically ill patient, followed by either rapid de-escalation or modification of the antimicrobial therapy

Although it is a fact that early antimicrobial therapy is life-saving, the indiscriminate use of broad-spectrum antibiotics has promoted the development of antimicrobial resistance and is furthermore associated with adverse effects during the clinical course of the intensive care patient. To date, there is hardly any literature on this important field of pharmacotherapy in sepsis. The paramount importance of antimicrobial resistance is underlined by the foundation of several taskforces such as the World Alliance Against Antibiotic Resistance or the WSES AGORA (Antimicrobials: a global alliance for optimizing their rational use in intra-abdominal infections) initiative [70, 71].

Furthermore, the inadequate, non-specific use of antibiotics in the ICU is accompanied by increased rates of pulmonary (30%) and urinary (8%) infections [72]. As published recently [73], none of the 10 bacteria most frequently isolated from peritoneal sources of infection was sensitive to ampicillin/sulbactam. Table 6 summarizes the potential new-generation antimicrobials, which could be useful as second-line therapy in ongoing peritonitis caused by resistant bacteria.

**Table 6** New-generation antibiotics and their potential indications

| Antibiotic | Class | Indication | Pathogen | Reference |
|---|---|---|---|---|
| Ceftobiprol | β-Lactam antibiotic | Pneumonia | MRSA, VRE, PNSP | [74] |
| Ceftarolin | β-Lactam antibiotic | SSI, pneumonia | MRSA, VRE, PNSP | [75, 76] |
| Ceftolozan/tazobactam | Cephalosporine + β-lactamase inhibitor | Intra-abdominal infections, urinary tract infection, pneumonia | *Pseudomonas aeruginosa*, Enterobacteriaceae ESBL | [77] |
| Ceftazidim/avibactam | | Intra-abdominal infections | *Pseudomonas aeruginosa*, Enterobacteriaceae, | [78–80] |
| | | Urinary infections, pneumonia, complicated infections "difficult-to-treat" | ESBL, carbapenemase-producing enterobacteria | |
| Tedizolid | Oxyzolidione | SSI | MRSA, *S. viridans*, bh-*Streptococcus* | [81] |
| Dalbavancin | Lipoglycopeptide | SSI, catheter-associated infection | MRSA, VRE, *S. pneumoniae* | [82, 83] |
| Telavancin | | pneumonia | MRSA | |
| Oritavancin | | SSI | MRSA | |

In cases of complicated ongoing peritonitis, antimicrobial therapy leads to selection pressure within the bacterial flora. This holds also true for *Candida* species, whose isolation from peritoneal fluid correlates with impaired clinical prognosis and persistent ongoing peritonitis [72]. Bassetti et al. reported up to 50% mortality of ICU patients with intra-abdominal candidiasis (!), while that of non-ICU patients was only half that. The European Society for Clinical Microbiology and Infectious Diseases (ESCMID) recommends echinocandins as first choice medication for *Candida* infections in ICU patients [84]. Fluconazole is a rational alternative for treating *C. parapsilosis*. It is important to know that medication must be administered up to a minimum duration of 14 days after a *Candida*-negative blood culture occurs. An inadequate therapeutic regimen of intra-abdominal candidiasis was proven to be an important negative prognostic survival parameter [72, 85].

Three key points should be kept in mind when discussing modern surgical antimicrobial therapy in ICU:

First, *rapid detection of specific bacteria* from the intra-abdominal source (e.g., from the peritoneal cavity) would shorten the period of empiric antimicrobial therapy to a tailored, more specific one. In contrast to blood culture, PCR-based techniques can allow the rapid identification of bacteria and associated antimicrobial resistances [22]. Particularly, surgical patients with ongoing, persisting peritonitis can be monitored by these modern approaches in the future.

Second, *antibiotic stewardship* should be implemented in any surgical ICU. The rapid, individualized de-escalation of the (broad-spectrum) antimicrobial therapy avoids bacterial in-hospital resistances and reduces pharmacological adverse effects such as renal and/or hepatic insufficiencies. A recent article on nosocomial pneumonia stated that de-escalation of antimicrobial therapy is postulated within 2–3 days after initiation [86]. On daily interdisciplinary rounds, multiple aspects such as clinical status and development; infectious parameters (e.g., PCT); metabolic, hepatic, and renal laboratory values; grade of source control, etc., have to be considered and result in flexible and individualized antimicrobial therapy. For uncomplicated intra-abdominal sepsis, an antimicrobial regimen should be finished after 7 days on average. A *Staphylococcus aureus* bloodstream infection (BSI) has to be treated for at least 14 days if uncomplicated; complicated *Staph. aureus* BSI require at least 4 weeks of antibiotic therapy.

For uncomplicated intra-abdominal sepsis, an antimicrobial regimen should be finished after 7 days on average, except for *Staph. aureus* infection, which requires up to 4 weeks of antibiotic therapy in the case of complicated infection.

Third, the differentiation between infection and *colonization* is of major importance for surgical patients with (ongoing) peritonitis. These patients are permanently threatened by hospital-acquired infections. While colonization by *multidrug-resistant pathogens* such as methicillin-resistant *Staph. aureus* (MRSA), vancomycin-resistant enterococci (VRE), or multidrug-resistant gram-negative bacteria (MRGN) is often diagnosed in surgical patients, it normally leads to isolation only. Whether the colonization of a patient with secondary and/or ongoing peritonitis should be treated with antibiotics should be investigated in future studies. The REDUCE (Randomized Evaluation of Decolonization versus Universal Clearance to Eliminate) MRSA trial changed the view on pharmacotherapy of colonized patients, showing a clear benefit for universal decolonization in comparison to screening plus isolation only [87]. Antibiotic treatment of colonized patients led to dramatically reduced rates of positive BSI in intensive care patients.

## Give your patients a FAST-HUG

Every surgical patient with secondary peritonitis requires certain key elements of intensive care therapy such as prophylaxis of ulcers (e.g., proton pump inhibitor), lung protective ventilation (according to the ARDS (acute respiratory distress syndrome) network protocol), hemodynamic stabilization (MAP >65 mmHg, inotropics in cases of myocardial dysfunction, invasive hemodynamic monitoring, glomerular filtration rate > 0.5 ml/kg body weight, repetitive serum lactate measurement), blood glucose 110–180 mg/dl, prophylaxis of thrombosis, and enteral nutrition, if possible.

While these values and target parameters provide valuable assistance during everyday rounds, the exact doses, the kind of monitoring, etc., remain a matter of debate in the recent literature. As an example, adjunctive sepsis therapy with corticosteroids is still intensively discussed within the expert literature. While hydrocortisone did not reduce the development of cardiovascular instability/septic shock in the HYPRESS trial [88], recent literature reveals that at least some subgroups of patients with septic shock appear to benefit from continuous hydrocortisone administration (ADRENAL [89], APROCCHSS [90] trials).

As another example, the target parameters of (lung-protective) ventilation in the septic patient have shifted to lower $PaO_2$ (partial pressure of oxygen) values. In contrast to the conventional ventilator regimen ($PaO_2$ up to 150 mmHg, $SpO_2$ (blood oxygen saturation) = 97–100%), a more restrictive ventilation ($PaO_2$ = 70–100 mmHg, $SpO_2$ = 94–98%) seems to be beneficial [91].

For everyday rounds, the surgeon should remember to monitor the key aspects of modern intensive care medicine for critically ill surgical patients. As introduced by Vincent into clinical routine [92], every patient should get a FAST-HUG (*F*eeding, *A*nalgesia, *S*edation, *T*hromboembolic prophylaxis, *H*ead-of-bed elevation, stress *U*lcer prevention, *G*lucose control) at least once a day by both intensivists, anesthesiologists, and the abdominal surgeon.

## Outcome and conclusions

Substantial improvement of sepsis survival is the main challenge of modern surgical research. In contrast to "historical" data reporting 40–60% hospital mortality for severe sepsis, more recent randomized trials that included strict implementation of protocol-based resuscitation therapy reported between 18% and 30% mortality [4, 93]. Nevertheless, both mortality and morbidity remain unacceptably high. Long-term morbidity leads to substantial functional disability, mental impairment, which finally is reflected in high rates of hospitalization in acute care or skilled nursing facilities. Permanent education, feedback, and audit initiatives are a new approach for monitoring the implementation of SSC sepsis measures. As stated by Levy et al., the strict transfer of the SSC guidelines into daily patient care led to a 9.6% decline in mortality [94].

Surgical source control is the obligatory treatment of every patient with secondary or ongoing peritonitis and is of both therapeutic and diagnostic importance. Future studies should evaluate the impact of damage-control surgery on the survival of patients with intra-abdominal sepsis. New diagnostic tools such as biomarker assays and PCR-based techniques for detecting microbes will accelerate the identification of complications after surgical treatment and will allow healthcare providers to initiate individualized antimicrobial therapy rapidly in the near future. The SSC constantly updates the guideline-based supportive care, but permanent medical education on sepsis diagnostics and therapy is required. Sepsis recognition and therapy require everyday re-evaluation of the patient during interdisciplinary rounds.

## Compliance with ethical standards

**Conflict of interest** The authors A.H., M.R., C.J.R., T.S., J.G.R., E.S., W.P., and M.H. declare that they have no conflict of interest. M.A.W. reports personal fees from MSD, personal fees from Pfizer, personal fees from Gilead, outside the submitted work. In addition, M.A.W. has a patent EP 17198330.7 issued.

**Ethical approval** This article does not contain any studies with animals performed by any of the authors. This article does not contain any studies with human participants or animals performed by any of the authors.

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

## References


1. Reinhart K, Daniels R, Kissoon N, Machado FR, Schachter RD, Finfer S (2017) Recognizing Sepsis as a Global Health Priority—A WHO Resolution. N Engl J Med 377:414–417. https://doi.org/10.1056/NEJMp1707170
2. Cecconi M, Evans L, Levy M, Rhodes A (2016) Sepsis and septic shock. Nat Rev Dis Prim 2:16046. https://doi.org/10.1038/nrdp.2016.46
3. Adhikari NKJ, Fowler RA, Bhagwanjee S, Rubenfeld GD (2010) Critical care and the global burden of critical illness in adults. Lancet (London, England). https://doi.org/10.1016/S0140-6736(10)60446-1
4. Cecconi M, Evans L, Levy M, Rhodes A (2018) Sepsis and septic shock. Lancet (London, England). https://doi.org/10.1016/S0140-6736(18)30696-2
5. Rhee C, Dantes R, Epstein L et al (2017) Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009–2014. JAMA. https://doi.org/10.1001/jama.2017.13836
6. Chalupka AN, Talmor D (2012) The economics of sepsis. Crit Care Clin 28:57–76. https://doi.org/10.1016/j.ccc.2011.09.003
7. Bernard GR, Vincent JL, Laterre PF, LaRosa S, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ Jr, Recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group (2001) Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 344:699–709. https://doi.org/10.1056/NEJM200103083441001
8. Barie PS, Williams MD, McCollam JS, Bates BM, Qualy RL, Lowry SF, Fry DE, PROWESS Surgical Evaluation Committee (2004) Benefit/risk profile of drotrecogin alfa (activated) in surgical patients with severe sepsis. Am J Surg 188:212–220. https://doi.org/10.1016/j.amjsurg.2004.06.008
9. RC B (1991) Sepsis syndrome. New insights into its pathogenesis and treatment. Infect Dis Clin N Am
10. Levy MM, Fink MP, Marshall JC et al (2003) 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med 29:530–538. https://doi.org/10.1007/s00134-003-1662-x
11. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, Angus DC, Rubenfeld GD, Singer M, for the Sepsis Definitions Task Force (2016) Developing a new definition and assessing new clinical criteria for septic shock. JAMA 315:775–787. https://doi.org/10.1001/jama.2016.0289
12. Vincent JL, Moreno R, Takala J et al (1996) The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med 22:707–710. https://doi.org/10.1007/BF01709751
13. Singer M, Deutschman CS, Seymour C et al (2016) The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA. https://doi.org/10.1001/jama.2016.0287
14. Raith EP, Udy AA, Bailey M, McGloughlin S, MacIsaac C, Bellomo R, Pilcher DV, for the Australian and New Zealand Intensive Care Society (ANZICS) Centre for Outcomes and Resource Evaluation (CORE) (2017) Prognostic accuracy of the SOFA score, SIRS criteria, and qSOFA score for in-hospital mortality among adults with suspected infection admitted to the intensive care unit. JAMA 317:290. https://doi.org/10.1001/jama.2016.20328
15. Donnelly JP, Safford MM, Shapiro NI, Baddley JW, Wang HE (2017) Application of the third international consensus definitions for Sepsis (Sepsis-3) classification: a retrospective population-based cohort study. Lancet Infect Dis 17:661–670. https://doi.org/10.1016/S1473-3099(17)30117-2
16. Shankar-Hari M, Harrison DA, Rubenfeld GD, Rowan K (2017) Epidemiology of sepsis and septic shock in critical care units: comparison between sepsis-2 and sepsis-3 populations using a national critical care database. Br J Anaesth 119:626–636. https://doi.org/10.1093/bja/aex234
17. Bader FG, Schröder M, Kujath P, Muhl E, Bruch HP, Eckmann C (2009) Diffuse postoperative peritonitis—value of diagnostic parameters and impact of early indication for relaparotomy. Eur J Med Res 14:491–496. https://doi.org/10.1186/2047-783X-14-11-491

18. Welsch T, Frommhold K, Hinz U, Weigand MA, Kleeff J, Friess H, Büchler MW, Schmidt J (2008) Persisting elevation of C-reactive protein after pancreatic resections can indicate developing inflammatory complications. Surgery 143:20–28. https://doi.org/10.1016/j.surg.2007.06.010
19. Parlato M, Philippart F, Rouquette A et al (2018) Circulating biomarkers may be unable to detect infection at the early phase of sepsis in ICU patients: the CAPTAIN prospective multicenter cohort study. Intensive Care Med 44:1061–1070. https://doi.org/10.1007/s00134-018-5228-3
20. Heyland DK, Johnson AP, Reynolds SC, Muscedere J (2011) Procalcitonin for reduced antibiotic exposure in the critical care setting: a systematic review and an economic evaluation. Crit Care Med 39:1792–1799. https://doi.org/10.1097/CCM.0b013e31821201a5
21. de Jong E, van Oers JA, Beishuizen A, Vos P, Vermeijden WJ, Haas LE, Loef BG, Dormans T, van Melsen GC, Kluiters YC, Kemperman H, van den Elsen MJ, Schouten JA, Streefkerk JO, Krabbe HG, Kieft H, Kluge GH, van Dam VC, van Pelt J, Bormans L, Otten MB, Reidinga AC, Endeman H, Twisk JW, van de Garde EMW, de Smet AMGA, Kesecioglu J, Girbes AR, Nijsten MW, de Lange DW (2016) Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. Lancet Infect Dis 16:819–827. https://doi.org/10.1016/S1473-3099(16)00053-0
22. Rivers EP, Jaehne AK, Nguyen HB, Papamatheakis DG, Singer D, Yang JJ, Brown S, Klausner H (2013) Early biomarker activity in severe sepsis and septic shock and a contemporary review of immunotherapy trials: not a time to give up, but to give it earlier. Shock 39:127–137. https://doi.org/10.1097/SHK.0b013e31827dafa7
23. Hecker A, Uhle F, Schwandner T, Padberg W, Weigand MA (2014) Diagnostics, therapy and outcome prediction in abdominal sepsis: current standards and future perspectives. Langenbeck's Arch Surg 399:11–22. https://doi.org/10.1007/s00423-013-1132-z
24. Xiao Z, Wilson C, Robertson HL, Roberts DJ, Ball CG, Jenne CN, Kirkpatrick AW (2015) Inflammatory mediators in intra-abdominal sepsis or injury—a scoping review. Crit Care 19:373. https://doi.org/10.1186/s13054-015-1093-4
25. Riché F, Gayat E, Collet C et al (2013) Local and systemic innate immune response to secondary human peritonitis. Crit Care 17:R201. https://doi.org/10.1186/cc12895
26. Tsujimoto H, Yaguchi Y, Hiraki S et al (2011) Peritoneal computed tomography attenuation values reflect the severity of peritonitis caused by gastrointestinal perforations. Am J Surg. https://doi.org/10.1016/j.amjsurg.2010.08.037
27. Tseng J-R, Chen K-Y, Lee M-H, Huang CT, Wen YH, Yen TC (2013) Potential usefulness of FDG PET/CT in patients with sepsis of unknown origin. PLoS One 8:e66132. https://doi.org/10.1371/journal.pone.0066132
28. Berrevoets MAH, Kouijzer IJE, Aarntzen EHJG, Janssen MJR, de Geus-Oei LF, Wertheim HFL, Kullberg BJ, Oever JT, Oyen WJG, Bleeker-Rovers CP (2017) 18F-FDG PET/CT optimizes treatment in Staphylococcus aureus bacteremia and is associated with reduced mortality. J Nucl Med 58:1504–1510. https://doi.org/10.2967/jnumed.117.191981
29. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M, Early Goal-Directed Therapy Collaborative Group (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377. https://doi.org/10.1056/NEJMoa010307
30. Investigators TP (2014) A randomized trial of protocol-based care for early septic shock. Process trial. N Engl J Med doi: https://doi.org/10.1056/NEJMoa1401602, 370, 1683, 1693
31. Bailey M, Bellomo R, Peter A et al (2014) Goal-directed resuscitation for patients with early septic shock. N Engl J Med. https://doi.org/10.1056/NEJMoa1404380
32. Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, Jahan R, Harvey SE, Bell D, Bion JF, Coats TJ, Singer M, Young JD, Rowan KM, ProMISe Trial Investigators (2015) Trial of early, goal-directed resuscitation for septic shock. N Engl J Med 372:1301–1311. https://doi.org/10.1056/NEJMoa1500896
33. Lewis SR, Pritchard MW, Evans DJW et al (2018) Colloids versus crystalloids for fluid resuscitation in critically ill people. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD000567.pub7
34. Young P, Bailey M, Beasley R, Henderson S, Mackle D, McArthur C, McGuinness S, Mehrtens J, Myburgh J, Psirides A, Reddy S, Bellomo R, SPLIT Investigators., ANZICS CTG (2015) Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit: the SPLIT randomized clinical trial. JAMA 314:1701–1710. https://doi.org/10.1001/jama.2015.12334
35. Semler MW, Wanderer JP, Ehrenfeld JM, Stollings JL, Self WH, Siew ED, Wang L, Byrne DW, Shaw AD, Bernard GR, Rice TW, Bernard GR, Semler MW, Noto MJ, Rice TW, Byrne DW, Domenico HJ, Wang L, Wanderer JP, Ehrenfeld JM, Shaw AD, Hernandez A, Kumar AB, Self WH, Siew ED, Dunlap DF, Stollings JL, Sullivan M, Knostman M, Mulherin DP, Hargrove FR, Janz DR, Strawbridge S (2017) Balanced crystalloids versus saline in the intensive care unit: the SALT randomized trial. Am J Respir Crit Care Med 195:1362–1372. https://doi.org/10.1164/rccm.201607-1345OC
36. Zampieri FG, Azevedo LCP, Corrêa TD, Falavigna M, Machado FR, Assunção MSC, Lobo SMA, Dourado LK, Berwanger O, Kellum JA, Brandão N, Cavalcanti AB, BaSICS Investigators and the BRICNet (2017) Study protocol for the balanced solution versus saline in intensive care study (BaSICS): a factorial randomised trial. Crit Care Resusc 19:175–182
37. Hammond NE, Bellomo R, Gallagher M, Gattas D, Glass P, Mackle D, Micallef S, Myburgh J, Saxena M, Taylor C, Young P, Finfer S (2017) The plasma-Lyte 148 v saline (PLUS) study protocol: a multicentre, randomised controlled trial of the effect of intensive care fluid therapy on mortality. Crit Care Resusc 19:239–246
38. Leisman DE, Doerfler ME, Schneider SM et al (2018) Predictors, prevalence, and outcomes of early crystalloid responsiveness among initially hypotensive patients with sepsis and septic shock. Crit Care Med. https://doi.org/10.1097/CCM.0000000000002834
39. Marik PE, Linde-Zwirble WT, Bittner EA, Sahatjian J, Hansell D (2017) Fluid administration in severe sepsis and septic shock, patterns and outcomes: an analysis of a large national database. Intensive Care Med 43:625–632. https://doi.org/10.1007/s00134-016-4675-y
40. Takala J (2016) Volume responsive, but does the patient need volume? Intensive Care Med 42:1461–1463. https://doi.org/10.1007/s00134-015-4172-8
41. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R, Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup (2013) Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 41:580–637. https://doi.org/10.1097/CCM.0b013e31827e83af
42. Marshall JC, Maier RV, Jimenez M, Dellinger EP (2004) Source control in the management of severe sepsis and septic shock: an evidence-based review. Crit Care Med 32:S513–S526. https://doi.org/10.1097/01.CCM.0000143119.41916.5D

43. Ceresoli M, Lo BG, Gianotti L, Nespoli L (2018) Inflammation management in acute diverticulitis: current perspectives. J Inflamm Res. https://doi.org/10.2147/JIR.S142990
44. Lyons PG, Micek ST, Hampton N, Kollef MH (2018) Sepsis-associated coagulopathy severity predicts hospital mortality. Crit Care Med 46:736–742. https://doi.org/10.1097/CCM.0000000000002997
45. Gordon AC, Perkins GD, Singer M, McAuley DF, Orme RML, Santhakumaran S, Mason AJ, Cross M, al-Beidh F, Best-Lane J, Brealey D, Nutt CL, McNamee JJ, Reschreiter H, Breen A, Liu KD, Ashby D (2016) Levosimendan for the prevention of acute organ dysfunction in sepsis. N Engl J Med 375:1638–1648. https://doi.org/10.1056/NEJMoa1609409
46. Schmittinger CA, Torgersen C, Luckner G, Schröder DCH, Lorenz I, Dünser MW (2012) Adverse cardiac events during catecholamine vasopressor therapy: a prospective observational study. Intensive Care Med 38:950–958. https://doi.org/10.1007/s00134-012-2531-2
47. Dünser MW, Ruokonen E, Pettilä V, Ulmer H, Torgersen C, Schmittinger CA, Jakob S, Takala J (2009) Association of arterial blood pressure and vasopressor load with septic shock mortality: a post hoc analysis of a multicenter trial. Crit Care 13:R181. https://doi.org/10.1186/cc8167
48. Weber DG, Bendinelli C, Balogh ZJ (2014) Damage control surgery for abdominal emergencies. Br J Surg 101:e109–e118. https://doi.org/10.1002/bjs.9360
49. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, de Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP (2017) Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 43:304–377. https://doi.org/10.1007/s00134-017-4683-6
50. Finlay IG, Edwards TJ, Lambert AW (2004) Damage control laparotomy. Br J Surg 91:83–85. https://doi.org/10.1002/bjs.4434
51. Banieghbal B, Davies MR (2004) Damage control laparotomy for generalized necrotizing enterocolitis. World J Surg 28:183–186. https://doi.org/10.1007/s00268-003-7155-9
52. Tamijmarane A, Ahmed I, Bhati CS, Mirza DF, Mayer AD, Buckels JAC, Bramhall SR (2006) Role of completion pancreatectomy as a damage control option for post-pancreatic surgical complications. Dig Surg 23:229–234. https://doi.org/10.1159/000095395
53. Person B, Dorfman T, Bahouth H, Osman A, Assalia A, Kluger Y (2009) Abbreviated emergency laparotomy in the non-trauma setting. World J Emerg Surg. 4:41. https://doi.org/10.1186/1749-7922-4-41
54. Kafka-Ritsch R, Birkfellner F, Perathoner A, Raab H, Nehoda H, Pratschke J, Zitt M (2012) Damage control surgery with abdominal vacuum and delayed bowel reconstruction in patients with perforated diverticulitis Hinchey III/IV. J Gastrointest Surg 16:1915–1922. https://doi.org/10.1007/s11605-012-1977-4
55. Goussous N, Jenkins DH, Zielinski MD (2014) Primary fascial closure after damage control laparotomy: sepsis vs haemorrhage. Injury 45:151–155. https://doi.org/10.1016/j.injury.2013.01.039
56. Girard E, Abba J, Boussat B, Trilling B, Mancini A, Bouzat P, Létoublon C, Chirica M, Arvieux C (2018) Damage control surgery for non-traumatic abdominal emergencies. World J Surg 42:965–973. https://doi.org/10.1007/s00268-017-4262-6
57. van Ruler O, Mahler CW, Boer KR, Reuland EA, Gooszen HG, Opmeer BC, de Graaf PW, Lamme B, Gerhards MF, Steller EP, Olivier van Till JW, de Borgie CJAM, Gouma DJ, Reitsma JB, Boermeester MA, Dutch Peritonitis Study Group (2007) Comparison of on-demand vs planned relaparotomy strategy in patients with severe peritonitis: a randomized trial. JAMA 298:865–872. https://doi.org/10.1001/jama.298.8.865
58. Kiewiet JJS, van Ruler O, Boermeester MA, Reitsma JB (2013) A decision rule to aid selection of patients with abdominal sepsis requiring a relaparotomy. BMC Surg 13:28. https://doi.org/10.1186/1471-2482-13-28
59. Koperna T, Schulz F (2000) Relaparotomy in peritonitis: prognosis and treatment of patients with persisting intraabdominal infection. World J Surg 24:32–37. https://doi.org/10.1007/s002689910007
60. Hecker A, Hecker B, Hecker M, Riedel JG, Weigand MA, Padberg W (2016) Acute abdominal compartment syndrome: current diagnostic and therapeutic options. Langenbeck's Arch Surg / Dtsch Gesellschaft für Chir 401:15–24. https://doi.org/10.1007/s00423-015-1353-4
61. Sartelli M, Abu-Zidan FM, Ansaloni L, Bala M, Beltrán MA, Biffl WL, Catena F, Chiara O, Coccolini F, Coimbra R, Demetrashvili Z, Demetriades D, Diaz JJ, di Saverio S, Fraga GP, Ghnnam W, Griffiths EA, Gupta S, Hecker A, Karamarkovic A, Kong VY, Kafka-Ritsch R, Kluger Y, Latifi R, Leppaniemi A, Lee JG, McFarlane M, Marwah S, Moore FA, Ordonez CA, Pereira GA, Plaudis H, Shelat VG, Ulrych J, Zachariah SK, Zielinski MD, Garcia MP, Moore EE (2015) The role of the open abdomen procedure in managing severe abdominal sepsis: WSES position paper. World J Emerg Surg 10:35. https://doi.org/10.1186/s13017-015-0032-7
62. Sartelli M, Chichom-Mefire A, Labricciosa FM, Hardcastle T, Abu-Zidan FM, Adesunkanmi AK, Ansaloni L, Bala M, Balogh ZJ, Beltrán MA, Ben-Ishay O, Biffl WL, Birindelli A, Cainzos MA, Catalini G, Ceresoli M, Che Jusoh A, Chiara O, Coccolini F, Coimbra R, Cortese F, Demetrashvili Z, di Saverio S, Diaz JJ, Egiev VN, Ferrada P, Fraga GP, Ghnnam WM, Lee JG, Gomes CA, Hecker A, Herzog T, Kim JI, Inaba K, Isik A, Karamarkovic A, Kashuk J, Khokha V, Kirkpatrick AW, Kluger Y, Koike K, Kong VY, Leppaniemi A, Machain GM, Maier RV, Marwah S, McFarlane ME, Montori G, Moore EE, Negoi I, Olaoye I, Omari AH, Ordonez CA, Pereira BM, Pereira Júnior GA, Pupelis G, Reis T, Sakakushev B, Sato N, Segovia Lohse HA, Shelat VG, Søreide K, Uhl W, Ulrych J, van Goor H, Velmahos GC, Yuan KC, Wani I, Weber DG, Zachariah SK, Catena F (2017) The management of intra-abdominal infections from a global perspective: 2017 WSES guidelines for management of intra-abdominal infections. World J Emerg Surg. 12:29. https://doi.org/10.1186/s13017-017-0141-6
63. Yuan Y, Ren J, He Y (2013) Current status of the open abdomen treatment for intra-abdominal infection. Gastroenterol Res Pract 2013:1–7. https://doi.org/10.1155/2013/532013
64. Chen Y, Ye J, Song W, Chen J, Yuan Y, Ren J (2014) Comparison of outcomes between early fascial closure and delayed abdominal closure in patients with open abdomen: a systematic review and meta-analysis. Gastroenterol Res Pract 2014:784056. https://doi.org/10.1155/2014/784056
65. Kirkpatrick AW, Coccolini F, Ansaloni L et al (2018) Closed or open after source control laparotomy for severe complicated intra-abdominal sepsis (the COOL trial): study protocol for a randomized controlled trial. World J Emerg Surg. 13:26. https://doi.org/10.1186/s13017-018-0183-4
66. Scerbo MH, Kaplan HB, Dua A, et al. (2016) Beyond blood culture and Gram stain analysis: a review of molecular techniques for the early detection of bacteremia in surgical patients. Surg Infect (Larchmt). doi: https://doi.org/10.1089/sur.2015.099
67. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, Suppes R, Feinstein D, Zanotti S, Taiberg L, Gurka D, Kumar A,

Cheang M (2006) Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 34:1589–1596. https://doi.org/10.1097/01.CCM.0000217961.75225.E9

68. Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, Artigas A, Schorr C, Levy MM (2014) Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour. Crit Care Med 42:1749–1755. https://doi.org/10.1097/CCM.0000000000000330
69. Bloos F, Rüddel H, Thomas-Rüddel D et al (2017) Effect of a multifaceted educational intervention for anti-infectious measures on sepsis mortality: a cluster randomized trial. Intensive Care Med 43:1602–1612. https://doi.org/10.1007/s00134-017-4782-4
70. Sartelli M, Weber DG, Ruppé E, Bassetti M, Wright BJ, Ansaloni L, Catena F, Coccolini F, Abu-Zidan FM, Coimbra R, Moore EE, Moore FA, Maier RV, de Waele JJ, Kirkpatrick AW, Griffiths EA, Eckmann C, Brink AJ, Mazuski JE, May AK, Sawyer RG, Mertz D, Montravers P, Kumar A, Roberts JA, Vincent JL, Watkins RR, Lowman W, Spellberg B, Abbott IJ, Adesunkanmi AK, al-Dahir S, al-Hasan MN, Agresta F, Althani AA, Ansari S, Ansumana R, Augustin G, Bala M, Balogh ZJ, Baraket O, Bhangu A, Beltrán MA, Bernhard M, Biffl WL, Boermeester MA, Brecher SM, Cherry-Bukowiec JR, Buyne OR, Cainzos MA, Cairns KA, Camacho-Ortiz A, Chandy SJ, Che Jusoh A, Chichom-Mefire A, Colijn C, Corcione F, Cui Y, Curcio D, Delibegovic S, Demetrashvili Z, de Simone B, Dhingra S, Diaz JJ, di Carlo I, Dillip A, di Saverio S, Doyle MP, Dorj G, Dogjani A, Dupont H, Eachempati SR, Enani MA, Egiev VN, Elmangory MM, Ferrada P, Fitchett JR, Fraga GP, Guessennd N, Giamarellou H, Ghnnam W, Gkiokas G, Goldberg SR, Gomes CA, Gomi H, Guzmán-Blanco M, Haque M, Hansen S, Hecker A, Heizmann WR, Herzog T, Hodonou AM, Hong SK, Kafka-Ritsch R, Kaplan LJ, Kapoor G, Karamarkovic A, Kees MG, Kenig J, Kiguba R, Kim PK, Kluger Y, Khokha V, Koike K, Kok KYY, Kong V, Knox MC, Inaba K, Isik A, Iskandar K, Ivatury RR, Labbate M, Labricciosa FM, Laterre PF, Latifi R, Lee JG, Lee YR, Leone M, Leppaniemi A, Li Y, Liang SY, Loho T, Maegele M, Malama S, Marei HE, Martin-Loeches I, Marwah S, Massele A, McFarlane M, Melo RB, Negoi I, Nicolau DP, Nord CE, Ofori-Asenso R, Omari AKH, Ordonez CA, Ouadii M, Pereira Júnior GA, Piazza D, Pupelis G, Rawson TM, Rems M, Rizoli S, Rocha C, Sakakhushev B, Sanchez-Garcia M, Sato N, Segovia Lohse HA, Sganga G, Siribumrungwong B, Shelat VG, Soreide K, Soto R, Talving P, Tilsed JV, Timsit JF, Trueba G, Trung NT, Ulrych J, van Goor H, Vereczkei A, Vohra RS, Wani I, Uhl W, Xiao Y, Yuan KC, Zachariah SK, Zahar JR, Zakrison TL, Corcione A, Melotti RM, Viscoli C, Viale P (2016) Antimicrobials: a global alliance for optimizing their rational use in intra-abdominal infections (AGORA). World J Emerg Surg. 11:33. https://doi.org/10.1186/s13017-016-0089-y
71. Sartelli M, Labricciosa FM, Barbadoro P, Pagani L, Ansaloni L, Brink AJ, Carlet J, Khanna A, Chichom-Mefire A, Coccolini F, di Saverio S, May AK, Viale P, Watkins RR, Scudeller L, Abbo LM, Abu-Zidan FM, Adesunkanmi AK, al-Dahir S, al-Hasan MN, Alis H, Alves C, Araujo da Silva AR, Augustin G, Bala M, Barie PS, Beltrán MA, Bhangu A, Bouchra B, Brecher SM, Caínzos MA, Camacho-Ortiz A, Catani M, Chandy SJ, Jusoh AC, Cherry-Bukowiec JR, Chiara O, Colak E, Cornely OA, Cui Y, Demetrashvili Z, de Simone B, de Waele JJ, Dhingra S, di Marzo F, Dogjani A, Dorj G, Dortet L, Duane TM, Elmangory MM, Enani MA, Ferrada P, Esteban Foianini J, Gachabayov M, Gandhi C, Ghnnam WM, Giamarellou H, Gkiokas G, Gomi H, Goranovic T, Griffiths EA, Guerra Gronerth RI, Haidamus Monteiro JC, Hardcastle TC, Hecker A, Hodonou AM, Ioannidis O, Isik A, Iskandar KA, Kafil HS, Kanj SS, Kaplan LJ, Kapoor G, Karamarkovic AR, Kenig J, Kerschaever I, Khamis F, Khokha V, Kiguba R, Kim HB, Ko WC, Koike K, Kozlovska I, Kumar A, Lagunes L, Latifi R, Lee JG, Lee YR, Leppäniemi A, Li Y, Liang SY, Lowman W, Machain GM, Maegele M, Major P, Malama S, Manzano-Nunez R, Marinis A, Martinez Casas I, Marwah S, Maseda E, McFarlane ME, Memish Z, Mertz D, Mesina C, Mishra SK, Moore EE, Munyika A, Mylonakis E, Napolitano L, Negoi I, Nestorovic MD, Nicolau DP, Omari AH, Ordonez CA, Paiva JA, Pant ND, Parreira JG, Pędziwiatr M, Pereira BM, Ponce-de-Leon A, Poulakou G, Preller J, Pulcini C, Pupelis G, Quiodettis M, Rawson TM, Reis T, Rems M, Rizoli S, Roberts J, Pereira NR, Rodríguez-Baño J, Sakakushev B, Sanders J, Santos N, Sato N, Sawyer RG, Scarpelini S, Scoccia L, Shafiq N, Shelat V, Sifri CD, Siribumrungwong B, Søreide K, Soto R, de Souza HP, Talving P, Trung NT, Tessier JM, Tumbarello M, Ulrych J, Uranues S, van Goor H, Vereczkei A, Wagenlehner F, Xiao Y, Yuan KC, Wechsler-Fördös A, Zahar JR, Zakrison TL, Zuckerbraun B, Zuidema WP, Catena F (2017) The global Alliance for infections in surgery: defining a model for antimicrobial stewardship—results from an international cross-sectional survey. World J Emerg Surg 12:34. https://doi.org/10.1186/s13017-017-0145-2
72. De Waele JJ (2016) Abdominal Sepsis. Curr Infect Dis Rep 18. https://doi.org/10.1007/s11908-016-0531-z
73. Hackel MA, Badal RE, Bouchillon SK, Biedenbach DJ, Hoban DJ (2015) Resistance rates of intra-abdominal isolates from intensive care units and non-intensive care units in the United States: the study for monitoring antimicrobial resistance trends 2010–2012. Surg Infect 16:298–304. https://doi.org/10.1089/sur.2014.060
74. Awad SS, Rodriguez AH, Chuang YC, Marjanek Z, Pareigis AJ, Reis G, Scheeren TWL, Sanchez AS, Zhou X, Saulay M, Engelhardt M (2014) A phase 3 randomized double-blind comparison of ceftobiprole medocaril versus ceftazidime plus linezolid for the treatment of hospital-acquired pneumonia. Clin Infect Dis 59:51–61. https://doi.org/10.1093/cid/ciu219
75. Kiang TKL, Wilby KJ, Ensom MHH (2015) A critical review on the clinical pharmacokinetics, pharmacodynamics, and clinical trials of ceftaroline. Clin Pharmacokinet 54:915–931. https://doi.org/10.1007/s40262-015-0281-3
76. Zhong NS, Sun T, Zhuo C, D'Souza G, Lee SH, Lan NH, Chiang CH, Wilson D, Sun F, Iaconis J, Melnick D (2015) Ceftaroline fosamil versus ceftriaxone for the treatment of Asian patients with community-acquired pneumonia: a randomised, controlled, double-blind, phase 3, non-inferiority with nested superiority trial. Lancet Infect Dis 15:161–171. https://doi.org/10.1016/S1473-3099(14)71018-7
77. Solomkin J, Hershberger E, Miller B, Popejoy M, Friedland I, Steenbergen J, Yoon M, Collins S, Yuan G, Barie PS, Eckmann C (2015) Ceftolozane/tazobactam plus metronidazole for complicated intra-abdominal infections in an era of multidrug resistance: results from a randomized, double-blind, phase 3 trial (ASPECT-cIAI). Clin Infect Dis 60:1462–1471. https://doi.org/10.1093/cid/civ097
78. Wagenlehner FM, Umeh O, Steenbergen J, Yuan G, Darouiche RO (2015) Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). Lancet 385:1949–1956. https://doi.org/10.1016/S0140-6736(14)62220-0
79. Vazquez J, González Patzán LD, Stricklin D et al (2012) Efficacy and safety of ceftazidime-avibactam versus imipenem-cilastatin in the treatment of complicated urinary tract infections, including acute pyelonephritis, in hospitalized adults: results of a prospective, investigator-blinded, randomized study. CurrMed ResOpin 28:1921–1931. https://doi.org/10.1185/03007995.2012.748653
80. Mazuski JE, Gasink LB, Armstrong J, Broadhurst H, Stone GG, Rank D, Llorens L, Newell P, Pachl J (2016) Efficacy and safety of ceftazidime-avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infection: results from

a randomized, controlled, double-blind, phase 3 program. Clin Infect Dis 62:1380–1389. https://doi.org/10.1093/cid/ciw133
81. Moran GJ, Fang E, Corey GR, Das AF, de Anda C, Prokocimer P (2014) Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis 14:696–705. https://doi.org/10.1016/S1473-3099(14)70737-6
82. Raad I, Darouiche R, Vazquez J, Lentnek A, Hachem R, Hanna H, Goldstein B, Henkel T, Seltzer E (2005) Efficacy and safety of weekly dalbavancin therapy for catheter-related bloodstream infection caused by gram-positive pathogens. Clin Infect Dis 40:374–380. https://doi.org/10.1086/427283
83. Roberts KD, Sulaiman RM, Rybak MJ (2015) Dalbavancin and oritavancin: an innovative approach to the treatment of gram-positive infections. Pharmacotherapy 35:935–948. https://doi.org/10.1002/phar.1641
84. Arendrup MC, Boekhout T, Akova M, Meis JF, Cornely OA, Lortholary O (2014) ESCMID and ECMM joint clinical guidelines for the diagnosis and management of rare invasive yeast infections. Clin Microbiol Infect 20:76–98. https://doi.org/10.1111/1469-0691.12360
85. Bassetti M, Righi E, Ansaldi F, Merelli M, Scarparo C, Antonelli M, Garnacho-Montero J, Diaz-Martin A, Palacios-Garcia I, Luzzati R, Rosin C, Lagunes L, Rello J, Almirante B, Scotton PG, Baldin G, Dimopoulos G, Nucci M, Munoz P, Vena A, Bouza E, de Egea V, Colombo AL, Tascini C, Menichetti F, Tagliaferri E, Brugnaro P, Sanguinetti M, Mesini A, Sganga G, Viscoli C, Tumbarello M (2015) A multicenter multinational study of abdominal candidiasis: epidemiology, outcomes and predictors of mortality. Intensive Care Med 41:1601–1610. https://doi.org/10.1007/s00134-015-3866-2
86. Dalhoff K, Abele-Horn M, Andreas S et al (2018) Epidemiologie, Diagnostik und Therapie erwachsener Patienten mit nosokomialer Pneumonie - Update 2017∗: S3-Leitlinie der Deutschen Gesellschaft für Anästhesiologie und Intensivmedizin e.V., der Deutschen Gesellschaft für Infektiologie e.V., der Deutschen. Pneumologie. https://doi.org/10.1055/s-0043-121734
87. Huang SS, Septimus E, Kleinman K, Moody J, Hickok J, Avery TR, Lankiewicz J, Gombosev A, Terpstra L, Hartford F, Hayden MK, Jernigan JA, Weinstein RA, Fraser VJ, Haffenreffer K, Cui E, Kaganov RE, Lolans K, Perlin JB, Platt R, CDC Prevention Epicenters Program, AHRQ DECIDE Network and Healthcare-Associated Infections Program (2013) Targeted versus universal decolonization to prevent ICU infection. N Engl J Med 368:2255–2265. https://doi.org/10.1056/NEJMoa1207290
88. Keh D, Trips E, Marx G, Wirtz SP, Abduljawwad E, Bercker S, Bogatsch H, Briegel J, Engel C, Gerlach H, Goldmann A, Kuhn SO, Hüter L, Meier-Hellmann A, Nierhaus A, Kluge S, Lehmke J, Loeffler M, Oppert M, Resener K, Schädler D, Schuerholz T, Simon P, Weiler N, Weyland A, Reinhart K, Brunkhorst FM, for the SepNet–Critical Care Trials Group (2016) Effect of hydrocortisone on development of shock among patients with severe sepsis: the HYPRESS randomized clinical trial. JAMA 316:1775–1785. https://doi.org/10.1001/jama.2016.14799
89. Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, Billot L, Correa M, Glass P, Harward M, Joyce C, Li Q, McArthur C, Perner A, Rhodes A, Thompson K, Webb S, Myburgh J, ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group (2018) Adjunctive glucocorticoid therapy in patients with septic shock. N Engl J Med 378:797–808. https://doi.org/10.1056/NEJMoa1705835
90. Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot JP, Siami S, Cariou A, Forceville X, Schwebel C, Martin C, Timsit JF, Misset B, Ali Benali M, Colin G, Souweine B, Asehnoune K, Mercier E, Chimot L, Charpentier C, François B, Boulain T, Petitpas F, Constantin JM, Dhonneur G, Baudin F, Combes A, Bohé J, Loriferne JF, Amathieu R, Cook F, Slama M, Leroy O, Capellier G, Dargent A, Hissem T, Maxime V, Bellissant E, CRICS-TRIGGERSEP Network (2018) Hydrocortisone plus fludrocortisone for adults with septic shock. N Engl J Med 378:809–818. https://doi.org/10.1056/NEJMoa1705716
91. Girardis M, Busani S, Damiani E, Donati A, Rinaldi L, Marudi A, Morelli A, Antonelli M, Singer M (2016) Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the oxygen-ICU randomized clinical trial. JAMA 316:1583–1589. https://doi.org/10.1001/jama.2016.11993
92. Vincent J-L (2005) Give your patient a fast hug (at least) once a day. Crit Care Med 33:1225–1229. https://doi.org/10.1097/01.CCM.0000165962.16682.46
93. Quinlan M (2014) A randomized trial of protocol-based care for early septic shock. J Emerg Med 47:256–257. https://doi.org/10.1016/j.jemermed.2014.06.009
94. Levy MM, Rhodes A, Phillips GS, Townsend SR, Schorr CA, Beale R, Osborn T, Lemeshow S, Chiche JD, Artigas A, Dellinger RP (2015) Surviving Sepsis Campaign: association between performance metrics and outcomes in a 7.5-year study. Crit Care Med 43:3–12. https://doi.org/10.1097/CCM.0000000000000723