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MY PAPER 20 YEARS LATER

Therapeutic management of peritonitis: a comprehensive guide for intensivists

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Abstract

Purpose: The management of peritonitis in critically ill patients is becoming increasingly complex due to their changing characteristics and the growing prevalence of multidrug-resistant (MDR) bacteria.

Methods: A multidisciplinary panel summarizes the latest advances in the therapeutic management of these critically ill patients.

Results: Appendicitis, cholecystitis and bowel perforation represent the majority of all community-acquired infections, while most cases of healthcare-associated infections occur following suture leaks and/or bowel perforation. The micro-organisms involved include a spectrum of Gram-positive and Gram-negative bacteria, as well as anaerobes and fungi. Healthcare-associated infections are associated with an increased likelihood of MDR pathogens. The key elements for success are early and optimal source control and adequate surgery and appropriate antibiotic therapy. Drainage, debridement, abdominal cleansing, irrigation, and control of the source of contamination are the major steps to ensure source control. In life-threatening situations, a "damage control" approach is the safest way to gain time and achieve stability. The initial empirical antiinfective therapy should be prescribed rapidly and must target all of the micro-organisms likely to be involved, including MDR bacteria and fungi, on the basis of the suspected risk factors. Dosage adjustment needs to be based on pharmacokinetic parameters. Supportive care includes pain management, optimization of ventilation, haemodynamic and fluid monitoring, improvement of renal function, nutrition and anticoagulation.

Conclusions: The majority of patients with peritonitis develop complications, including worsening of pre-existing organ dysfunction, surgical complications and healthcare-associated infections. The probability of postoperative complications must be taken into account in the decision-making process prior to surgery.

Keywords: Peritonitis, Source control, Multidrug-resistant bacteria, Fungal infection, Postoperative complications, Intra-abdominal hypertension

Introduction

Despite the considerable improvement in perioperative care and empirical antibiotic therapy over recent decades, community-acquired and healthcare-associated peritonitis remain a leading cause of death, morbidity and resource utilization in ICU patients. Their management is becoming increasingly complex because of their changing characteristics, ageing of the population, higher rates of comorbid conditions and the growing prevalence of multidrug-resistant (MDR) bacteria. Several medical specialities are involved to ensure a combined approach to timely surgical source control and adequate anti-infective treatment. In this review, a multidisciplinary panel summarizes the latest advances in the therapeutic management of these critically ill patients.

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Take-home message: Critically ill patients with peritonitis require an early combined operative and medical approach. The key elements for success are appropriate anti-infective therapy (in terms of the most appropriate drug, at an adequate dosage with satisfactory tissue penetration to target the microorganisms concerned) and early and optimal source control and adequate surgery, comprising a "damage control" approach in life-threatening situations.

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Epidemiology of peritonitis in the ICU

Peritonitis is the second leading cause of ICU admission after complicated pneumonia, accounting for 5.8–10 % of all patients [1, 2] and almost 20 % of infected patients [2]. Appendicitis, cholecystitis and bowel perforation (including colon, small bowel and gastroduodenal) represent more than 80 % of all community-acquired infections [3–5]. Most cases of healthcare-associated infections occur following suture leaks and/or colorectal, gastroduodenal and small bowel perforation [3, 4]. Despite technical improvements, these proportions have remained stable over recent decades. Interestingly, recent studies have reported increasing rates (about 50 % of patients) of healthcare-associated peritonitis, mainly related to postoperative infection [6].

Supportive and perioperative care

Supportive care of vital organs is essential in patients with peritonitis whenever severe sepsis is suspected, starting before the surgical procedure and continued for as long as necessary postoperatively [7–10]. Supportive care includes pain management, sedation, optimization of ventilation, haemodynamic and fluid monitoring, improvement of renal function, nutrition and anticoagulation. Patients can be stratified on the basis of risk factors, comprising not only severity of illness (assessed by APACHE II, SOFA or Mannheim scores) [9] but also individual patient-related factors such as age and comorbidities (assessed by ASA or Charlson scores) in order to tailor perioperative monitoring and management, and to assess prognosis [2, 4, 6, 11].

Pain management depends on the extent of tissue damage. Multimodal analgesia is recommended to decrease the adverse effects related to the use of a single agent administered at high doses, and should be given according to adequacy of pain relief, regularly assessed by an appropriate scale [12]. The drugs most commonly used include non-opioid analgesics alone or combined with opioids at doses determined by titration. Sedation is another important issue, especially in elderly patients, in whom close monitoring and selection of short-acting agents could shorten the time to extubation [13].

Acute respiratory failure is frequently observed during the postoperative care, mainly because of worsening of the underlying disease, atelectasis, pneumonia or acute respiratory distress syndrome [2, 4, 14]. The optimal volume, pressure level and positive expiratory pressure adjustments remain controversial in mechanically ventilated patients. Non-invasive positive pressure ventilation has been proposed as an alternative option in the less severe cases [15].

Haemodynamic monitoring and fluid management are also challenging issues. About 10 % of all patients with diffuse peritonitis develop septic shock, associated with a significantly higher mortality than that observed in haemodynamically stable patients [2, 16, 17]. The need for fluid loading is mainly assessed by cardiac output and oxygen delivery measurements using various devices, none of which have been shown to be superior to the others. The use of dynamic parameters (e.g. variations of stroke volume or pulse pressure) and continuous measurements are sensitive methods to guide fluid therapy and titration of vasoactive agents. Crystalloids are recommended for initial fluid resuscitation, but when large volumes of fluid are administered, interstitial overload and hyperchloraemic acidosis limit their prescription, leading to the use of colloids as one of the only available alternatives [18].

Acute kidney injury (AKI) is a common complication resulting from functional, metabolic or haemodynamic disorders leading to acute tubular necrosis [2, 4, 14]. Reversible causes require special attention and supportive therapies (e.g. fluids, vasoactive agents, interruption of nephrotoxic drugs) [19]. Subclinical AKI is a clearly recognized early stage of renal failure, at which no elevation of serum creatinine and/or decreased urinary output can be confirmed by available biomarkers [19]. There is no evidence to support the superiority of continuous renal replacement therapy over intermittent haemodialysis apart from easier management of fluid balance [9].

Nutrition support plays a crucial role by supplying energy and preserving body proteins, but this practice has not been extensively investigated. Enteral or parenteral nutrition can usually be implemented during the first 48 h following ICU admission, once the patient's condition has been stabilized [20]. Enteral feeding can be administered via various routes including placement of a feeding tube into the bowel remnant or in the jejunum below the anastomotic leak. Most studies recommend a protein intake ranging between 1.2 and 3.0 g/kg/day to improve nitrogen balance [21]. This broad range reflects the insufficient level of available evidence as well as the difficulty of assessing the efficacy of protein intake. Many issues remain unresolved in ICU patients with peritonitis regarding the appropriate timing of nutrition support, enteral versus parenteral routes, the need for micronutrients, and the use of biomarkers and scoring systems to identify patients at risk [20].

Deep vein thrombosis prophylaxis is recommended in septic postoperative patients [9]. Subcutaneous low molecular weight heparin (LMWH) is the method of choice, while unfractionated heparin or LMWH with a low degree of renal metabolism is preferred in the presence of renal failure. The therapeutic effect must be monitored and doses can be adjusted according to the

Table 1 Step by step approach for the treatment of patients with peritonitis

Phase	Goal	Manoeuvre
Initial	Severity assessment	Applying score of sepsis
	Sepsis containment	Adequate and early empirical antibiotic therapy
	Preparing for surgery	Adequate haemodynamic monitoring and fluid management
Source control		
1st	SSI prevention (incisional)	Wound protection
	Microbiological diagnosis	Peritoneal cultures
	Decrease peritoneal inoculum	Initial abdominal cleansing
	Peritonitis assessment	Looking for the source of the infection
2nd	Source control	Simple closure
		Resection ± intestinal anastomosis
		Stoma
	Decrease peritoneal inoculum	Final abdominal cleansing
3rd	Abdominal closure	Primary or deferred abdominal wall closure
Final	Treatment of residual inoculum and perioperative resuscitation	Adequate empirical antibiotic therapy
		Endorsement to Survival Sepsis Campaign principles

SSI surgical site infection

response. When pharmacological therapy is contraindicated, mechanical methods are used.

Importance of source control

The term source control was first used in the early twentieth century and has been the subject of renewed interest with the Surviving Sepsis Campaign Guidelines [9]. Foci of infection readily amenable to source control measures are mainly intra-abdominal sites. Drainage of abscesses, debridement of infected necrotic tissues, removal of potentially infected devices, abdominal compartment cleansing, irrigation and definitive control of a source of ongoing microbial contamination are the usual consecutive steps to ensure source control (Table 1).

Few guidelines have been published for the surgical management of peritonitis, as most strategies depend on intraoperative findings, severity of disease, time to source control and underlying diseases. The surgical dilemma usually concerns conservative vs operative management, but also laparoscopic vs open surgery. Minimally invasive or conservative approaches including percutaneous and endoscopic treatments have been advocated by many authors for the management of uncomplicated cases (diverticulitis, appendicitis, cholecystitis, etc.). Percutaneous drainage may be especially relevant in complex cases such as hostile abdomen provided the collections are technically drainable. In critically ill patients requiring individualized management, especially when surgery is delayed, the surgeon must perform "damage control" surgery, a concept derived from trauma and applied to sepsis, which may include open abdomen management, exteriorization and colostomies, drainage, stapled resections without anastomosis, etc.

The technical aspects of timely and adequate surgical management are critical, although the quality of source control is difficult to evaluate [22] [electronic supplementary material (ESM) Table S1]. Without adequate surgical source control, mortality rates can reach almost 100 %. Early management is the second key to successful treatment [23]. Short-term outcomes appear to be essentially related to the "time" factor.

Surgery provides an ideal opportunity for microbiological samples, as interpretation of samples collected from suction drains and drainage systems is difficult or misleading. Routine intraoperative cultures remain debated in mild-to-moderate community-acquired peritonitis and in patients with a low suspicion of multidrug resistance. In these cases, intraoperative cultures may be useful as a baseline measure to monitor subsequent emergence of epidemiologically important microorganisms [8, 10]. On the contrary, it is usually recommended to obtain peritoneal fluid cultures in the most severe patients, even with community-acquired peritonitis, in the case of previous antibiotic therapy and in all healthcare-associated infections [5, 7, 8, 10].

Source control can be completed by a single operation, but many studies have reported that additional procedures are required to remove persistent clusters of infection. Systematic reoperations are no longer recommended in routine practice [7, 8, 10]. Progression or failure of resolution of organ dysfunction is highly suggestive of persistence of disease and requires re-evaluation [8, 10].

Organ-specific management

The concepts of adequate, inadequate and difficult types of source control depend on the specific organ constituting the source of infection (Table 2). Fresh, small perforated duodenal ulcer is best treated by laparoscopy-assisted intracorporeal suture closure. In protracted peritonitis secondary to large, chronic and/or friable peptic ulcers in an unstable patient, quick and safe open repair via a conservative midline incision may suffice [24, 25]. As a result of the serious consequences of protracted infection after bariatric surgery, considerable attention has been recently paid to early detection and treatment (either laparoscopic or endoscopic) of any leaks [26].

Peritonitis due to small bowel perforation is not uncommon. In faecal peritonitis or when a damage control open-abdomen technique has been used, primary anastomosis should be delayed until improvement of the peritoneal compartment and the patient's general condition. In such circumstances, the principles of damage control surgery with temporary ostomy should prevail [27]. The most common abdominal source after complicated appendicitis is probably colorectal [6]. Complicated diverticulitis is the leading cause of colonic peritonitis. Radical source control (Hartmann's procedure) from perforated, laparoscopic washout and intra-abdominal drainage has raised much attention as a low-grade, easy, straightforward approach to source control [28]. Recent evidence is clearly against less invasive procedures in patients with complicated diverticulitis and diffuse peritonitis [29, 30]. This policy should also be applied to leaks following colorectal surgery with temporary ostomy.

Management of postoperative complications

Surgical operations can cause significant morbidity and mortality as a result of postoperative complications [16, 17]. Peritonitis may decompensate and worsen pre-existing organ dysfunction, resulting in increased mortality. More than 70 % of these patients develop complications [16]. The probability of postoperative complications must be taken into account in the decision-making process prior to surgery. Several scoring systems have been proposed to predict complications, but with disappointing results [2, 16, 17, 31]. Table 3 presents an overview of surgical and non-surgical complications in peritonitis and their frequency.

An association is very commonly observed between the characteristics of the initial surgical procedure and postoperative surgical complications [16, 17, 32]. Surgical site infections (SSI), among the most common surgical complications, are associated with the extent of stool contamination of the wound, surgical techniques and the patient's comorbidities [17]. Superficial and deep SSI must be treated by incision and drainage. Organ/space SSI require more intensive intervention (CT-guided drainage, relaparotomy), as SSI are usually a sign of an occult intra-abdominal problem such as anastomotic leak. Rectal stump insufficiency, dehiscence of the abdominal fascia and colostomy are less common complications of emergency surgery and can be repaired by limited invasive procedures.

Surgical complications usually require reoperation. The extent of source control interventions for complications varies substantially: from incision and drainage of a superficial surgical site infection to CT-guided drainage of an intra-abdominal abscess and relaparotomy comprising various types of surgical interventions. The surgical procedure may range from "simple" lavage to resection of parts of the small or large bowel and may require temporary or permanent ileostomy or colostomy, possibly leaving the abdomen open.

The role of an open abdomen technique in the management of severe peritonitis remains controversial [33]. The abdominal contents are exposed and bowel loops are protected by placement of the omentum majus or a specific artificial layer and a vacuum sponge. Temporary coverage usually comprises negative pressure devices (maximum negative pressure of minus 75 mmHg) to prevent abdominal compartment syndrome (ACS) and allows a re-look every 24–48 h.

Tertiary peritonitis is persistent intra-abdominal infection without a surgically treatable focus, following previous surgery and source control [14, 31]. This form of nosocomial peritonitis is caused by a specific spectrum of MDR microorganisms, including enterococci, *Enterobacteriaceae*, pseudomonas and candida. Tertiary peritonitis does not require surgery, but only a non-contributive reoperation can confirm the diagnosis.

A high rate of healthcare-associated infections is observed in patients with peritonitis. Up to 30 % of patients with abdominal sepsis develop pneumonia, which can be associated with unplanned re-intubation, ARDS and significant mortality rates [2]. Urinary tract infections are documented in 2–8 % of patients with diffuse peritonitis [2, 16].

Intra-abdominal hypertension

Patients with peritonitis, especially in the presence of organ failure, present many of the known risk factors for intra-abdominal hypertension (IAH) [34]. The two main determinants of increased intra-abdominal pressure (IAP) may contribute to the development of IAH and ultimately ACS: intra-abdominal volume may be increased as a result of ischaemia/reperfusion-related oedema, postoperative fluid accumulation and ileus, whereas abdominal wall compliance is decreased as a result of surgical trauma, oedema and postoperative pain.

Table 2 Quality of peritonitis control derived from different organ-specific infection sources

Infection source	Quality of source control		
	Accepted or adequate	Risky or inadequate	Difficult/controversial management
Gastroduodenal	Perforated duodenal ulcer: OPEN: simple closure LAP: simple closure for fresh, small and non-friable ulcer	Perforated duodenal ulcer: LAP: simple closure for protracted, large and friable ulcer	Postoperative leak of duodenal stump
Hepatobiliopancreatic	Perforated cholecystitis: OPEN or LAP cholecystectomy in stable patients OPEN partial cholecystectomy in patients with shock- and/or sepsis-related intraoperative coagulopathy	Perforated cholecystitis: LAP complete cholecystectomy in patients with shock- and/or sepsis-related intraoperative coagulopathy	Infected pancreatic necrosis
Appendix	Perforated appendicitis: OPEN appendectomy LAP appendectomy in obese patients	Perforated appendicitis: Prolonged LAP, non-converted appendicectomy with friable necrotic appendix, diffuse peritonitis or patients in septic shock	Perforated appendix with diffuse peritonitis in a patient with previous abdominal surgery and peritoneal adhesions
Small bowel	Resection and primary anastomosis in stable patients Temporary stoma for neglected laceration or oedematous intestine	Resection and primary anastomosis in patients with septic shock or longstanding perforation with oedematous intestine	Mesenteric ischaemia
Colorectal	OPEN: Hartmann procedure OPEN: resection and primary anastomosis in stable patients	LAP washout for perforated Hinchey III diverticulitis OPEN resection and primary anastomosis for faecaloid peritonitis or in septic shock	Mesenteric ischaemia

OPEN surgical procedure performed via laparotomy, *LAP* laparoscopy

Table 3 Surgical and non-surgical infectious complications in patients with diffuse secondary peritonitis

Complications	Clinical setting	Frequency	Treatment
Severe bleeding	Haemodynamic instability Significant blood loss	++	Reoperation, bleeding control
SSI (superficial/deep)	Putrid wound secretion	+++	Incision and drainage
SSI (organ space)	Faecal wound secretion	++	Relaparotomy, source control, open wound therapy
Dehiscence of abdominal fascia	Fascia necrosis/abdominal compartment syndrome	+	Relaparotomy, mesh implant/open abdomen/negative pressure therapy
Intra-abdominal abscess	Evidence on imaging (CT, US)	+/++	CT-guided drainage
Anastomotic leakage	Evidence on imaging, drain fluid	+/++	Relaparotomy, source control/drainage
Rectal stump insufficiency	Putrid anal secretion following Hartmann procedure	(+)	Transrectal drainage, negative pressure therapy
Rupture of stoma	Stool in soft tissue around stoma	(+)	Reoperation, reinsertion of stoma
Tertiary peritonitis	Persistent abdominal infection despite adequate source control	+	Antibiotic and/or antifungal treatment Source control sufficient?
Septic shock	Haemodynamic instability	++	Haemodynamic stabilization, anti-infective treatment Diagnostic investigations for source of infection
Pneumonia	Respiratory insufficiency, unplanned (re)intubation	+++	Antibiotic therapy
Urinary tract infection (UTI)	Lower UTI or pyelonephritis	+	Antibiotic therapy, source control

(+) very rare (<1 %), + rare (1–5 %), ++ common (5–10 %), +++ very common (>10 %)

All these factors, particularly fluid resuscitation and surgery, may play a role in the development of IAH.

IAH has been found to impair gut perfusion [35], causing structural changes in the gut [36] and bacterial translocation [37]. In animal studies, IAH has been found to delay healing of colonic anastomoses (ESM Fig. S1). In summary, IAH has multiple effects that extend beyond the abdominal cavity.

IAH should be anticipated and IAP monitoring is advised in patients with severe sepsis or septic shock. When IAH develops, fluid administration should be considered carefully, as parameters such as urinary output are unreliable to assess organ perfusion.

Adequate analgesia and removal of constrictive bandages can help to increase abdominal wall compliance. Postoperative bleeding or fluid accumulation may accentuate IAH and ultrasound may be helpful to identify these lesions and guide drainage. Postoperative ileus and gut distension are other common contributors to IAH, for which nasogastric drainage and suctioning may be required. If these interventions are unsuccessful and ACS ensues, abdominal decompression with open abdomen treatment may be necessary.

In some situations, an intraoperative decision to perform temporary abdominal closure may be preferable. Consequently, postoperative IAP monitoring is mandatory to guide subsequent abdominal closure.

Microbiological considerations

The variety of pathogens isolated in the context of peritonitis represents a limited part of gastrointestinal flora. Culture results cannot discriminate contaminating bacteria from true pathogens. The microorganisms involved include a spectrum of Gram-positive and Gram-negative bacteria, as well as anaerobes and fungi, with a highly variable mix depending on several factors including the site of perforation (ESM Fig. S2) [3]. Gram-negative and anaerobic bacteria are increasingly involved, ranging from about 15–20 % in gastroduodenal perforation to about 80 % in appendicitis-related peritonitis. The proportion of cultures isolating Gram-positive bacteria does not vary substantially according to the primary source of perforation and remains about 30–40 %.

Healthcare-associated infections are associated with an increased likelihood of pathogens with reduced susceptibility to standard ("first-line") antibiotic regimens. The term MDR therefore covers methicillin-resistant *Staphylococcus aureus*, coagulase-negative staphylococci, vancomycin-resistant enterococci, extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*, quinolone-resistant *Escherichia coli*, and non-fermenting Gram-negative bacteria such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Factors predisposing to MDR bacteria include corticosteroid use, recent exposure to broad-spectrum antibiotics (less than 3 months),

underlying conditions such as liver disease, pulmonary disease, organ transplantation and a length of hospitalization greater than 5 days [38–40]. However, geographical and local (in-hospital) ecology also plays a key role in this setting, hence the critical importance of local antibiotic susceptibility testing for both bacteria and fungi. For example, patients with a recent history of travelling in regions known to have particular resistance problems deserve special attention (Table 4).

Antibiotic therapy in peritonitis: 10 years of consensus

Over the last decade, several guidelines have been published for antibiotic therapy in community-acquired and healthcare-associated infections (Table 5) [5, 7, 8, 10, 41–43]. The most appropriate initial empirical therapy should be prescribed early (ideally preoperatively for sepsis containment and SSI prevention) and must target all of the microorganisms likely to be involved, including MDR bacteria, on the basis of the suspected risk factors. Broad-spectrum treatments are recommended in critically ill patients, but targets are different in community-acquired and healthcare-associated infections. Coverage of enterococci and MDR bacteria is not recommended in patients with community-acquired peritonitis, but should be applied in patients with septic shock who have received prolonged cephalosporin therapy, in immunosuppressed patients and in patients with recurrent intra-abdominal infections. The community and/or hospital ecology needs to be considered when starting antimicrobial therapy: the recent spread of carbapenemases in *Enterobacteriaceae* has raised a serious concern worldwide, similar to that raised by the pattern of spread of ESBL [7, 8, 10, 41–43].

Dosage adjustment needs to be based on pharmacokinetic parameters reported in patients with severe sepsis as few data are available on peritoneal diffusion of antibiotics. De-escalation has not been shown to be detrimental in patients with peritonitis. Antibacterial therapy is usually administered for 5–7 days [44] after adequate source control. Antibiotics can be discontinued once clinical and laboratory signs of infection have resolved. The use of procalcitonin to determine the duration of antibiotic therapy has not been assessed in peritonitis and remains debated [10]. Only a few guidelines have proposed specific regimens in patients with documented beta-lactam allergy.

Peritonitis in obese patients

While the prevalence of community-acquired peritonitis in obese patients appears to be similar to that observed in the overall population, a growing number of perioperative complications and postoperative or short-term adverse outcomes following bariatric surgery have been reported over recent years. The surgical complications most commonly requiring ICU admission include fistulas and anastomosis leaks [45].

Only limited pharmacological data are available in morbidly obese patients and the appropriate doses of anti-infective agents remain controversial. As in other septic patients, pharmacokinetic variables may be altered during peritonitis in obese patients (ESM Table S2). Volume of distribution (Vd) usually increases as a result of capillary leak syndrome, increased cardiac output or fluid resuscitation. Antibiotic clearance (Ac) may also either increase because of increased glomerular filtration or decrease because of organ failure [46]. However, obesity may further increase Vd as a result of increased lean body mass and increased adipose tissue. Obesity may also increase Ac as a result of increased kidney mass and global filtration, or decrease Ac as a result of chronic hypertensive or diabetic nephropathy. Hydrophilic and lipophilic antibiotics differ in terms of their pharmacokinetics and pharmacokinetic parameters are modified by obesity [47]. Since 30 % of adipose tissue is water, an empirical, but never validated, approach is to use the Devine formula to calculate ideal body weight (IBW), to which is added a dosing weight correction factor of 0.4 times the difference between total body weight (TBW) and IBW ($IBW + 0.4 \times [TBW - IBW]$) to estimate adjusted body weight, on which the dosage of hydrophilic antibiotics should be based [47].

Standard drug regimens can therefore potentially result in a higher rate of inadequate serum drug concentrations in critically ill obese patients, which may be responsible for increased treatment failure or emergence of bacterial resistance. A study in critically ill obese patients receiving cefepime, piperacillin/tazobactam or meropenem at standard dosing regimens demonstrated considerable variability of antibiotic concentrations, resulting in insufficient plasma concentrations in 32 % of patients and overdosed concentrations in 25 % [48], and 35 % of obese patients treated with meropenem had concentrations below therapeutic targets. In the same study, obese patients on continuous renal replacement therapy were more likely to have supratherapeutic and less likely to have insufficient beta-lactam antibiotic concentrations [48].

High doses of piperacillin/tazobactam, at least 4.5 g intravenously every 6 h, are commonly used in obese patients and longer infusion times may be required [49]. The upper limit of the normal dose range of cephalosporins is recommended in these patients [50]. The upper limit of the normal dose range of carbapenems (6–8 g/day meropenem, with extended infusions over approximately 3–4 h) is also recommended [51], while no dose

Table 4 Potential pathogens in peritonitis

Microorganism	Predisposing clinical condition requiring coverage beyond standard first-line antimicrobial therapy	Resistance considerations
Gram-positive bacteria		
Streptococci	None. Covered by first-line antibiotic regimen	No clinically relevant resistance problem
Enterococci	Septic shock, failure of early surgical source control, recent antibiotic exposure (particularly prolonged cephalosporin treatment), immunosuppression and prosthetic heart valves	Resistance likely in healthcare-associated infections, especially when caused by *E. faecium*. Ampicillin resistance and associated production of beta-lactamases are a concern in some geographical areas, as well as glycopeptide resistance
Coagulase-negative staphylococci	Clinical relevance uncertain	Methicillin-resistance likely in healthcare-associated infection
Staphylococcus aureus	None. Methicillin-susceptible *S. aureus* is covered by first-line antibiotic regimen	Methicillin-resistance possible in healthcare-associated infection
Gram-negative bacteria		
Enterobacteriaceae (*Escherichia coli*, *Enterobacter* spp., *Klebsiella* spp., *Serratia* spp., *Proteus* spp., etc.)	None. Non-extended-spectrum beta-lactamase (ESBL)-producing strains are covered by first-line antibiotic regimen	ESBL-producing strains likely in healthcare-associated infection and should be considered in patients with a history of recent travel in regions with high prevalence (Egypt, Thailand, India). Fluoroquinolone-resistance of *E. coli* may be as high as 20 % in some geographical areas
Non-fermenting Gram-negative bacteria (*Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, etc.)	Healthcare-associated infection, especially with length of hospital stay >5 days. Recent antibiotic exposure. Chronic underlying diseases leading to immunocompromised status (e.g. due to corticosteroid use)	Multidrug resistance most likely in healthcare-associated infection
Anaerobe bacteria (*Bacteroides fragilis*, *Clostridium* spp., etc.)	None. Covered by first-line antibiotic regimen	High rates of resistance to clindamycin and cefoxitin in certain geographical areas. Resistance to metronidazole is rare
Candida spp.	Immunodeficiency and prolonged antibiotic exposure. Tertiary peritonitis following failure of source control, especially in peritonitis originating from upper GI tract perforation	Selection towards *Candida* non-albicans spp. with dose-dependent susceptibility to fluconazole in patients with prior fluconazole exposure

Table 5 Empirical antibiotic regimens proposed in recent guidelines for community-acquired and healthcare-associated infections

Expert groups	Community-acquired peritonitis		Healthcare-associated peritonitis	
	Mild to moderate cases	Severe or at-risk cases	Mild to moderate cases	Severe or at-risk cases
2006—Belgium [42]	Amoxicillin/clavulanate, cefuroxime + metronidazole Fluoroquinolones + metronidazole		Piperacillin/tazobactam or carbapenems Allergy to β-lactams: fluoroquinolones or aztreonam + metronidazole ± vancomycin	
2009—Spain [41]	Amoxicillin/clavulanate, ceftriaxone or cefotaxime + metronidazole, ertapenem In case of β-lactams allergy: gentamicin or aztreonam + metronidazole, tigecycline For suspected MDR *Enterobacteriaceae* ertapenem or tigecycline	Piperacillin/tazobactam or imipenem, meropenem or tigecycline (+ antipseudomonal drug in case of septic shock) In case of β-lactam allergy: tigecycline	Piperacillin/tazobactam or imipenem, meropenem or tigecycline In case of β-lactam allergy: tigecycline	Imipenem or meropenem + linezolid or daptomycin or glycopeptide Tigecycline + ceftazidime or amikacin
2009—USA [8]	Monotherapy: cefoxitin, ertapenem, moxifloxacin, tigecycline or ticarcillin/clavulanate Combination therapy: cefazolin, cefuroxime, ceftriaxone, cefotaxime, ciprofloxacin or levofloxacin + metronidazole	Monotherapy: imipenem, meropenem, doripenem or piperacillin/tazobactam Combination therapy: cefepime, ceftazidime, ciprofloxacin, or levofloxacin + metronidazole	Piperacillin/tazobactam or imipenem, meropenem ± aminoglycoside Ceftazidime or cefepime + metronidazole ± aminoglycoside MRSA infection: vancomycin	
2010—Canada [7]	Mild to moderate cases: monotherapy: cefoxitin, amoxicillin/clavulanate, ticarcillin/clavulanate, ertapenem, moxifloxacin, tigecycline Combination therapy: cefuroxime, ceftriaxone, cefotaxime or ciprofloxacin + metronidazole	Piperacillin/tazobactam or Imipenem or meropenem ± aminoglycoside ceftazidime or cefepime or ciprofloxacin + metronidazole tigecycline + ciprofloxacin	Piperacillin/tazobactam or imipenem or meropenem ± aminoglycoside Ceftazidime or cefepime or ciprofloxacin + metronidazole Tigecycline + ciprofloxacin MRSA or enterococcal infections: vancomycin or linezolid or daptomycin or tigecycline	
2013—International [5]	Amoxicillin/clavulanate, ciprofloxacin + metronidazole At risk of ESBL infection: ertapenem or tigecycline Biliary tract infections and at risk of ESBL infection: tigecycline	Piperacillin/tazobactam At risk of ESBL infection: imipenem or meropenem Biliary tract infections: piperacillin/tazobactam Biliary tract infections and at risk of ESBL infection: piperacillin + tigecycline	Piperacillin + tigecycline Imipenem or meropenem + teicoplanin	
2015—France [10]	Amoxicillin/clavulanate + gentamicin or cefotaxime/ceftriaxone + metronidazole In case of β-lactams allergy: levofloxacin + gentamicin + metronidazole, or tigecycline	Piperacillin/tazobactam + gentamicin	Piperacillin/tazobactam + amikacin ± vancomycin Allergy to β-lactams: ciprofloxacin or aztreonam + amikacin + metronidazole + vancomycin Or tigecycline + ciprofloxacin	Severe cases or patients at risk of MDR bacteria Imipenem or meropenem ± amikacin ± vancomycin

Table 5 continued

Expert groups	Community-acquired peritonitis		Healthcare-associated peritonitis	
	Mild to moderate cases	Severe or at-risk cases	Mild to moderate cases	Severe or at-risk cases
2015—Germany [43]	Localized infection: cefotaxime, cefuroxime, ceftriaxone, ciprofloxacin, levofloxacin, + metronidazole Amoxicillin/clavulanate Ampicillin/sulbactam	Generalized infection: piperacillin/tazobactam Ertapenem Moxifloxacin Tigecycline	Piperacillin/tazobactam Tigecycline Meropenem Imipenem/cilastatin Ceftolozane/tazobactam + metronidazole MRSA/VRE infections: add linezolid (not necessary for tigecycline)	

adjustment appears to be required for ertapenem [52]. Optimal dosing of fluoroquinolones is more difficult to determine, but dosage adjustment is probably not warranted, at least for levofloxacin and moxifloxacin [47]. A loading dose of colistin should be administered and subsequent dosing should be calculated for IBW [47]. For aminoglycosides, a loading dose should be based on adjusted or lean body weight and subsequent doses should be based on serum drug levels [53]. No adjustment is needed for tigecycline [54]. For vancomycin, the loading dose is 25–30 mg/kg of TBW in seriously ill patients and the maintenance dose is 15–20 mg/kg of TBW every 8–12 h, without exceeding 2 g per dose for patients with normal kidney function; serum trough concentrations of 15–20 mg/ml are recommended; doses greater than 1.5 g should be infused over at least 1.5 h [55].

Role of *Candida* in peritonitis

Non-candidemic systemic candidiasis accounts for the majority of cases of invasive candidiasis observed in patients with peritonitis. Up to 80 % of these patients are colonized, but only 5–30 % develop intra-abdominal candidiasis requiring antifungal treatment [56–58]. Combined exposure to several risk factors such as broad-spectrum antibiotics, parenteral nutrition and renal replacement therapy for 7–10 days is required to transform colonization into local invasion and then documented invasive infection [58].

Non-candidemic invasive candidiasis is microbiologically difficult to prove. The definition of fungal peritonitis is restrictive, based on histological criteria and cannot be used to guide initiation of antifungal therapy [59, 60]. Experts therefore recommend that early empirical treatment be based on risk-assessment strategies, such as colonization index, *Candida* scores and predictive rules. These strategies are based on combinations of several risk factors, such as *Candida* colonization, previous use of broad-spectrum antibiotics and previous abdominal surgery. Their positive predictive values (PPV) are used for the early prediction of invasive candidiasis. The negative predictive values (NPV) of these scores are much higher than their PPV. This situation has resulted in two opposing strategies: clinicians concerned by the poorer prognosis of delayed treatment start antifungal therapy early, even in low-risk patients (especially patients with perforated gastroduodenal ulcers), leading to major overuse of antifungals; while other clinicians, more concerned by the negative ecological impact and the costs of antifungal agents, delay prescription with a risk of missing patients requiring early treatment.

The colonization index may be used to identify patients likely to benefit from early empirical antifungal therapy, but this strategy is work-intensive, expensive and difficult

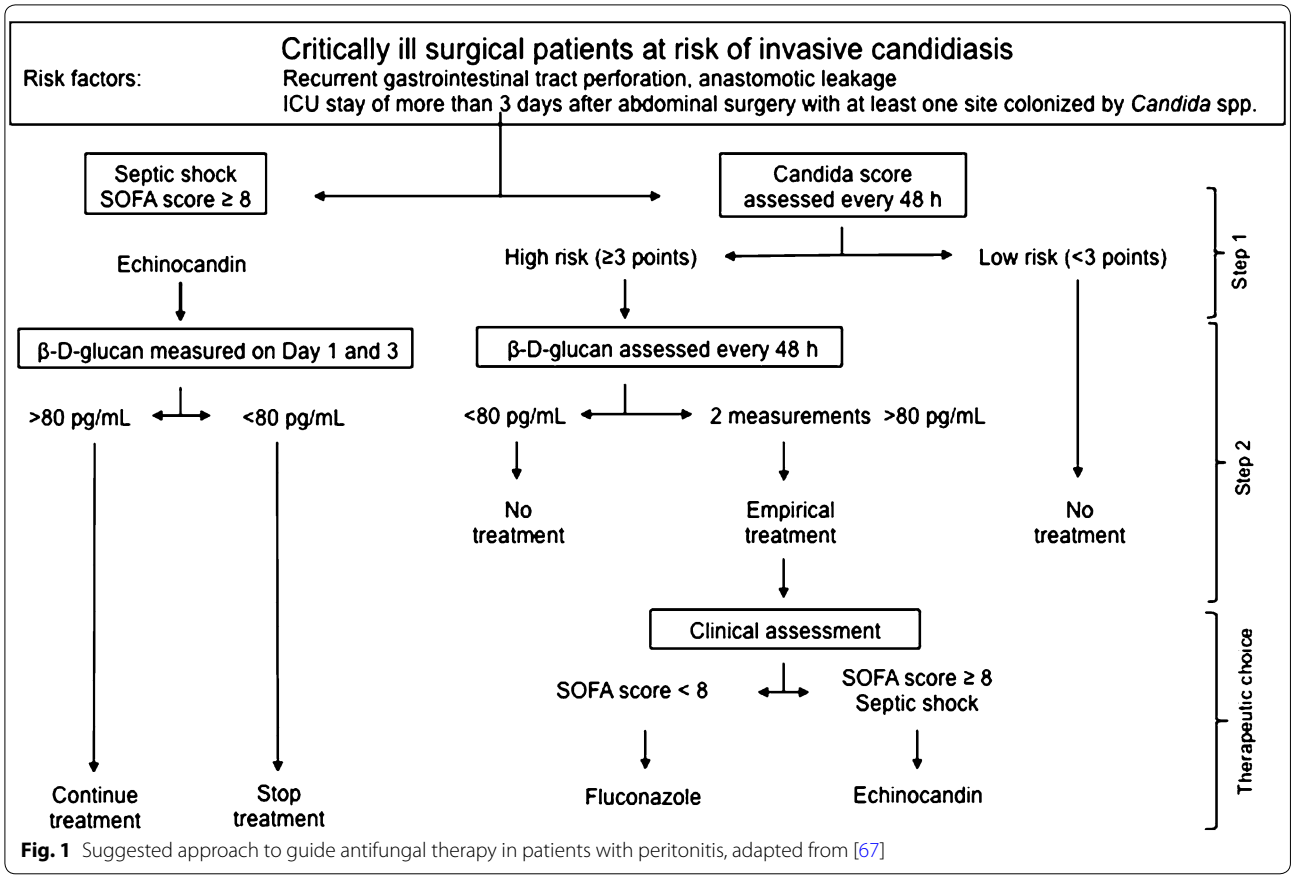

Fig. 1 Suggested approach to guide antifungal therapy in patients with peritonitis, adapted from [67]

to implement [60]. The usefulness of the *Candida* score to guide empirical antifungal therapy has not been tested in prospective clinical trials [61]. Dupont et al. developed peritonitis scores with relatively high PPV and NPV, but their clinical value needs to be confirmed by large prospective clinical trials [62]. Other investigators have proposed predictive scores based on combinations of risk factors, but their clinical usefulness has not been formally demonstrated.

Biomarkers may be useful for the diagnosis of invasive candidiasis but have yet to be confirmed by large prospective clinical trials. *Candida* DNA and mannan antigen/anti-mannan antibodies are of limited value. The European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guidelines considered 1,3-β-D-glucan a very useful biomarker to rule out infection [63]. Preliminary data suggest that 1,3-β-D-glucan can also be detected early in the course of non-candidemic systemic candidiasis, including peritonitis [64]. Preliminary results suggest that *Candida albicans* germ tube antibody can also be detected early in patients with peritonitis [65].

Early empirical and pre-emptive antifungal therapy has been suggested to decrease mortality, but this remains highly controversial [56]. No study has ever addressed the issue of empirical antifungal therapy in a specific population of patients with peritonitis. Evidence-based guidelines for proven invasive candidiasis emphasize the need for early treatment to improve outcome but do not provide any practical measures to guide this treatment [56, 66], leading to major overuse of antifungal agents, contributing to a high financial burden, and promotion of a shift towards species and strains that are less susceptible to antifungals.

A practical two-step approach based on the use of biomarkers could be proposed to improve the selection of patients likely to benefit from empirical antifungal therapy, while avoiding overuse of antifungal agents (Fig. 1) [67]. The first step could rule out patients at low risk of documented fungal infection. The second step would limit empirical antifungal therapy to patients with increased 1,3-β-D-glucan levels over 80 pg/ml, as proposed by some authors [64, 65]. Alternatively, clinicians may decide to initiate antifungal therapy (with an echinocandin) in patients with septic shock and organ failures in the context of complications after surgery for peritonitis [8, 10]. Antifungal therapy can be continued, with

possible de-escalation to fluconazole in patients with resolving septic shock, provided sensitive candidas are documented [8, 10, 66].

Conclusion

Critically ill patients with peritonitis require an early combined operative and medical approach. The key elements for success are early and optimal source control and adequate surgery and appropriate anti-infective therapy (in terms of the most appropriate drug, at an adequate dosage with satisfactory tissue penetration to target the microorganisms concerned). In life-threatening situations, a "damage control" approach is the safest way to gain time and achieve stability.

Electronic supplementary material

The online version of this article (doi:10.1007/s00134-016-4307-6) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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