Ongoing Peritonitis

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14.1 Introduction

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

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

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

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

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

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

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

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

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

14.2 Diagnosis of Ongoing Peritonitis

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

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

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

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

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

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

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

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

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

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

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

14.3 Therapy

14.3.1 Surgery

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

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

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

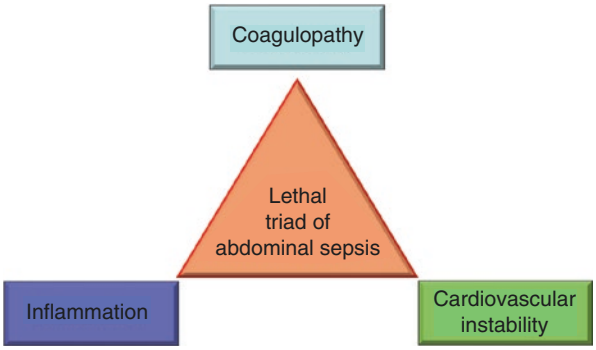

Fig. 14.1 The lethal triad of abdominal sepsis consists of coagulopathy, inflammation, and cardiovascular instability. These clinical conditions are indicators for immediate surgery. In ongoing peritonitis, patients have to be monitored both technically and clinically and carefully be reevaluated during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

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

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

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

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

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

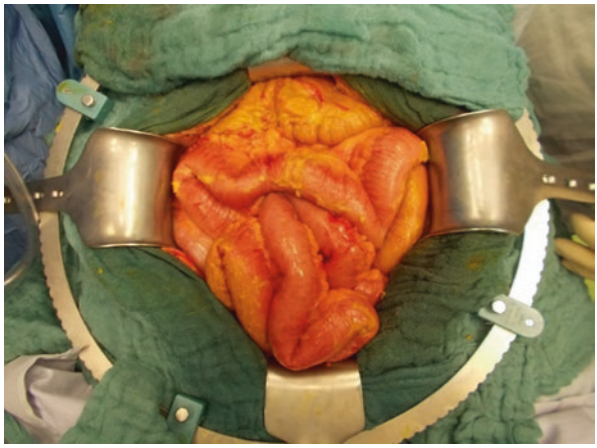

Fig. 14.2 Second look 48 h after initial emergency operation. In cases of persisting or new organ failure, a relaparotomy should be evaluated. If so, surgery should be performed within 48 h after the first operation

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

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

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

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

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

14.3.2 Intensive Care

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

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

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

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

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

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

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

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

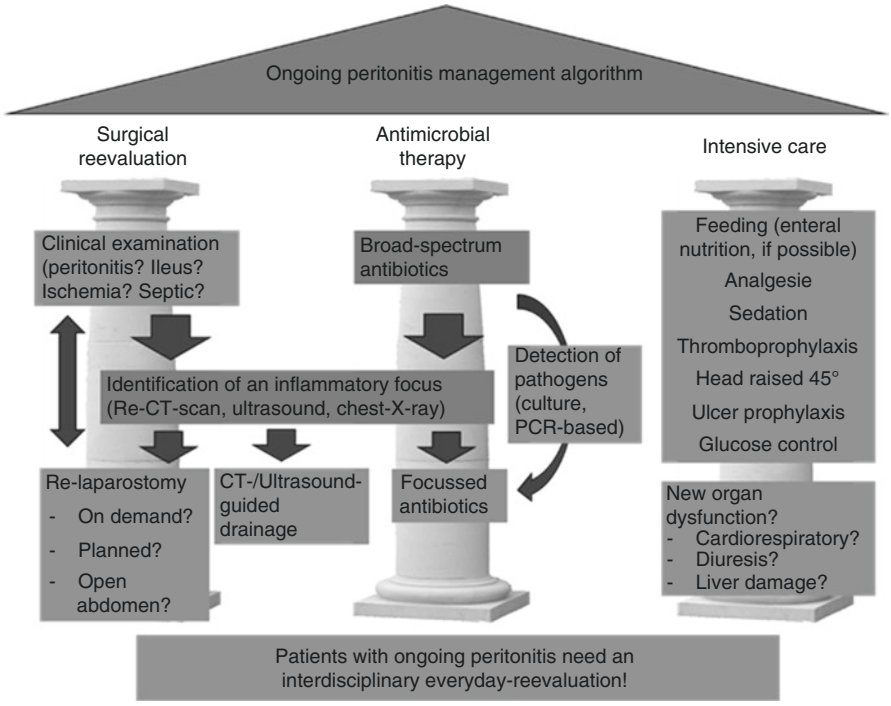

Fig. 14.3 Schematic drawing of the three columns of modern therapy of ongoing peritonitis. Essential is the interdisciplinary everyday reevaluation of the patients [14]. (Reproduced with permission from Springer)

14.3.3 Antimicrobial Therapy

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

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

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

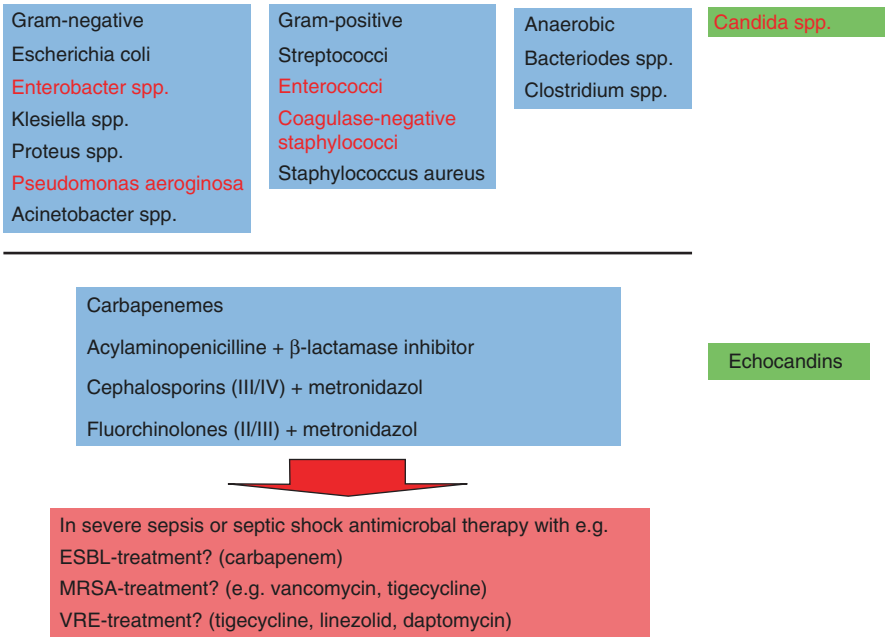

Fig. 14.4 Typical microbial flora in intra-abdominal sepsis. In cases of ongoing peritonitis, the spectrum shifts to nosocomial flora with typical pathogens (in *red*) [14] (Reproduced with permission from Springer)

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

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

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

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

Table 14.2 New-generation antibiotics and their potential indications

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

The corresponding literature is provided in the right column

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

References

1. De Waele JJ. Abdominal sepsis. Curr Infect Dis Rep. 2016;18(8):23.
2. Rotstein OD, Meakins JL. Diagnostic and therapeutic challenges of intraabdominal infections. World J Surg. 1990;14(2):159–66.
3. Sartelli M, Abu-Zidan FM, Ansaloni L, Bala M, Beltrán MA, Biffl WL, et al. The role of the open abdomen procedure in managing severe abdominal sepsis: WSES position paper. World J Emerg Surg. 2015;10:35.
4. Calandra T, Cohen J. The international sepsis forum consensus conference on definitions of infection in the intensive care unit. Crit Care Med. 2005;33(7):1538–48.
5. Dellinger EP, Wertz MJ, Meakins JL, Solomkin JS, Allo MD, Howard RJ, et al. Surgical infection stratification system for intra-abdominal infection. Multicenter trial. Arch Surg. 1985;120(1):21–9.
6. Bohnen JM, Mustard RA, Oxholm SE, Schouten BD. APACHE II score and abdominal sepsis. A prospective study. Arch Surg. 1988;123(2):225–9.
7. Nathens AB, Rotstein OD, Marshall JC. Tertiary peritonitis: clinical features of a complex nosocomial infection. World J Surg. 1998;22(2):158–63.
8. 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.
9. Poeze M, Ramsay G, Gerlach H, Rubulotta F, Levy M. An international sepsis survey: a study of doctors' knowledge and perception about sepsis. Crit Care. 2004;8(6):R409–13.
10. Rubulotta FM, Ramsay G, Parker MM, Dellinger RP, Levy MM, Poeze M. An international survey: public awareness and perception of sepsis. Crit Care Med. 2009;37(1):167–70.
11. Robson W, Beavis S, Spittle N. An audit of ward nurses' knowledge of sepsis. Nurs Crit Care. 2007;12(2):86–92.
12. Moore LJ, Moore F. Early diagnosis and evidence-based care of surgical sepsis. J Intensive Care Med. 2011;28(2):107–17.
13. Bader FG, Schröder M, Kujath P, Muhl E, Bruch H-P, Eckmann C. Diffuse postoperative peritonitis – value of diagnostic parameters and impact of early indication for relaparotomy. Eur J Med Res. 2009;14(11):491–6.
14. Hecker A, Uhle F, Schwandner T, Padberg W, Weigand MA. Diagnostics, therapy and outcome prediction in abdominal sepsis: current standards and future perspectives. Langenbeck's Arch Surg. 2014;399(1):11–22.
15. Henriquez-Camacho C, Losa J. Biomarkers for sepsis. Biomed Res Int. 2014;2014:547818.
16. Welsch T, Frommhold K, Hinz U, Weigand MA, Kleeff J, Friess H, et al. Persisting elevation of C-reactive protein after pancreatic resections can indicate developing inflammatory complications. Surgery. 2008;143(1):20–8.
17. Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. Lancet Infect Dis. 2013;13(5):426–35.
18. Liu D, Su LX, Guan W, Xiao K, Xie LX. Prognostic value of procalcitonin in pneumonia: a systematic review and meta-analysis. Respirology. 2016;21(2):280–8.

19. Uzzan B, Cohen R, Nicolas P, Cucherat M, Perret G-Y. Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: a systematic review and meta-analysis. Crit Care Med. 2006;34(7):1996–2003.
20. Heyland DK, Johnson AP, Reynolds SC, Muscedere J. Procalcitonin for reduced antibiotic exposure in the critical care setting: a systematic review and an economic evaluation. Crit Care Med. 2011;39:1792–9.
21. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet. 2010;375(9713):463–74.
22. de Jong E, van Oers JA, Beishuizen A, Vos P, Vermeijden WJ, Haas LE, et al. 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. 2016;16(7):819–27.
23. Rivers EP, Jaehne AK, Nguyen HB, Papamatheakis DG, Singer D, Yang JJ, et al. 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. 2013;39(2):127–37.
24. Gastmeier P, Schwab F, Behnke M, Geffers C. Less blood culture samples – less infections? Anaesthesist. 2011;60(10):902–7.
25. Opal SM, Garber GE, LaRosa SP, Maki DG, Freebairn RC, Kinasewitz GT, et al. Systemic host responses in severe sepsis analyzed by causative microorganism and treatment effects of drotrecogin alfa (activated). Clin Infect Dis. 2003;37(1):50–8.
26. Huang SS, Septimus E, Kleinman K, Moody J, Hickok J, Avery TR, et al. Targeted versus universal decolonization to prevent ICU infection. N Engl J Med. 2013;368(24):2255–65.
27. Grumaz S, Stevens P, Grumaz C, Decker SO, Weigand MA, Hofer S, et al. Next-generation sequencing diagnostics of bacteremia in septic patients. Genome Med. 2016;8(1):73.
28. Vincent J-L, Brealey D, Libert N, Abidi NE, O'Dwyer M, Zacharowski K, et al. Rapid diagnosis of infection in the critically ill, a multicenter study of molecular detection in bloodstream infections, pneumonia, and sterile site infections. Crit Care Med. 2015;43(11):2283–91.
29. Cohen J, Vincent JL, Adhikari NKJ, Machado FR, Angus DC, Calandra T, et al. Sepsis: a roadmap for future research. Lancet Infect Dis. 2015;15:581–614.
30. Bloos F, Thomas-Rüddel D, Rüddel 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.
31. Hecker A, Schneck E, Rohrig R, Roller F, Hecker B, Holler J, et al. The impact of early surgical intervention in free intestinal perforation: a time-to-intervention pilot study. World J Emerg Surg. 2015;10:54. eCollection 2015
32. Vester-Andersen M, Lundstrøm LH, Buck DL, Møller MH. Association between surgical delay and survival in high-risk emergency abdominal surgery. A population-based Danish cohort study. Scand J Gastroenterol. 2016;51(1):121–8.
33. Buck DL, Vester-Andersen M, Møller MH. Surgical delay is a critical determinant of survival in perforated peptic ulcer. Br J Surg. 2013;100(8):1045–9.
34. Gajic O, Urrutia LE, Sewani H, Schroeder DR, Cullinane DC, Peters SG. Acute abdomen in the medical intensive care unit. Crit Care Med. 2002;30(6):1187–90.
35. van Ruler O, Mahler CW, Boer KR, Reuland EA, Gooszen HG, Opmeer BC, et al. Comparison of on-demand vs planned relaparotomy strategy in patients with severe peritonitis: a randomized trial. JAMA. 2007;298(8):865–72.
36. Kiewiet JJS, van Ruler O, Boermeester MA, Reitsma JB. A decision rule to aid selection of patients with abdominal sepsis requiring a relaparotomy. BMC Surg. 2013;13:28.
37. van Ruler O, Lamme B, Gouma DJ, Reitsma JB, Boermeester M. Variables associated with positive findings at relaparotomy in patients with secondary peritonitis. Crit Care Med. 2007;35(2):468–76.
38. Koperna T, Schulz F. Relaparotomy in peritonitis: Prognosis and treatment of patients with persisting intraabdominal infection. World J Surg. 2000;24(1):32–7.
39. Hecker A, Hecker B, Hecker M, Riedel JG, Weigand MA, Padberg W. Acute abdominal compartment syndrome: current diagnostic and therapeutic options. Langenbeck's Arch Surg. 2016;401(1):15–24.

40. Kirkpatrick AW, Roberts DJ, De Waele J, Jaeschke R, Malbrain MLNG, De Keulenaer B, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive Care Med. 2013;39:1190–206.
41. Yuan Y, Ren J, He Y. Current status of the open abdomen treatment for intra-abdominal infection. Gastroenterol Res Pract. 2013;2013:Article ID 532013.
42. Chen Y, Ye J, Song W, Chen J, Yuan Y, Ren J. 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;2014:784056.
43. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41(2):580–637.
44. Girardis M, Busani S, Damiani E, Donati A, Rinaldi L, Marudi A, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the oxygen-ICU randomized clinical trial. JAMA. 2016;316(15):1583–9.
45. Keh D, Trips E, Marx G, Wirtz SP, Abduljawwad E, Bercker S, et al. Effect of hydrocortisone on development of shock among patients with severe sepsis: the HYPRESS randomized clinical trial. JAMA. 2016;316(15):1583–9.
46. Gordon AC, Perkins GD, Singer M, McAuley DF, Orme RML, Santhakumaran S, et al. Levosimendan for the prevention of acute organ dysfunction in sepsis. N Engl J Med. 2016;375(17):1638–48.
47. Vincent J-L. Give your patient a fast hug (at least) once a day. Crit Care Med. 2005;33(6):1225–9.
48. Abdul-Aziz MH, Sulaiman H, Mat-Nor MB, Rai V, Wong KK, Hasan MS, et al. Beta-lactam infusion in severe sepsis (BLISS): a prospective, two-centre, open-labelled randomised controlled trial of continuous versus intermittent beta-lactam infusion in critically ill patients with severe sepsis. Intensive Care Med. 2016;42:1535–45.
49. Hackel MA, Badal RE, Bouchillon SK, Biedenbach DJ, Hoban DJ. 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. 2015;16(3):298–304.
50. Awad SS, Rodriguez AH, Chuang YC, Marjanek Z, Pareigis AJ, Reis G, et al. A phase 3 randomized double-blind comparison of ceftobiprole medocaril versus ceftazidime plus linezolid for the treatment of hospital-acquired pneumonia. Clin Infect Dis. 2014;59(1):51–61.
51. Kiang TKL, Wilby KJ, Ensom MHH. A critical review on the clinical pharmacokinetics, pharmacodynamics, and clinical trials of ceftaroline. Clin Pharmacokinet. 2015;54:915–31.
52. Zhong NS, Sun T, Zhuo C, D'Souza G, Lee SH, Lan NH, et al. 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. 2015;15(2):161–71.
53. Solomkin J, Hershberger E, Miller B, Popejoy M, Friedland I, Steenbergen J, et al. 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. 2015;60(10):1462–71.
54. Wagenlehner FM, Umeh O, Steenbergen J, Yuan G, Darouiche RO. 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. 2015;385(9981):1949–56.
55. Vazquez J, González Patzán LD, Stricklin D, Duttaroy DD, Kreidly Z, Lipka J, et al. 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. Curr Med Res Opin. 2016;28:1921–31.
56. Mazuski JE, Gasink LB, Armstrong J, Broadhurst H, Stone GG, Rank D, et al. 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. 2016;62(11):1380–9.

57. Moran GJ, Fang E, Corey GR, Das AF, De Anda C, Prokocimer P. 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. 2014;14(8):696–705.
58. Raad I, Darouiche R, Vazquez J, Lentnek A, Hachem R, Hanna H, et al. Efficacy and safety of weekly dalbavancin therapy for catheter-related bloodstream infection caused by gram-positive pathogens. Clin Infect Dis. 2005;40(3):374–80.
59. Roberts KD, Sulaiman RM, Rybak MJ. Dalbavancin and oritavancin: an innovative approach to the treatment of gram-positive infections. Pharmacotherapy. 2015;35(10):935–48.
60. Bassetti M, Righi E, Ansaldi F, Merelli M, Scarparo C, Antonelli M, et al. A multicenter multinational study of abdominal candidiasis: epidemiology, outcomes and predictors of mortality. Intensive Care Med. 2015;41(9):1601–10.
61. Arendrup MC, Boekhout T, Akova M, Meis JF, Cornely OA, Lortholary O, et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of rare invasive yeast infections. Clin Microbiol Infect. 2014;20(S3):76–98.
62. Timsit J-F, Azoulay E, Schwebel C, Charles PE, Cornet M, Souweine B, et al. Empirical micafungin treatment and survival without invasive fungal infection in adults with ICU-acquired sepsis, Candida colonization, and multiple organ failure: the EMPIRICUS randomized clinical trial. JAMA. 2016;316(15):1555–64.