Clinical Infectious Diseases

SUPPLEMENT ARTICLE

Diagnosis and Management of Intraabdominal Infection: Guidelines by the Chinese Society of Surgical Infection and Intensive Care and the Chinese College of Gastrointestinal Fistula Surgeons

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The Chinese guidelines for IAI presented here were developed by a panel that included experts from the fields of surgery, critical care, microbiology, infection control, pharmacology, and evidence-based medicine. All questions were structured in population, intervention, comparison, and outcomes format, and evidence profiles were generated. Recommendations were generated following the principles of the Grading of Recommendations Assessment, Development, and Evaluation system or Best Practice Statement (BPS), when applicable. The final guidelines include 45 graded recommendations and 17 BPSs, including the classification of disease severity, diagnosis, source control, antimicrobial therapy, microbiologic evaluation, nutritional therapy, other supportive therapies, diagnosis and management of specific IAIs, and recognition and management of source control failure. Recommendations on fluid resuscitation and organ support therapy could not be formulated and thus were not included. Accordingly, additional high-quality clinical studies should be performed in the future to address the clinicians' concerns.

Keywords. intraabdominal infection; source control; antimicrobial therapy; nutrition; treatment failure.

OVERVIEW

The preparation of these guidelines was led by the Chinese Society of Surgical Infection and Intensive Care and the Chinese College of Gastrointestinal Fistula Surgeons. Available guidelines on the management of intraabdominal infection (IAI) are predominantly written for the Western context. International guidelines often fail to take into account factors specific to China. For example, the microbial etiology and susceptibility of IAI pathogens in China differ substantially from those in other countries. Here, we present evidence-based recommendations on the management of IAI, with a view to making the approaches practical and reasonable in the Chinese setting.

When preparing these guidelines, the target population was adult patients with IAI. IAI is classified into community-acquired IAI (CA-IAI) and healthcare- or hospital-associated IAI (HA-IAI) considering the source of disease. CA-IAI is

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Clinical Infectious Diseases® 2020;71(S4):S337–62

DOI: 10.1093/cid/ciaa1513

further divided into mild to moderate CA-IAI and severe CA-IAI on the basis of the disease severity.

1. Classification of disease severity and prognostic assessment
   - An Acute Physiology and Chronic Health Evaluation II (APACHE II) score of 10 can be the recommended criterion for classifying mild to moderate IAI or severe IAI (strong recommendation, low quality of evidence).
   - IAI associated with sepsis can be classified as severe IAI (strong recommendation, low quality of evidence).
   - IAI associated with grade III and grade IV acute gastrointestinal injury can be classified as severe IAI (strong recommendation, very low quality of evidence).
   - The APACHE II and Sequential Organ Failure Assessment scores can be used to assess the prognosis of patients with IAI (strong recommendation, low quality of evidence). The Mannheim peritonitis index score could also be used to assess the prognosis (conditional recommendation, low quality of evidence).

2. Diagnosis
   - Computed tomography examination will identify patients with suspected IAI (conditional recommendation, low quality of evidence).
   - Ultrasonography will identify patients with suspected IAI (conditional recommendation, low quality of evidence).
   - Laboratory studies as diagnostic adjuncts are recommended for patients with suspected IAI (strong recommendation, moderate quality of evidence).
   - Procalcitonin as a diagnostic adjunct is recommended for patients with suspected IAI (strong recommendation, moderate quality of evidence).
   - For patients with undetermined IAI and its source, laparoscopy can be considered (conditional recommendation, moderate quality of evidence).

3. Source control
   - Source control should be conducted as soon as possible for patients with IAI (Best Practice Statement [BPS]).
   - Percutaneous drainage should be performed as soon as possible when the presence of infectious effusions in the abdominal cavity is confirmed by diagnostic imaging (BPS).
   - Timing of open abdomen should be determined after comprehensive discussions among clinicians. The indications for open abdomen include severe IAI/intraabdominal sepsis, increased abdominal pressure/abdominal compartment syndrome, or the inability to close the abdomen/presence of massive active hemorrhage in the abdominal cavity (BPS).
   - Open abdomen therapy is recommended for patients with severe IAI (strong recommendation, very low quality of evidence).
   - Negative pressure wound therapy can be considered for temporary abdominal closure after open abdomen (conditional recommendation, high quality of evidence).

4. Antimicrobial therapy
   4.1 Timing of antimicrobial therapy
      - Empiric antimicrobial therapy should be initiated within 1 hour of a confirmed diagnosis of IAI-induced sepsis or septic shock provided that the administration is possible; for other patients with IAI, antimicrobial therapy should be initiated as soon as possible, and the timely management of the primary source should be considered (BPS).
      - For patients already receiving empiric antimicrobial therapy, if the time interval between last administration and source control was greater than 2 half-lives, the antimicrobials should be readministered within 1 hour before or during surgical procedures for source control (BPS).

   4.2 Selection of antimicrobial agents
      4.2A Initial empiric therapy
         - For patients with mild to moderate CA-IAI, the recommended antimicrobial regimens of empiric single-agent therapy are moxifloxacin, cefoperazone-sulbactam, and ertapenem (strong recommendation, moderate quality of evidence), and the regimens of combination therapy are cefazolin, cefuroxime, ceftriaxone, cefotaxime, ciprofloxacin, or levofloxacin with nitroimidazoles (strong recommendation, moderate quality of evidence).
         - For patients with severe CA-IAI, the recommended antimicrobial regimens of empiric single-agent therapy are carbapenems, including imipenem-cilastatin and meropenem, or piperacillin-tazobactam (strong recommendation, moderate quality of evidence), and the regimens of combination therapy are third- and fourth-generation cephalosporins, including ceftazidime and cefepime, with nitroimidazoles (strong recommendation, moderate quality of evidence).
         - For patients with HA-IAI, the recommended antimicrobial regimens of empiric single-agent therapy are carbapenems, including imipenem-cilastatin and meropenem (strong recommendation, moderate quality of evidence), and the regimens of combination therapy are third- and fourth-generation cephalosporins, including ceftazidime and cefepime, with nitroimidazoles (strong recommendation, moderate quality of evidence).

- For CA-IAI patients with allergies to β-lactams, initial therapy of moxifloxacin or ciprofloxacin in combination with nitroimidazole is appropriate (conditional recommendation, high quality of evidence).
- Tigecycline is not recommended for routine empiric therapy. This agent should be considered as a component of a combination regimen for therapy of IAI patients with resistant pathogens or no other suitable agents (BPS).

4.2B De-escalation strategy

- For patients with severe CA-IAI and HA-IAI, de-escalation of antimicrobial therapy is recommended once definitive culture results are available (strong recommendation, very low quality of evidence).

4.2C Antifungal therapy

- Fluconazole or echinocandins are recommended for the treatment of intraabdominal candidiasis. Fluconazole is recommended for patients with mild to moderate CA-IAI, and echinocandins are recommended for patients with severe CA-IAI and HA-IAI (strong recommendation, moderate quality of evidence).
- Amphotericin B is associated with a high incidence of adverse reactions and is recommended for the treatment of intraabdominal candidiasis only if no other antifungal agents are suitable (strong recommendation, moderate to low quality of evidence).

4.2D Anti-enterococcal therapy

- Empiric anti-enterococcal therapy is not necessary for patients with mild to moderate CA-IAI (strong recommendation, high quality of evidence).
- Empiric anti-enterococcal therapy is recommended for patients with severe CA-IAI and HA-IAI (conditional recommendation, moderate quality of evidence).

4.3 Duration of antimicrobial therapy

- Antimicrobial therapy should be limited to 4 days in mild to moderate CA-IAI patients who have had adequate source control (strong recommendation, moderate quality of evidence).
- Antimicrobial therapy could be limited to 7–10 days in patients with severe CA-IAI and HA-IAI (conditional recommendation, moderate quality of evidence).
- The measurement of procalcitonin levels is suggested to support shortening the duration of antimicrobial therapy in IAI patients (conditional recommendation, moderate quality of evidence).

5. Microbiologic evaluation

- Routine aerobic cultures of peritoneal fluid from mild to moderate CA-IAI patients should be considered. Routine aerobic and anaerobic cultures of peritoneal fluid should be obtained from severe CA-IAI and HA-IAI patients (BPS).
- Blood cultures are not routinely recommended for patients with mild to moderate CA-IAI. Blood cultures should be performed for patients with severe CA-IAI and HA-IAI, particularly for those with concomitant sepsis or those who are immunocompromised, in order to confirm the presence of bacteremia (BPS).
- Blood cultures and peritoneal fluid cultures for fungal should be considered for IAI patients with risk factors (BPS).

6. Nutrition

- Nutritional Risk Screening 2002 and Nutrition Risk in Critically Ill should be considered for assessment of IAI patients' nutritional status (BPS).
- Enteral or parenteral nutrition is recommended for IAI patients with malnutrition risk to improve prognosis (strong recommendation, very low quality of evidence).
- Early enteral nutrition (24–72 hours) should be administered in IAI patients who can be fed enterally (strong recommendation, moderate to very low quality of evidence). Parenteral nutrition should be administered as early as possible if enteral feeding is not feasible (strong recommendation, very low quality of evidence). Parenteral nutrition in combination with enteral feeds should be considered if the targeted energy supply cannot be achieved by enteral nutrition alone (conditional recommendation, low to very low quality of evidence).
- The initial amount of nonprotein calories should be considered as 20–25 kcal/(kg·d) when administering enteral nutrition for severe IAI patients. Feeds should then be advanced according to patient tolerance (conditional recommendation, low to moderate quality of evidence). Low-calorie parenteral nutrition (≤20 kcal/(kg·d)) should be considered as the initial strategy in patients with feeding intolerance. When feasible, advance enteral feeds as tolerated (BPS).
- When administering parenteral nutrition to patients with mild to moderate IAI, the protein intake is suggested to be 1.5 g/(kg·d) (conditional recommendation, very low quality of evidence). For patients with severe IAI, the suggested protein intake is 1.5–2 g/(kg·d) (conditional recommendation, moderate quality of evidence).
- For patients with IAI who require parenteral nutrition, glutamine-containing immunonutrients may be used (conditional recommendation, low quality of evidence).

- Vitamins with antioxidant effects (vitamins E and C) should be considered in severe IAI patients who require immunonutrition (conditional recommendation, low quality of evidence).
- The routine use of fish oil as an immune supplement in IAI patients is recommended (strong recommendation, very low quality of evidence). Arginine should not be administrated as an immune supplement (strong recommendation, very low quality of evidence).

7. Other supportive therapies
   7.1 Continuous renal replacement therapy
   - Continuous renal replacement therapy (CRRT) plus conventional treatment for sepsis should be considered when necessary (conditional recommendation, moderate quality of evidence).
   - Both high-dose and conventionally low-dose CRRT can be used for sepsis (conditional recommendation, moderate quality of evidence).

   7.2 Glucocorticoids
   - Use of glucocorticoids should be considered when adequate fluid resuscitation and vasopressor agents cannot restore hemodynamic stability for sepsis and septic shock that originated from IAI. Low-dose hydrocortisone is suggested for IAI patients who require glucocorticoids (conditional recommendation, moderate quality of evidence).

   7.3 Immunoglobulins
   - The use of immunoglobulins is not suggested in IAI patients with sepsis (conditional recommendation, low quality of evidence).

8. Diagnosis and management of specific IAI
   8.1 Pancreatic infection
   - Delayed source control should be considered for moderately severe acute pancreatitis (conditional recommendation, very low quality of evidence).
   - The use of antimicrobial therapy is preferred for severe acute pancreatitis. Minimally invasive procedures such as CT- or ultrasound-guided percutaneous drainage or endoscopic therapy are a reasonable alternative provided that nonoperative management is ineffective. In cases where drainage or endoscopic therapy is ineffective, surgery may be considered (strong recommendation, moderate quality of evidence).

   8.2 Acute appendicitis
   - Imaging procedures are recommended for the diagnosis of patients with suspected acute appendicitis (strong recommendation, moderate quality of evidence).
   - Ultrasound is the preferred diagnostic imaging technique for suspected appendicitis, particularly for adolescent patients and pregnant women (strong recommendation, moderate quality of evidence).
   - For patients with ultrasound findings equivocal or negative for suspected appendicitis, CT is a reasonable alternative (strong recommendation, moderate quality of evidence).
   - CT is the recommended imaging procedure for acute appendicitis patients without contraindication of ionizing radiation or availability of ultrasound (strong recommendation, moderate quality of evidence).
   - Magnetic resonance imaging (MRI) is not recommended as a routine imaging test for the diagnosis of suspected acute appendicitis (strong recommendation, moderate quality of evidence).
   - For pregnant women whose ultrasonography results are equivocal or negative, MRI is recommended (strong recommendation, moderate quality of evidence).
   - For patients with acute appendicitis who refuse to undergo emergency surgery or do not wish to undergo surgery, antimicrobial therapy should be initiated. Risks of recurrence and conversion to surgery from nonoperative management should be clarified. The above recommendations are applicable for both simple and complicated appendicitis (strong recommendation, very low quality of evidence).
   - Appendectomy should be performed within 24 hours for patients undergoing surgical procedures (conditional recommendation, low quality of evidence). Laparoscopic appendectomy may be considered if there are no relevant contraindications (conditional recommendation, low quality of evidence).
   - Patients with a well-circumscribed periappendiceal abscess can be managed with percutaneous drainage when necessary (strong recommendation, moderate to very low quality of evidence).
   - The use of interval appendectomy after nonoperative management for acute appendicitis is not necessary due to the low recurrence rate (strong recommendation, high quality of evidence).

9. Source control failure
   - Use of systemic inflammation or organ system dysfunction measures to identify patients with likely source control failure is recommended (BPS).
   - The following should be considered as source control failure: progressive organ dysfunction within the first 24–48 hours after source control, no clinical improvement in organ dysfunction 48 hours or more after source control, or persistent signs of inflammation 5–7 days after source control (BPS).
   - Abdominal exploration should be considered in patients who had clinical deterioration or no improvement within 48–72 hours of the initial procedure. CT scanning and then percutaneous aspiration or drainage of any potentially infected fluid collections is suggested for likely

source control failure at 48–72 hours after the initial procedure (BPS).
- Use of the least invasive approach that will achieve definitive source control is recommended to allow resolution of the inflammatory response and organ dysfunction (BPS).
- Further source control should be considered within 24 hours once source control failure is identified but as soon as feasible in patients with physiologic instability or progressive organ dysfunction (BPS).
- Routine peritoneal cultures for patients with source control failure are recommended so that pathogen-directed antimicrobial therapy can be used (BPS).

Intraabdominal infection (IAI) is a common problem managed by surgical practitioners. IAI can be secondary to perforation, necrosis, or gangrene of the gastrointestinal tract. In addition, IAI is a common surgical complication from abdominal surgical procedures, including gastrointestinal dehiscence and fistula. IAI represents the second most common cause of infectious disease among hospitalized patients, with a mortality rate of up to 20%, thereby having a significant impact on public health and safety [1].

In recent years, the Infectious Diseases Society of America, the Surgical Infection Society, and the World Society of Emergency Surgery have published and revised several guidelines for the diagnosis and management of IAI in order to provide a basis for the timely and appropriate clinical diagnosis and treatment of the disease based on local settings [2–7]. However, these guidelines are mostly based on evidence and epidemiological status of IAI pathogens from countries other than China. Clinical practice guidelines that can be followed by physicians in China have been lacking. Along with the progress in relevant research, China has also accumulated significant research data regarding the diagnosis and management of IAI. Moreover, the distribution of IAI etiological agents and the drug resistance in China differ from those in other countries. Therefore, there was an urgent need to develop guidelines for the diagnosis and management of IAI in China in order to provide better guidance in clinical practice.

METHODS

The current guidelines were developed by a panel comprising Chinese experts in the fields of surgery, critical care, microbiology, infection control, pharmacology, and evidence-based medicine. From 2017 to 2019, the guidelines panel convened several face-to-face meetings and teleconference discussions to reach a consensus regarding the final recommendations. Below is a summary of the important methodologic considerations for developing these recommendations.

Question Development

The scope of these guidelines is focused on diagnosis and management of patients with IAI. Topic selection was the responsibility of all panel members, and prioritization of the topics was completed by discussion through face-to-face meetings. All questions were structured in population, intervention, comparison, and outcomes format. The decision regarding question inclusion was reached by discussion and consensus among the guidelines panel.

The following clinical questions are addressed within the guidelines:

- How should the severity of patients with IAI be classified? How should outcomes be evaluated?
- What are the appropriate procedures for initial evaluation of patients with suspected IAI?
- When should fluid resuscitation be started for patients with suspected IAI?
- When should mechanical ventilation be provided for patients with IAI? What are appropriate procedures to prevent and intervene with liver dysfunction and acute gastrointestinal dysfunction and failure?
- When should source control be conducted? What are the proper procedures?
- When should antimicrobial therapy be initiated for patients with suspected or confirmed IAI?
- What are appropriate antimicrobial regimens for patients with community-acquired IAI and healthcare- or hospital-associated IAI?
- How should a de-escalation strategy for antimicrobial therapy be conducted?
- What antimicrobial regimens should be used in patients with IAI, particularly with regard to *Candida* and enterococcus?
- What is the appropriate duration of antimicrobial therapy for patients with IAI?
- When and how should microbiological specimens be obtained and processed?
- When and how should nutrition therapy be provided for patients with IAI?
- What is the role of continuous renal replacement therapy, glucocorticoids, and immunoglobulins in the treatment of patients with IAI?
- What are appropriate diagnostic antimicrobial regimens and surgical strategies for pancreatic infection and acute appendicitis?
- How should suspected source control failure be detected and managed?

Evidence Identification and Retrieval

With the assistance of professional librarians, an independent literature search was performed for each defined question. Search terms that included, at a minimum, various descriptions of IAI combined with appropriate keywords specific to the question were posed.

An electronic search was conducted of a minimum of 3 major English databases (Cochrane Registry, MEDLINE, and EMBASE) and major Chinese databases (China Biology Medicine Disc, China National Knowledge Internet, China Science and Technology Journal Database, Wanfang Data Knowledge Service Platform) to identify relevant systematic reviews and clinical trials. Both randomized clinical trials (RCTs) and observational studies published after 1 January 1990 were considered. In a few reviews, the panel determined that relevant studies had been published before 1990 and no time limit was used. Studies in at least English and Chinese were included; some reviews had no language restrictions.

Using the assembled list of priority topics, questions, and critical outcomes from the scoping exercise identified by the guidelines panel, the systematic review team conducted 42 systematic reviews to provide the supporting evidence for development of the recommendations. Two independent reviewers screened the titles and abstracts of retrieved references for potentially relevant studies. Reference management software (eg, Endnote, NoteExpress) was used for the screening. The full text of all potentially eligible articles was obtained and then reviewed independently by 2 authors based on inclusion criteria. Both authors extracted data in a predefined evidence table and critically appraised the retrieved studies.

Quality was assessed using the Cochrane Collaboration tool to assess the risk of bias of RCTs and the Newcastle-Ottawa Quality Assessment Scale for cohort studies. Meta-analyses of available comparisons were performed using Review Manager version 5.3, as appropriate. Crude estimates were pooled as odds ratios (ORs) with 95% confidence intervals (CIs) using a random effects model or risk ratios (RRs) with 95% CIs using a fixed effects model.

Grading of Recommendations

The results of the systematic reviews and meta-analyses were presented at 8 face-to-face meetings between July 2017 and November 2019. According to a standard Grading of Recommendations Assessment, Development, and Evaluation (GRADE) decision-making table proposed by the methodologist, recommendations were formulated based on the overall quality of the evidence, the balance between benefits and harms, values and preferences, and implications for resource use [8]. The strength of each recommendation was rated as either "strong" (the panel was confident that the benefits of the intervention outweighed the risks) or "conditional" (the panel considered that the benefits of the intervention probably outweighed the risks). A number of best practice statements (BPSs) appear throughout the document; these statements represent ungraded strong recommendations and are used under strict criteria [9]. A BPS would be appropriate, for example, when the benefit or harm is unequivocal, but the evidence is hard to summarize or assess using GRADE methodology. These were assessed through discussion among panel members (Delphi methods).

Voting Process

Following formulation of statements through discussion among panel members during face-to-face meetings at which the groups presented their draft statements, all panel members voted using voting machines (Sun Vote, Changsha, China) to indicate agreement or disagreement with the statement, or abstention.

Sponsorship

Funding for the development of these guidelines was provided by the Chinese Society of Surgical Infection and Intensive Care and the Chinese College of Gastrointestinal Fistula Surgeons.

1. Classification of disease severity and prognostic assessment
   - 1.1 An Acute Physiology and Chronic Health Evaluation II (APACHE II) score of 10 can be the recommended criterion for classifying mild to moderate IAI or severe IAI (strong recommendation, low quality of evidence).
   - 1.2 IAI associated with sepsis can be classified as severe IAI (strong recommendation, low quality of evidence).
   - 1.3 IAI associated with grade III and grade IV acute gastrointestinal injury can be classified as severe IAI (strong recommendation, very low quality of evidence).
   - 1.4 The APACHE II and Sequential Organ Failure Assessment (SOFA) scores can be used to assess the prognosis of patients with IAI (strong recommendation, low quality of evidence). The Mannheim peritonitis index (MPI) score could also be used to assess the prognosis (conditional recommendation, low quality of evidence).

The previous guidelines make therapeutic recommendations on the basis of the severity of infection, which is defined by these guidelines as a composite of risk factors including patient age, physiologic derangements, and background medical conditions. The 2017 IAI guidelines published by the Surgical Infection Society list the risk factors associated with patient death and treatment failure [2]. Although certain characteristics can be used to guide patient stratification, these had not been established by evidence-based systematic review. In the Chinese guidelines, we stratified IAI patients according to the severity of illness. "Severe" infection is intended to describe IAI patients with sepsis or septic shock. "Mild to moderate" infection aims to describe IAI patients with a lower severity of infection. The scoring systems, rather than risk factors, were used to stratify IAI patients. We investigated the correlations between APACHE II, SOFA, MPI, clinical manifestations, and mortality in IAI patients.

The sensitivity and specificity analysis of the APACHE II for predicting mortality showed that an APACHE II score of

10 exhibited better sensitivity and specificity for predicting mortality than a score of 15 or 20 [10–13]. The APACHE II score of 10 had a sensitivity of 0.893 (95% CI, .886–.917) and specificity of 0.884 (95% CI, .834–.828). The quality of evidence was low. Therefore, an APACHE II score of 10 can be used as a criterion for classifying the severity of IAI. In addition to objective indicators, the presence of concomitant diseases, such as sepsis and grade III or grade IV acute gastrointestinal injury (AGI), may be used as a basis for identifying the severity of disease. A total of 10 observational studies evaluated the difference in the death rates of IAI patients with or without sepsis [14–23]. A meta-analysis showed that the RR of mortality for IAI patients with sepsis vs those without sepsis was 4.71 (95% CI, 2.67–8.29), and the difference was significant. The quality of evidence was low. The effect of concomitant AGI on the mortality from IAI was evaluated in 9 studies [24–32]. A meta-analysis showed that the OR for adverse outcomes in patients with IAI and concomitant grade III or grade IV AGI vs those with grade I or grade II AGI was 0.21 (95% CI, .13–.34), and the difference was significant. The quality of evidence was very low.

Considering the prediction of prognosis, the area under the curve (AUC) of the APACHE II score in predicting the poor prognosis of IAI was 0.8220 [10–14, 22, 23, 33–38]. The AUC of the MPI in predicting the poor prognosis of IAI was 0.8579, the sensitivity was 0.718 (95% CI, .664–.768), and the specificity was 0.815 (95% CI, .773–.851) [12, 13, 23, 38–47]. The AUC of the SOFA score in predicting the poor prognosis of IAI was 0.8444, the sensitivity was 0.782 (95% CI, .721–.835), and the specificity was 0.815 (95% CI, .773–.851) [13, 23, 38, 41, 43]. Therefore, the APACHE II, MPI, and SOFA scores can predict the prognosis of IAI to a certain extent. The guidelines panel recommended the preferred use of the APACHE II score because the APACHE II score is the most commonly used clinical system, followed by the SOFA score. As the MPI has not been widely adopted in clinical practice, the guidelines panel adjusted their recommendation level for MPI as a conditional recommendation.

2. Diagnosis

2.1 Computed tomography (CT) examination will identify patients with suspected IAI (conditional recommendation, low quality of evidence).

2.2 Ultrasonography will identify patients with suspected IAI (conditional recommendation, low quality of evidence).

2.3 Laboratory studies as diagnostic adjuncts are recommended for patients with suspected IAI (strong recommendation, moderate quality of evidence).

2.4 Procalcitonin as a diagnostic adjunct is recommended for patients with suspected IAI (strong recommendation, moderate quality of evidence).

2.5 For patients with undetermined IAI and its source, laparoscopy can be considered (conditional recommendation, moderate quality of evidence).

The diagnosis of IAI primarily depends on the findings obtained on medical history, physical examination, laboratory studies, imaging investigations, and percutaneous intervention. A systematic review of the medical history and physical examination findings could not be conducted owing to limited evidence. Thus, for this section, we evaluated only the role of imaging and laboratory investigations and laparoscopy findings for the diagnosis of suspected IAI. A total of 13 studies on CT-assisted diagnosis of IAI were retrieved [48–60]. A meta-analysis of the diagnostic test accuracy revealed that the combined sensitivity of CT for the diagnosis of IAI was 0.91 (95% CI, .89–.94), the specificity was 0.97 (95% CI, .95–.98), and the AUC was 0.9758 (standard error = 0.0160). Although the original data were mainly derived from colonic diverticulitis [48–58, 60], the guidelines panel affirmed the role of CT in the diagnosis of suspected IAI. Seven studies on ultrasound-assisted diagnosis of IAI were retrieved [54, 55, 57, 61–64], all of which were based on colonic diverticulitis. The analysis indicated that the combined sensitivity of ultrasound for the diagnosis of IAI was 0.87 (95% CI, .83–.90), the specificity was 0.95 (95% CI, .93–.97), and the AUC was 0.9754. The sensitivity, specificity, and AUC of ultrasound for the diagnosis of IAI were inferior to those of CT. However, ultrasound is still a good first choice for diagnosis of IAI, especially when CT is unavailable. Considering the ease of access of ultrasound equipment and the fact that no imaging ionizing radiation is involved, ultrasound is recommended for patients with suspected IAI.

Laboratory investigation is an important diagnostic adjunct for IAI. Increasing numbers of studies have used biomarkers such as procalcitonin (PCT) to perform quantitative diagnosis of IAI. In fact, 12 studies on PCT-assisted diagnosis of IAI were retrieved [65–76]. The combined sensitivity of PCT for the diagnosis of IAI was 0.794 (95% CI, .757–.829), the specificity was 0.679 (95% CI, .655–.702), and the AUC was 0.8694. These results suggest that serum PCT has a moderate diagnostic value for patients with IAI.

For patients with IAI whose imaging and laboratory investigations fail to confirm the source, diagnostic laparoscopy may be considered as it is useful for both diagnosis and treatment. A total of 31 studies were included to evaluate the importance of laparoscopy for the diagnosis of IAI [77–107]. The analysis showed that the sensitivity and specificity of laparoscopy for the diagnosis of IAI were 0.99 (95% CI, .99–.99) and 0.83 (95% CI, .80–.86), respectively, and the AUC was 0.9084. These results indicate that laparoscopy has a high diagnostic value for patients with IAI in whom a definitive diagnosis cannot be confirmed. However, laparoscopy also has certain risks. The guidelines panel believes that laparoscopy may be used when imaging or

other testing cannot confirm the diagnosis of primary source. Nevertheless, noninvasive procedures should be given priority in the diagnostic workup. In addition, the surgical indications for laparoscopy should be strictly followed, and the various vital signs of patients should be maintained during surgery.

3. Source control
   - 3.1 Source control should be conducted as soon as possible for patients with IAI (BPS).
   - 3.2 Percutaneous drainage should be performed as soon as possible when the presence of infectious effusions in the abdominal cavity is confirmed by diagnostic imaging (BPS).
   - 3.3 Timing of open abdomen should be determined after comprehensive discussions among clinicians. The indications for open abdomen include severe IAI/intraabdominal sepsis, increased abdominal pressure/abdominal compartment syndrome, or the inability to close the abdomen/presence of massive active hemorrhage in the abdominal cavity (BPS).
   - 3.4 Open abdomen therapy is recommended for patients with severe IAI (strong recommendation, very low quality of evidence).
   - 3.5 Negative pressure wound therapy can be considered for temporary abdominal closure after open abdomen (conditional recommendation, high quality of evidence).

Achieving prompt and adequate control over the anatomic source of infection is a cornerstone in the management of IAI. The purposes of source control are to reduce bacterial loads and toxins by removing the infected organs as well as to improve the local environment in order to prevent further microbial growth and optimize the body's defense capability. Current source control measures for IAI include surgical (laparotomy or laparoscopy) and nonsurgical (percutaneous drainage) approaches. Both timing and procedures of source control are critical, and an appropriate treatment plan should be formulated according to the disease conditions and medical resources available.

Regarding the timing of source control, early source control has gained support. Owing to ethical guidelines, no studies have evaluated the safety and effectiveness of delayed source control for the treatment of IAI. In the current guidelines, the panel emphasizes early control of infection sources. However, for certain types of IAI, such as simple appendicitis and severe acute pancreatitis, timing of source control should be handled on a case-by-case basis.

The use of open abdomen as a treatment modality for severe trauma, abdominal compartment syndrome (ACS), and IAI has been progressively reported in the literature worldwide. The current literature search did not identify any studies that provide a clear indication of open abdomen. Most studies suggested that the use of open abdomen should be determined after comprehensive discussions among clinicians. The indications for open abdomen may include severe IAI/intraabdominal sepsis, increased abdominal pressure/ACS, or the inability to close the abdomen/presence of massive active hemorrhage in the abdominal cavity.

Currently, no RCT has evaluated the safety and efficacy of open abdomen for the treatment of IAI. On the basis of the results of a meta-analysis of 7 observational studies [108–114], patients who underwent open abdomen exhibited a significantly increased survival rate (OR, 0.63; 95% CI, .49–.82) and significantly reduced mortality rate (OR, 1.43; 95% CI, 1.17–1.75). The quality of evidence was very low.

Bogotá bags, patches, and negative pressure wound therapy (NPWT) are common approaches for temporary abdominal closure (TAC) after open abdomen. NPWT is a highly advanced TAC technique that has been widely commercialized and handmade. Five RCTs [115–119] and 21 non-RCTs [120–140] evaluated the effects of different TAC techniques on patient outcomes. A meta-analysis of RCTs showed that compared with other TAC techniques, NPWT did not affect the survival rate, mortality rate, abdominal closure rate, and incidence of enteroatmospheric fistula (EAF). The quality of the evidence was high. However, based on data from non-RCTs, NPWT significantly improved the survival rate (OR, 3.01; 95% CI, 2.41–3.76) and reduced the mortality rate (OR, 0.61; 95% CI, .49–.76) of patients with IAI. The successful abdominal closure rate increased (OR, 1.36; 95% CI, 1.14–1.62), while the incidence of EAF increased significantly (OR, 0.65; 95% CI, .47–.90; $P = .009$; $I^2 = 59\%$). The quality of the evidence from non-RCT studies was very low. After considering the quality of evidence, the potential of secondary EAF, and the resources required to install the device, the guidelines panel believes that the use of NPWT requires further investigation considering its advantages and disadvantages. Since there is high quality of evidence retrieved from RCT studies, the recommendation with regard to NPWT is graded as high quality.

4. Antimicrobial therapy
   - 4.1 Timing of antimicrobial therapy
     - 4.1.1 Empiric antimicrobial therapy should be initiated within 1 hour of a confirmed diagnosis of IAI-induced sepsis or septic shock provided that the administration is possible; for other patients with IAI, antimicrobial therapy should be initiated as soon as possible, and the timely management of the primary source should be considered (BPS).
     - 4.1.2 For patients already receiving empiric antimicrobial therapy, if the time interval between last administration and source control was greater than 2 half-lives, the antimicrobials should be readministered within 1 hour before or during surgical procedures for source control (BPS).

The standardization of the timing for antimicrobials can optimize the management of IAI. The 2016 Surviving Sepsis Guidelines recommend that antimicrobial therapy be initiated within 1 hour for both sepsis and septic shock [141]. An observational study on sepsis that resulted from IAI showed that delaying antimicrobial use increased the mortality rate [142]. Considering the above factors, the guidelines panel suggests that the timing for initial therapy for patients diagnosed with intraabdominal sepsis be strictly controlled to within 1 hour of diagnosis and that the early use of antimicrobials be emphasized. Moreover, timely source control is equally important. The timing of antimicrobial therapy for IAI patients without sepsis also lacks medical evidence. Initiation of antimicrobials only after etiologic evidence is obtained is not recommended as delaying treatment may lead to adverse consequences.

Patients with IAI may have undergone empiric antimicrobial therapy a few hours before surgery, and the drug concentrations in the blood and tissues may not be sufficiently maintained during the surgery. Therefore, if the time interval between last administration and source control is greater than 2 half-lives, the drug should be readministered. In addition, as minimally invasive surgery has a risk of pathogen spread, the use of control measures other than surgery for source control should also follow this recommendation.

4.2 Selection of antimicrobial agents

A. Initial empiric therapy

4.2.1 For patients with mild to moderate CA-IAI, the recommended antimicrobial regimens of empiric single-agent therapy are moxifloxacin, cefoperazone-sulbactam, and ertapenem (strong recommendation, moderate quality of evidence), and the regimens of combination therapy are cefazolin, cefuroxime, ceftriaxone, cefotaxime, ciprofloxacin, or levofloxacin with nitroimidazoles (strong recommendation, moderate quality of evidence).

4.2.2 For patients with severe CA-IAI, the recommended antimicrobial regimens of empiric single-agent therapy are carbapenems, including imipenem-cilastatin and meropenem, or piperacillin-tazobactam (strong recommendation, moderate quality of evidence), and the regimens of combination therapy are third- and fourth-generation cephalosporins, including ceftazidime and cefepime, with nitroimidazoles (strong recommendation, moderate quality of evidence).

4.2.3 For patients with HA-IAI, the recommended antimicrobial regimens of empiric single-agent therapy are carbapenems, including imipenem-cilastatin and meropenem (strong recommendation, moderate quality of evidence), and the regimens of combination therapy are third- and fourth-generation cephalosporins, including ceftazidime and cefepime, with nitroimidazoles (strong recommendation, moderate quality of evidence).

4.2.4 For CA-IAI patients with allergies to β-lactams, initial therapy of moxifloxacin or ciprofloxacin in combination with nitroimidazole is appropriate (conditional recommendation, high quality of evidence).

4.2.5 Tigecycline is not recommended for routine empiric therapy. This agent should be considered as a component of a combination regimen for therapy of IAI patients with resistant pathogens or no other suitable agents (BPS).

A total of 76 RCTs to evaluate the agents used for empiric therapy for IAI were included [143–218]. The findings obtained by Barie et al in 1997 [219] showed that the degree of disease severity was higher in the imipenem-cilastatin group than in the cefepime group, leading to considerable bias in the study. Therefore, the study was excluded from the analysis. After excluding that study, only 1 study evaluated fourth-generation cephalosporins, which cannot facilitate net meta-analysis. Thus, fourth-generation cephalosporins were not included in the comparison for the network meta-analysis and were not mentioned in the recommendations.

CA-IAI is usually a mixed infection that involves multiple enteric pathogens. The major pathogen is *Escherichia coli*, followed by *Klebsiella* species, *Pseudomonas aeruginosa*, and streptococci. The detection rate of enterococci is relatively low in CA-IAI. Enteric anaerobic bacteria, which are dominated by *Bacteroides* such as *Bacteroides fragilis*, are commonly found in infections of the distal gastrointestinal tract [220, 221]. The rate of resistance of Enterobacteriaceae is higher in China than in Western countries, particularly the resistance to ampicillin-sulbactam, quinolones, and cephalosporins [222]. The primary mechanism for drug resistance in these pathogens is through β-lactamase enzymes, among which the production of extended-spectrum β-lactamases (ESBLs) has attracted the most attention. The detection rates of ESBL-producing *E. coli* and *Klebsiella pneumoniae* are higher in China than in developed Western countries. However, the detection rates of ESBL-producing bacteria are slightly lower in community-acquired infections than in hospital-acquired infections, and a decreasing trend has been observed in recent years [223]. ESBL-producing *E. coli* and *K. pneumoniae* exhibit good sensitivity to amikacin, ertapenem, imipenem, and piperacillin-tazobactam, while their sensitivity to third- and fourth-generation cephalosporins is poor [224]. Patients who have received third-generation cephalosporins or quinolones within 90 days and patients with

known colonization with ESBL-producing bacteria should be suspected to have infections with ESBL-producing organisms [225].

The drugs for initial empiric therapy for mild to moderate CA-IAI should include non–drug-resistant Enterobacteriaceae and anaerobic bacteria. Additional broad-spectrum antibiotics or agents against enterococci and *P. aeruginosa* are not required. The ranking obtained from the network meta-analysis combined with expert opinions of the guidelines panel suggest that moxifloxacin, cefoperazone-sulbactam, or ertapenem may be used in empiric monotherapy for mild to moderate CA-IAI and that combination regimens should include first- and second-generation cephalosporins such as cefazolin and cefuroxime, third-generation cephalosporins such as ceftriaxone and cefotaxime, and quinolones such as ciprofloxacin and levofloxacin, in combination with nitroimidazoles (Table 1). The quality of the evidence was moderate. All the combined regimens in the literature that were included in the analysis involved the use of metronidazole. Metronidazole has been available in the market for a long time, but its long-term use has caused problems such as drug resistance, high incidence of adverse reactions, and poor patient compliance. New-generation nitroimidazoles have been developed with good efficacy against anaerobic bacteria, and the associated rate of adverse reaction is low.

In addition, ertapenem shows an unsatisfactory antibacterial activity against *P. aeruginosa* compared with other carbapenems. Nonetheless, ertapenem exhibits a broader antibacterial spectrum and higher antibacterial activity in vitro compared with other regimens used for mild to moderate CA-IAI. Meanwhile, the ranking results from the network meta-analysis also confirmed that ertapenem displayed the most optimal efficacy. Therefore, ertapenem can achieve the goal of effective treatment for mild to moderate CA-IAI, but it is not recommended for patients with severe infection.

The pathogenic microorganisms in HA-IAI are significantly different from those in CA-IAI. The incidence of *E. coli* isolates is lower, while the incidence of other Enterobacteriaceae and gram-negative bacilli isolates (*P. aeruginosa* and *Acinetobacter*) is higher [226]. The positive rates of staphylococci, streptococci, and enterococci are also higher in HA-IAI than in CA-IAI, particularly considering the positive rate of enterococci in patients who underwent surgery. Nonbacterial pathogens, especially *Candida*, are more common in HA-IAI, particularly in patients who have previously received broad-spectrum antibiotics [2, 227]. Therefore, patients with HA-IAI should receive broad-spectrum antibiotics.

The pathogenic bacteria in HA-IAI are more resistant to various common antibiotics than those in CA-IAI. These common multidrug-resistant bacteria are *K. pneumoniae*, *P. aeruginosa*, *Acinetobacter baumannii*, vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, and non–*Candida albicans*. The positive rate of ESBL-producing pathogens is significantly higher in HA-IAI than in CA-IAI. Thus, a higher proportion of carbapenems is used for treating HA-IAI, leading to the critical issue of carbapenem resistance. The Study for Monitoring Antimicrobial Resistance Trends conducted from 2012 to 2013 in China showed that the resistance rate to carbapenem was approximately 16.9% among *K. pneumoniae*, 38.4% among *P. aeruginosa*, and 73.6% among *A. baumannii* [224].

A total of 33 studies [155, 157, 162, 167, 168, 170, 175–177, 180, 181, 184, 186, 188–192, 195, 196, 198, 203, 206–210, 214, 216, 218, 228–230] on 9 major classes of antibiotics that were used in empiric therapy for HA-IAI were included. On the basis of the ranking from the network meta-analysis combined with expert opinions, the recommended single agent for severe CA-IAI is a carbapenem, such as imipenem-cilastatin and meropenem, or enzyme inhibitors, such as piperacillin-tazobactam. For combination regimens, third- and fourth-generation cephalosporins such as ceftazidime and cefepime may be used in combination with nitroimidazoles. Most of the pathogenic bacteria that cause HA-IAI are drug-resistant bacteria. Specifically, in China, there is an increasing trend of drug-resistant bacteria. Thus, it is even more crucial to evaluate the potential resistance of pathogens considering the local epidemiological status of the bacteria. These findings should be combined with the medical history on anti-infective therapy in order to rationally select an anti-infective agent.

Table 1. Regimens for Initial Empiric Therapy in Intraabdominal Infection

Regimen	Single Agent	Combination
IAI Type		
Mild to moderate CA-IAI	Moxifloxacin, cefoperazone-sulbactam, ertapenem	Cefazolin, cefuroxime, ceftriaxone, cefotaxime, ciprofloxacin, or levofloxacin in combination with nitroimidazoles
Severe CA-IAI	Imipenem-cilastatin, meropenem, piperacillin-tazobactam	Ceftazidime or cefepime in combination with nitroimidazoles
CA-IAI in patients with allergies to β-lactams		Moxifloxacin or ciprofloxacin in combination with nitroimidazoles
HA-IAI	Imipenem-cilastatin, meropenem, piperacillin-tazobactam	Ceftazidime or cefepime in combination with nitroimidazoles

Abbreviations: CA-IAI, community-acquired intraabdominal infection; HA-IAI, healthcare- or hospital-associated intraabdominal infection; IAI, intraabdominal infection.

Quinolone resistance is severe in China. Data from the 2017 China Antimicrobial Surveillance Network showed that the resistance rates to quinolones among *E. coli*, *K. pneumoniae*, *A. baumannii*, and *Enterococcus faecium* were as high as 57%, 31.3%, 68.3%, and 88.3%, respectively. As *Bacteroides* and *E. coli* exhibit high resistance rates to cefoxitin and fluoroquinolones in vitro [231], quinolones should be used only in patients with allergies to β-lactams.

Compared with agents in the control group, tigecycline displayed no significant differences in the clinical cure rate, microbial clearance rate, incidence of certain adverse reactions, and mortality rate, but the incidence of secondary infection was higher in the tigecycline group (RR, 1.95; 95% CI, 1.19–3.18; P = .008) [168, 207]. The US Food and Drug Administration issued a warning in 2013 stating that tigecycline could increase mortality. Tigecycline is only recommended for complicated IAI, severe skin and soft tissue infections, and community-acquired bacterial pneumonia. If infection with drug-resistant bacteria is suspected, a combination regimen that contains tigecycline is an option. The guidelines panel believes that the current medical evidence on tigecycline for IAI treatment is limited and insufficient to formulate recommendations. However, it is necessary to emphasize the rational use of tigecycline in the form of BPS.

4.2B De-escalation strategy

4.2.6 For patients with severe CA-IAI and HA-IAI, de-escalation of antimicrobial therapy is recommended once definitive culture results are available (strong recommendation, very low quality of evidence).

The main purpose of de-escalated antibiotic therapy is to use antibiotics rationally in order to reduce the selection pressure for drug-resistant strains. This strategy is widely recommended in major antimicrobial management guidelines. Currently, the following definitions of de-escalation therapy are accepted: narrowing the spectrum of antimicrobials; switching from combination therapy to monotherapy or reducing the types of antibiotics; and shortening the treatment duration or discontinuing antimicrobials. Owing to the limited number of studies on de-escalation strategies for antibiotic therapy for IAI, the literature search for this section was extended to include sepsis and septic shock. A total of 11 studies were included in the meta-analysis [232–242]. The results showed that the mortality rate was significantly lower in the de-escalation therapy group than in the non–de-escalation therapy group (RR, 0.66; 95% CI, .55–.78; P < .05), whereas the incidence of multidrug-resistant bacteria (RR, 0.77; 95% CI, .40–1.49; P = .43) and the recurrent infection rate (RR, 0.97; 95% CI, .50–1.89; P = .94) were not significantly different. The quality of the evidence was very low. Considering the role of de-escalation strategies in reducing bacterial resistance, the guidelines panel decided to recommend de-escalation strategies.

4.2C Antifungal therapy

4.2.7. Fluconazole or echinocandins are recommended for the treatment of intraabdominal candidiasis. Fluconazole is recommended for patients with mild to moderate CA-IAI, and echinocandins are recommended for patients with severe CA-IAI and HA-IAI (strong recommendation, moderate quality of evidence).

4.2.8 Amphotericin B is associated with a high incidence of adverse reactions and is recommended for the treatment of intraabdominal candidiasis only if no other antifungal agents are suitable (strong recommendation, moderate to low quality of evidence).

In our systematic review, we were unable to identify the indications for empiric antifungal initiation. Hence, there is no recommendation regarding use of empiric antifungals in patients with IAI. However, the guidelines panel pointed out that IAI patients with risk factors for fungal infection and accompanying symptoms, such as unexplained fever, or with laboratory results, such as positive fungal blood culture, in particular critically ill patients with septic shock, should be treated with empiric antifungal therapy as early as possible. The risk factors for intraabdominal fungal infection include a history of abdominal surgery, recurrent gastrointestinal perforation, upper gastrointestinal perforation, gastrointestinal fistula, use of broad-spectrum antibiotics (for more than 72 hours), pancreatitis, total parenteral nutrition, extensive burns, central venous catheterization, long intensive care unit (ICU) stay, sepsis, and severe disease (APACHE II score ≥25 points). Concomitant diabetes, heart disease, renal failure, immunosuppressive status, and multisite colonization of *Candida* are also risk factors for fungal infections.

Regarding the agents used for clearly diagnosed intraabdominal fungal infections, 2 recommendations were developed. It was found that fluconazole and amphotericin B displayed no difference in the clinical cure rate (RR, 0.45; 95% CI, .12–1.71) and mortality rate (RR, 0.65; 95% CI, .31–1.38). The mortality rate was significantly lower in the fluconazole group than in the echinocandin group (RR, 0.75; 95% CI, .57–.98) [227, 243–250]. This was mainly because echinocandin was primarily used for the treatment of patients with severe fungal infections, among whom most patients had septic shock, were admitted to the ICU, and had high APACHE II scores. The guidelines panel recommended fluconazole for patients with mild to moderate CA-IAI and echinocandins for patients with severe CA-IAI and HA-IAI. The quality of evidence was moderate.

Amphotericin B treatment more commonly causes adverse reactions such as hypokalemia and increased creatinine compared with nonamphotericin treatment (hypokalemia: RR, 0.49; 95% CI, .33–.73; elevated liver enzymes: RR, 0.29; 95% CI, .16–.54) [244, 248, 249]. Therefore, owing to its high toxicity,

amphotericin B is rarely used as a first-line medication in clinics, while the use of its derivatives is more common. Although the derivatives of amphotericin B are associated with few adverse reactions, clinical studies on their utility for IAI treatment are lacking. The guidelines panel recommends amphotericin B for the treatment of intraabdominal candidiasis only if other antifungal agents are not suitable.

4.2D Anti-enterococcal therapy

4.2.9 Empiric anti-enterococcal therapy is not necessary for patients with mild to moderate CA-IAI (strong recommendation, high quality of evidence).

4.2.10 Empiric anti-enterococcal therapy is recommended for patients with severe CA-IAI and HA-IAI (conditional recommendation, moderate quality of evidence).

Enterococci are important pathogens in hospital-acquired infections. The need for empiric anti-enterococcal therapy in IAI remains under debate. This section discusses whether patients with mild to moderate CA-IAI, severe CA-IAI, and HA-IAI require empiric anti-enterococcal therapy.

A total of 24 RCTs investigated whether enterococci should be treated with empiric anti-infective therapy when the patient has mild to moderate CA-IAI [151, 152, 156, 161, 162, 171, 182, 184, 186, 188, 191, 196, 198, 199, 203, 207, 210, 219, 251–256]. Using the treatment success rate as the main observation indicator, the results showed that empiric therapies that covered enterococci did not improve patient prognosis compared with empiric therapies in which enterococci were not covered, regardless of whether the population was clinically evaluable (CE), modified intent-to-treat (mITT), or microbiological intent-to-treat (MITT) (CE: RR, 0.99; 95% CI, .97–1.01; mITT: RR, 0.99; 95% CI, .95–1.03; MITT: RR, 1.02; 95% CI, .95–1.05). The quality of the evidence was high.

A total of 13 observational studies investigated whether severe CA-IAI and HA-IAI required empiric therapy against enterococci [230, 257–268]. The risk factors for enterococcal infection were revealed using meta-analysis. The results showed that malignant tumors (OR, 1.53; 95% CI, 1.16–2.03; $P = .003$) and hormone use (OR, 2.46; 95% CI, 1.71–3.54; $P < .00001$) were risk factors for enterococcal infection in severe CA-IAI. The quality of the evidence was moderate. For HA-IAI, the disease itself was a risk factor for enterococcal infection (OR, 2.81; 95% CI, 2.34–3.39). Concomitant surgery (OR, 2.88; 95% CI, 2.21–3.75; $P < .00001$), use of broad-spectrum antibiotics (OR, 2.40; 95% CI, 1.74–3.31), placement of a urinary catheter (OR, 1.78; 95% CI, 1.02–3.11), and ICU admission (OR, 2.54; 95% CI, 1.75–3.68) further increased the risk of enterococcal infection. Therefore, empiric anti-infective therapy for HA-IAI must cover enterococci. The quality of the evidence was moderate.

4.3 Duration of antimicrobial therapy

4.3.1 Antimicrobial therapy should be limited to 4 days in mild to moderate CA-IAI patients who have had adequate source control (strong recommendation, moderate quality of evidence).

4.3.2 Antimicrobial therapy could be limited to 7–10 days in patients with severe CA-IAI and HA-IAI (conditional recommendation, moderate quality of evidence)

4.3.3 The measurement of procalcitonin levels is suggested to support shortening the duration of antimicrobial therapy in IAI patients (conditional recommendation, moderate quality of evidence).

A total of 12 studies investigated the effects of different durations of antimicrobial therapies on the infectious complications of IAI. For mild to moderate CA-IAI with successful source control, the incidence of infection-related complications was lower after a short treatment duration of 4 days than after the standard treatment duration (OR, 1.27; 95% CI, 1.01–1.59) [269–279]. Only 1 study evaluated the duration of antimicrobial therapy for severe IAI (the DURAPOP study), which showed that there was no significant difference in infection-related complications between the 8-day short duration group and the longer duration group (OR, 1.17; 95% CI, .69–1.96) [280]. The guidelines panel believes that in order to avoid bacterial resistance caused by antibiotic overuse, a short treatment duration of less than 4 days after source control is recommended for mild to moderate CA-IAI and that the antimicrobial treatment duration for severe CA-IAI and HA-IAI should be 7–10 days. However, these recommendations cannot be generalized because short-term treatment may not be suitable for all mild to moderate infections owing to large variations in the immune status among patients. Hence, additional studies are needed to determine the population that is suitable for short-term therapy.

The use of PCT to guide discontinuation of antibiotics remains controversial. Two cohort studies suggested that the use of PCT significantly shortened the duration of antibiotic therapy but had no significant effect on prognosis [281, 282]; only 1 RCT did not reveal this trend [283]. To avoid bacterial resistance caused by long-term treatment, the guidelines panel maintains their recommendation that PCT is considered to support shortening the duration of antimicrobial therapy in IAI patients.

5. Microbiologic evaluation

5.1 Routine aerobic cultures of peritoneal fluid from mild to moderate CA-IAI patients should be considered. Routine aerobic and anaerobic cultures of peritoneal fluid should be obtained from severe CA-IAI and HA-IAI patients (BPS).

5.2 Blood cultures are not routinely recommended for patients with mild to moderate CA-IAI. Blood cultures

should be performed for patients with severe CA-IAI and HA-IAI, particularly for those with concomitant sepsis or those who are immunocompromised, in order to confirm the presence of bacteremia (BPS).

5.3 Blood cultures and peritoneal fluid cultures for fungal should be considered for IAI patients with risk factors (BPS).

Owing to the serious issue of bacterial resistance in China, the guidelines panel believes that peritoneal specimens should be routinely obtained from patients with IAI for culture and drug sensitivity testing in order to guide the appropriate use of antibiotics in clinics. Routine peritoneal fluid aerobic culture should be performed for mild to moderate CA-IAI, and routine peritoneal fluid aerobic and anaerobic cultures should be performed for severe CA-IAI and HA-IAI. Blood culture is not routinely recommended for mild to moderate CA-IAI. Blood culture should be performed for patients with severe CA-IAI and HA-IAI, particularly for those with concomitant sepsis or immunosuppression, in order to confirm the presence of bacteremia. For patients with risk factors of fungal infections, fungal blood culture and peritoneal fluid culture should be performed.

6. Nutrition

6.1 Nutritional Risk Screening 2002 and Nutrition Risk in Critically Ill should be considered for assessment of IAI patients' nutritional status (BPS).

6.2 Enteral or parenteral nutrition is recommended for IAI patients with malnutrition risk to improve prognosis (strong recommendation, very low quality of evidence).

6.3 Early enteral nutrition (24–72 hours) should be administered in IAI patients who can be fed enterally (strong recommendation, moderate to very low quality of evidence). Parenteral nutrition should be administered as early as possible if enteral feeding is not feasible (strong recommendation, very low quality of evidence). Parenteral nutrition in combination with enteral feeds should be considered if the targeted energy supply cannot be achieved by enteral nutrition alone (conditional recommendation, low to very low quality of evidence).

6.4 The initial amount of nonprotein calories should be considered as 20–25 kcal/(kg·d) when administering enteral nutrition for severe IAI patients. Feeds should then be advanced according to patient tolerance (conditional recommendation, low to moderate quality of evidence). Low-calorie parenteral nutrition (≤20 kcal/(kg·d)) should be considered as the initial strategy in patients with feeding intolerance. When feasible, advance enteral feeds as tolerated (BPS).

6.5 When administering parenteral nutrition to patients with mild to moderate IAI, the protein intake is suggested to be1.5 g/(kg·d) (conditional recommendation, very low quality of evidence). For patients with severe IAI, the suggested protein intake is 1.5–2 g/(kg·d) (conditional recommendation, moderate quality of evidence).

6.6 For patients with IAI who require parenteral nutrition, glutamine-containing immunonutrients may be used (conditional recommendation, low quality of evidence).

6.7 Vitamins with antioxidant effects (vitamins E and C) should be considered for severe IAI patients who require immunonutrition (conditional recommendation, low quality of evidence).

6.8 The routine use of fish oil as an immune supplement in IAI patients is recommended (strong recommendation, very low quality of evidence). Arginine should not be administrated as an immune supplement (strong recommendation, very low quality of evidence).

Screening for the risk of malnutrition is the first step in nutrition support. Serological indicators, physical examination, and various comprehensive assessment scales may be used to assess malnutrition. Our literature search did not reveal any evidence to support the optimal indicators or scales for screening malnutrition risk in patients with IAI. Accordingly, based on practical experience, the guidelines panel recommends using the NRS2002 and NUTRIC scales to assess the nutritional status of patients. These scales integrate data obtained from laboratory testing, physical examination, and medical history. These scales have widespread applications and do not require additional resources. For critically ill patients and patients treated in the emergency room, serological indicators or physical examination indicators may first be used to evaluate the nutritional status of patients. The accurate diagnosis can be made after the patient's condition becomes stable.

A systematic review indicated that the mortality rate was significantly higher among malnourished patients with IAI than among those with a normal nutritional status (RR, 2.21; 95% CI, 1.59–3.07) [284–293], and the incidence rate of multiple organ dysfunction syndrome (MODS) was increased (43 of 66 vs 27 of 134) [294]. The overall analysis suggested that malnutrition had an impact on prognosis and that patients with malnutrition should receive intervention.

A total of 30 studies on nutrition support methodologies for patients with IAI were included [295–324], of which 22 were RCTs and 8 were non-RCTs. The prognosis of the enteral nutrition group was significantly better than that of the parenteral nutrition group (RCTs: RR, 0.69; 95% CI, .54–.88 [296, 302, 303, 306, 308, 311, 315, 318, 323]; non-RCTs: RR, 0.64; 95% CI, .47–.86 [299, 300, 304, 317]). The sequential enteral and parenteral nutrition group did not display apparent advantages compared with the parenteral nutrition–alone group in the RCTs and non-RCTs. Similarly, the prognosis of the concurrent enteral and parenteral nutrition group was not different from that of the enteral nutrition–alone group or parenteral nutrition–alone

group. Compared with conventional fluid therapy, a meta-analysis based on RCTs showed that enteral or parenteral nutrition support did not improve the mortality rate (RR, 0.93; 95% CI, .76–1.13) [307, 319], but analysis based on non-RCTs showed a significant reduction in mortality rate, and the difference was significant (P = .008) [321]. Considering nutrition support methods, the guidelines panel believes that when patients are malnourished or are at risk of malnutrition, enteral or parenteral nutrition support should be provided as conventional fluid therapy alone is insufficient. Enteral nutrition is preferred over parenteral nutrition. Concurrent or sequential administration of enteral nutrition and parenteral nutrition cannot further improve patient prognosis. Thus, these should only be used when enteral nutrition alone cannot achieve the target energy supply.

Regarding the timing of nutrition support, 16 studies were included in the meta-analysis [314, 325–339]. Except for 1 study that compared the efficacy of early parenteral nutrition vs late parenteral nutrition [326], all other studies compared the timing of enteral nutrition. A meta-analysis of RCTs showed that the timing of enteral nutrition did not affect patient prognosis (RR, 1.11; 95% CI, .70–1.76) [314, 325–327, 329, 330, 332, 334, 336]. The quality of evidence was moderate. Another analysis of non-RCTs suggested that early enteral nutrition effectively improved patient prognosis and reduced the mortality rate (RR, 0.73; 95% CI, .61–.87) [328, 331, 333, 335, 337–339]. The quality of evidence was very low. The guidelines panel recommends early initiation of enteral nutrition. However, the definition of "early" is not standardized. It is recommended that enteral nutrition be administered to patients who are tolerant to gastrointestinal feeding within 24–72 hours.

A total of 19 studies that investigated the required amount of nutrients were included [340–358]. Nine studies that investigated nonprotein calorie requirements included patients with severe IAI who had an APACHE II score of ≥10 [340–343, 348, 352, 353, 355, 358]. The meta-analysis revealed that compared with 25–30 kcal/kg/d of nutrients, 20–25 kcal/kg/d of nutrients reduced the mortality rate (OR, 0.76; 95% CI, .60–.96) and shortened ICU stay (OR, 3.11; 95% CI, 4.59–1.62). Therefore, the guidelines panel recommends that while administering enteral nutrition to patients with severe IAI, the initial amount of nonprotein calories should be 20–25 kcal/(kg·d). If the patient is tolerant to the treatment, the amount can be gradually increased to normal levels. However, if enteral nutrition cannot be administered, low-calorie parenteral nutrition (≤20 kcal/[kg·d]) should be administered first. Then, depending on the patient's tolerance, this can be followed by enteral nutrition, and the amount of enteral nutrition can be gradually increased. Of 12 studies that investigated protein requirements, 10 included patients with severe IAI who had an APACHE II score of ≥10 [340, 344–347, 349–351, 356, 357], and 2 included patients with mild to moderate IAI who had an APACHE II score of <10 [354, 358]. When administering parenteral nutrition to patients with mild to moderate disease, 1.5 g/(kg·d) of protein could improve patients' nitrogen balance. For patients with severe IAI, the network meta-analysis showed that compared with 0.8 g/kg/d or 1–1.2 g/kg/d of protein, 1.5–2 g/(kg·d) of protein led to the lowest mortality rate. The quality of the evidence was moderate.

Glutamine, fish oil, vitamins, and arginine are common immunonutrients that are added to conventional nutritional preparations. A total of 12 RCTs evaluated the use of glutamine in critically ill patients with IAI [359–370]. A multicenter RCT performed by Heyland et al in 2013 [365] enrolled almost all types of patients, including those with cardiovascular disease, respiratory disease, gastrointestinal disease, and neurological disease. That study was excluded from the meta-analysis owing to the high level of heterogeneity. The meta-analysis suggested that the addition of glutamine to parenteral nutrition could reduce 6-month mortality (RR, 0.61; 95% CI, .44–.84). The quality of evidence was low. The addition of glutamine to enteral nutrition had no effect on 28-day mortality and 6-month mortality of patients with severe IAI (RR, 1.26; 95% CI, .95–1.68; RR, 1.11; 95% CI, .86–1.43) [360, 367–370]. There is a lack of medical evidence regarding the use of glutamine in patients with mild to moderate IAI; therefore, recommendations could not be formulated. Vitamins with antioxidant effects (vitamins E and C) significantly reduced the mortality rate of patients with IAI (RR, 0.67; 95% CI, .52–.85) [371, 372]. The quality of evidence was low.

Nine RCTs evaluated the effects of adding fish oil to parenteral nutrition on patient prognosis [373–381]. Our analysis suggested that the addition of fish oil to parenteral nutrition could reduce patient mortality (RR, 0.66; 95% CI, .46–.94). The quality of evidence was very low. Two studies that investigated the addition of fish oil to enteral nutrition were retrieved; 1 was an RCT [382] and the other was a cohort study [383]. According to these studies, adding fish oil to enteral nutrition did not increase the mortality rate and the incidence of complications in IAI patients. The guidelines panel does not recommend the routine use of arginine-containing immunonutrients, as the results of the meta-analysis suggest that adding arginine can significantly increase the mortality of IAI patients (RR, 1.22; 95% CI, 1.01–1.47) [306, 360, 369, 384–389].

7. Other supportive therapies

7.1 Continuous renal replacement therapy

7.1.1 Continuous renal replacement therapy (CRRT) plus conventional treatment for sepsis should be considered when necessary (conditional recommendation, moderate quality of evidence).

7.1.2 Both high-dose and conventionally low-dose CRRT can be used for sepsis (conditional recommendation, moderate quality of evidence).

CRRT can eliminate excessive inflammatory factors from the body and maintain fluid balance. It has been used for sepsis treatment; however, its effectiveness remains controversial. Owing to the limited literature regarding the use of CRRT for the treatment of IAI with concomitant sepsis, this section has been extended to CRRT application in the treatment of sepsis due to various etiologies.

A total of 18 RCTs evaluated the efficacy of CRRT on sepsis [390–407], of which 7 were in English and 11 were in Chinese. The results of the meta-analysis showed that compared with conventional therapies alone, the addition of CRRT to conventional therapies significantly reduced the overall mortality (RR, 0.59; 95% CI, .46–.71) and 28-day mortality (RR, 0.56; 95% CI, .45–.70). In addition, subgroup analysis in patients with sepsis and concomitant acute kidney injury (AKI) revealed that CRRT could reduce the death rate of patients with sepsis and concomitant AKI compared with conventional therapies (RR, 0.35; 95% CI, .22–.54). The quality of evidence was moderate.

A total of 11 RCTs that evaluated the effectiveness of different doses of CRRT in treating sepsis were included [409–418]. Currently, high-dose CRRT is administered with a minimum dose of 35 mL//kg/h. The criteria for the low doses varied across the included studies. The meta-analysis showed that high-dose CRRT of >35 mL/kg/h could not significantly improve the survival rate of patients with sepsis or septic shock compared with low-dose CRRT. The quality of evidence was moderate.

The results of the meta-analysis demonstrate definitive efficacy of CRRT when combined with conventional therapies for the treatment of sepsis. However, after comprehensively considering factors such as the resources required for CRRT, the guidelines panel indicated that the relevant recommendations are conditional.

7.2 Glucocorticoids

7.2.1 Use of glucocorticoids should be considered when adequate fluid resuscitation and vasopressor agents cannot restore hemodynamic stability for sepsis and septic shock that originated from IAI. Low-dose hydrocortisone is suggested for IAI patients who require glucocorticoids (conditional recommendation, moderate quality of evidence).

This section describes the evaluation of the use of glucocorticoids for IAI that has progressed to sepsis and septic shock. Eight RCTs were included [419–426]. The meta-analysis showed no improvement in 28-day mortality after glucocorticoid therapy (RR, 0.91; 95% CI, .79–1.06). The risk of secondary infections was not increased (RR, 1.04; 95% CI, .85–1.28), while the rate of shock reversal on day 7 increased significantly (OR, 2.09; 95% CI, 1.42–3.06). The quality of the evidence was moderate. The guidelines panel believes that glucocorticoid therapy may be used for patients with IAI whose hemodynamic stability cannot be maintained after treatment with fluid resuscitation and vasoactive agents. When glucocorticoid therapy is required, low-dose hydrocortisone is recommended.

7.3 Immunoglobulins

7.3.1 The use of immunoglobulins is not suggested in IAI patients with sepsis (conditional recommendation, low quality of evidence).

In addition to persistent inflammation, immunosuppression occurs during the course of sepsis owing to IAI or other conditions. Therefore, considering the effects of source control, antibiotic therapy, and organ support, the changes to the immune system have the potential to improve outcomes. A meta-analysis based on 7 RCTs revealed that the administration of immunoglobulins did not reduce overall mortality (RR, 0.99; 95% CI, .84–1.16; $P = .87$) or 28-day mortality (RR, 0.65; 95% CI, .42–1.0; $P = .05$) [427–433]. Current evidence does not support the routine use of immunoglobulins in adult patients with sepsis. In addition, immunoglobulin preparations are expensive and not suitable for routine clinical use. Therefore, the guidelines panel decided not to recommend the use of immunoglobulins for treatment of sepsis in adults.

8. Diagnosis and treatment of specific IAI

In preparing the guidelines, the original plan was to evaluate IAI that involved specific organs, such as the liver, gallbladder, pancreas, and appendix. However, owing to limited evidence, recommendations were only formulated for 2 major areas: pancreatic infection and appendicitis (Supplementary Material 1).

9. Source control failure

9.1 Use of systemic inflammation or organ system dysfunction measures to identify patients with likely source control failure is recommended (BPS).

9.2 The following should be considered as source control failure: progressive organ dysfunction within the first 24–48 hours after source control, no clinical improvement in organ dysfunction 48 hours or more after source control, or persistent signs of inflammation 5–7 days after source control (BPS).

9.3 Abdominal exploration should be considered in patients who had clinical deterioration or no improvement within 48–72 hours of the initial procedure. CT scanning and then percutaneous aspiration or drainage of any potentially infected fluid collections is suggested for likely source control failure at 48–72 hours after the initial procedure (BPS).

9.4 Use of the least invasive approach that will achieve definitive source control is recommended to allow resolution of the inflammatory response and organ dysfunction (BPS).

9.5 Further source control within 24 hours should be considered once source control failure is identified but as soon as feasible in patients with physiologic instability or progressive organ dysfunction (BPS).

9.6 Routine peritoneal cultures for patients with source control failure are recommended so that pathogen-directed antimicrobial therapy can be used (BPS).

Most studies used technical and procedural success criteria to define the adequacy of source control. Even after "adequate" source control, physicians still need to recognize and develop a therapeutic plan for the possibility that patients would fail that intervention. Given the importance of source control, source control failure also implies treatment failure. Hence, the recognition of source control failure becomes the primary issue to be solved. The guidelines panel believes that it is important to pay attention to the fluctuation of physiological parameters after surgical intervention. In fact, indicators that may be associated with source control failure include body temperature, heart rate, partial pressure of oxygen in arterial blood, inhaled oxygen concentration (ratio of partial pressure of oxygen to fraction of inspired oxygen), C-reactive protein, PCT, simplified acute physiology score II, MODS, fascial dehiscence, and inadequate coverage during initial empiric therapy [2]. Therefore, it is recommended that the aforementioned indicators be used to aid in the recognition of source control failure. It is recommended that systemic inflammation or organ system dysfunction be monitored in order to identify patients with source control failure.

Treatment can be considered a failure if the following signs occur after initial source control: progressive organ dysfunction occurs within 24–48 hours after source control, there is no clinical improvement in organ dysfunction after 48 hours or more after source control, or persistent inflammation exists 5–7 days after source control. Surgery is the most common modality for additional source control after failure of initial source control. However, it is still recommended that minimally invasive measures be started to reduce systemic inflammation and improve organ dysfunction. If minimally invasive measures cannot resolve large-scale or multiple sources of infection, it is recommended that open abdomen be considered for drainage and debridement.

Treatment failures that occur within 48 hours after initial source control are mostly due to improper control of the infection source rather than improper antimicrobial therapy. These patients usually receive a limited number of antimicrobial agents, and these agents are unlikely to exert selective pressure on the pathogen at the time of initial source control. In contrast, late treatment failures that occur 48 hours after source control may result from the selection of resistant bacteria owing to the long duration of antimicrobial therapy. The guidelines panel believes that the regimens for antibiotic therapy do not need to be changed for patients with IAI who have early treatment failure and for those who have had additional source control within 48 hours of initial source control. Patients with IAI who have late treatment failure may switch to antibiotics suitable for HA-IAI; if feasible, the type of drug should be changed. Considering microbiological examination, peritoneal fluid culture should be performed for all patients with treatment failure to guide the selection of targeted therapy. This may also facilitate the use of de-escalation therapy.

The success of IAI treatment is usually indicated by the restoration of normal body temperature, inflammatory indicators, and gastrointestinal function. However, in certain groups of patients with infection, these symptoms remain even if the infection has been controlled. Patients with persistent inflammation should undergo imaging tests to determine the presence of recurrent or persistent IAI and to exclude the presence of other infection sources. The guidelines panel believes that antibiotic therapy should be discontinued for patients with relapsed or persistent IAI who exhibit clinical signs of treatment failure but whose imaging findings are negative. In contrast, the choice of anti-infective agents is the same as that for HA-IAI for patients with IAI who exhibit clinical signs of treatment failure and whose imaging findings show persistent intraabdominal inflammation. If feasible, the type of drug should be changed. If clinical symptoms do not improve after treatment, antibacterial therapy should be discontinued; therapy should only be resumed if the patient's condition worsens.

For patients with relapsed or persistent IAI confirmed on imaging tests, the first consideration should be additional source control. However, if the risk of surgical reexploration is too high and the infection cannot be controlled with less-invasive procedures, further intervention should not be performed. The only treatment option for this type of patient is to adjust the drugs being used. The guidelines panel recommends that antibacterial therapy be continued for patients with IAI with clinical evidence of treatment failure, whose imaging tests suggest relapse or persistent IAI, and who are unable to undergo source control. Antibacterial therapy should be discontinued when systemic inflammation or organ dysfunction improves. Immediate intervention should be provided when the patient's condition permits the readministration of drugs for source control. These patients should be monitored for drug-resistant pathogens, and the drug regimens should be adjusted according to culture results.

CONCLUSIONS

The treatment of IAI is a comprehensive undertaking that combines multiple measures, including fluid resuscitation, source control, organ function support, antimicrobial therapy, nutrition, and other supportive therapies. The panel elected to focus on these issues in these guidelines, which cover more aspects of

management compared with US and European IAI guidelines. The current guidelines were developed on the basis of the results from existing medical research and the clinical practice in China. The final guidelines were formulated after repeated discussions among experts. However, certain limitations still exist, such as the timing of organ function support for severe IAI and the empiric antimicrobial regimens in regions with different drug-resistant conditions. These unresolved issues need to be evaluated via additional high-quality clinical research studies in the future. Nevertheless, clinicians should consider the conditions of the hospitals in which they are located and the specific patient circumstances when applying these recommendations. This will align treatments closer to practical situations and ensure patient safety.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Financial support. This work was supported by the National Major Scientific and Technological Special Project for "Significant New Drugs Development" (2017ZX09304005-002), Distinguished Scholars Foundation of Jiangsu Province (JCRCB2016006), and Innovation Project of Military Medicine (16CXZ007).

Supplement sponsorship. This supplement was sponsored by MSD.

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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