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REVIEW ARTICLE

Is fixed short-course antimicrobial therapy justified for patients who are critically ill with intra-abdominal infections?

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Abstract:

A long-course antibiotic therapy increases the risk of antibiotic resistance. A 7- to 14-day duration of therapy has been traditionally adopted in patients with intra-abdominal infections (IAIs). Prophylactic antibiotic use is warranted in uncomplicated IAIs, in which the infection involves a single organ, and the source of the infection is completely eradicated by a surgical procedure. A large, randomized clinical trial of the treatment of complicated IAIs recently demonstrated that a fixed 4-day course of antibiotic therapy was as effective as a long-course therapy in patients who underwent adequate source control. Considering the poor prognosis and lack of clear evidence available for shortening the duration of antibiotic therapy in patients who are critically ill or those with ongoing signs of sepsis, the duration of therapy for complicated IAIs should be individually determined according to the clinical course. Limiting therapy to no more than 7 days seems to be warranted in patients who are critically ill with a good clinical response.

Keywords:

duration of therapy, antimicrobial agents, intra-abdominal infection, critically ill patients

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Introduction

Complicated intra-abdominal infections (IAIs) lead to abscess formation or generalized peritonitis, and patients with IAIs are at risk of sepsis and mortality. Clinical guidelines include recommendations for source control and appropriate selection of antimicrobial agents based on high-quality evidence[1-4)]. A treatment effect of antibiotics is not expected unless source control has been adequately performed. Early treatment failure within 48 hours of source control results from an inadequate initial intervention in patients with IAIs. In contrast, late treatment failure occurring after 48 hours is probably due to failure of antimicrobial therapy caused by resistant organisms[5)].

Traditionally, surgeons treat patients until the resolution of physiological abnormalities[2)]. However, limiting the duration of antibiotic therapy is an important way to decrease the development of antibiotic resistance. Many attempts have been made to demonstrate the efficacy of short-course therapy. A large, randomized clinical trial (RCT)[6)] recently demonstrated that a fixed 4-day course of antibiotic therapy was as effective as a long-course therapy in patients who underwent adequate source control. In this review, we have summarized the duration of antimicrobial therapy in patients with IAIs and have evaluated whether a short-course antibiotic therapy can be applied to patients who are critically ill with complicated IAIs.

1. Peritoneal Contamination

Contamination of the abdominal cavity by organisms is not synonymous with an established IAI. The use of antimicrobial agents for contaminated wounds (wound class III) is classified as prophylaxis and not as treatment of a presumed

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infection[1,2]. Patients with significant intraoperative slippage of intestinal contents are recommended to undergo treatment with prophylactic antibiotics despite the fact that such patients are at an increased risk for surgical site infections (SSI). Fabian et al.[7] reported that 24-hour antibiotic therapy is satisfactory for penetrating abdominal trauma regardless of the presence of contamination and the degree of injury. The abdominal cavity needs to be exposed to organisms for at least 12-24 hours for the development of an IAI. Perioperative antimicrobial therapy for no more than 24 hours is recommended in patients with traumatic and iatrogenic perforations who undergo surgeries within 12 hours and in patients with gastroduodenal perforations who undergo surgeries within 24 hours[1,2,8].

2. Uncomplicated IAIs

Uncomplicated IAIs involve intramural inflammation of the gastrointestinal tract without anatomical disruption, and the infection is contained within a single organ[1]. Although a complicated IAI extending beyond the source organ into the peritoneal space to cause localized or diffuse peritonitis should be treated with a source control procedure[5], surgical management may or may not be required in patients with uncomplicated IAIs.

a. Patients with source control procedures

Patients with an infected focus that was completely eradicated at the time of surgery including those with non-perforated appendicitis[9,10], non-perforated acute cholecystitis[11], or bowel necrosis caused by emboli or adhesive intestinal obstruction without perforation can be treated with antimicrobials for 24 hours or less[12]. In an RCT of patients with non-perforated appendicitis undergoing open appendectomy[9], 92 patients received a single dose of a preoperative antibiotic, 94 received three doses of a perioperative antibiotic, and 83 received a 5-day perioperative antibiotic therapy. The postoperative infective complication rate was not significantly different among the groups (6.5%, 6.4%, and 3.6%, respectively). Complications related to antibiotic treatment were significantly more common in the 5-day perioperative antibiotic group than in the single-dose preoperative antibiotic group. Hussain et al.[10] also reported that a single dose of a preoperative antibiotic can sufficiently reduce the incidence of SSI following appendectomy for non-perforated appendicitis. Regimbeau et al.[11] performed a study in which patients with grade I or II acute calculous cholecystitis received preoperative and intraoperative antibiotics and were randomly allocated after surgery to either discontinue the antibiotic or to 5-day antibiotic therapy. The researchers reported that the lack of postoperative antibiotic treatment did not result in a greater incidence of postoperative infections.

b. Patients without a source control procedure

Computed tomography confirmed that uncomplicated colonic diverticulitis[13] and uncomplicated appendicitis[14] can be treated without a source control procedure. Although a recent RCT[12] demonstrated that observational treatment without antibiotics can be appropriate in patients with uncomplicated diverticulitis[13], omission of antimicrobial therapy should be indicated only in selected patients who are low-risk[2]. Regarding the duration of antimicrobial therapy, no more than 5-7 days is suggested in the revised guidelines established by the Surgical Infection Society (SIS)[2]. However, there are insufficient data to recommend a short-course therapy in patients with uncomplicated IAIs and in these patients, a definitive source control procedure is not performed. Therefore, continuing antimicrobial therapy until the resolution of symptoms is reasonable in these patients. Because a clear distinction between a complicated and uncomplicated disease is difficult in some patients with IAIs and uncomplicated IAIs have a probability of progressing to complicated infections if not adequately treated, cautious monitoring of clinical parameters is required during administration of antimicrobial therapy, and patients with persistent infections after 5-7 days should be reassessed for a potential source control intervention[2].

3. Complicated IAIs

In complicated IAIs, the infectious process proceeds beyond the organ and extends to the peritoneum. Source control intervention is mandatory in patients with complicated IAIs[5]. Antibiotic treatment of complicated IAIs can prevent local and hematogenous spread and may reduce late complications. In the development of antimicrobial agents for the treatment of IAI, phase 3 clinical trials are performed in patients with complicated IAIs to confirm the effectiveness of the new treatment compared with the current standard treatment.

a. Conventional duration of antimicrobial therapy

Antimicrobial therapy generally continues until resolution of the patient's symptoms and clinical abnormalities, and a conventional duration of 7-14 days of therapy has been adopted in patients with complicated IAIs[15-17]. In a phase 3 study on the efficacy of ceftazidime and avibactam plus metronidazole versus meropenem in patients with complicated IAIs, the study treatments were administered for 5-14 days[15]. After ≥ 5 full days of administration, treatment could be discontinued if patients showed clinical improvement. In a phase 3 study of ceftolozane and tazobactam plus metronidazole versus meropenem[16], treatment could be continued for up to 14 days in patients with non-appendix-related diffuse peritonitis. Similarly, the study drugs were administered

for a maximum of 14 days in phase 3 and 4 trials of tigecycline for treatment of complicated IAIs[17]. These protocols were established based on the belief that a longer duration of antimicrobial administration decreases the risk of treatment failure, including recurrent IAIs.

b. Short-course antimicrobial therapy

Possible disadvantages of prolonged antimicrobial treatment include the induction of resistance among organisms, adverse effects of the antimicrobial agent used, and increased cost. Riccio et al.[18] demonstrated that a long-course antibiotic therapy for IAI was associated with an increased risk of subsequent extra-abdominal infections and high mortality. Guidelines established by the Infectious Disease Society of America and SIS recommend limiting the duration of antibiotics to 4-7 days in patients with complicated IAIs[1]. Recent studies[6,19,20] supported an even shorter duration of therapy.

1) IAIs with mild severity including perforated acute appendicitis

Van Rossem et al.[19] compared two protocols involving either 3-5 days of postoperative antibiotic treatment in patients with an appendectomy for complicated appendicitis, and no difference was found in terms of developing an intra-abdominal abscess or any infectious complications. Basoli et al.[20] conducted an RCT that compared the clinical efficacy of ertapenem for 3 days versus ≥5 days in patients with localized peritonitis requiring surgical intervention. Appendicitis was found in 45 of 90 evaluable patients, and the mean Acute Physiology and Chronic Health Evaluation II (APACHE II) score was 6.2, indicating that the severity of the disease was mild. In total, 92.9% of patients in the 3-day therapy group and 89.6% in the prolonged therapy group were cured. The difference between the two groups was not statistically significant. Short-course antibiotic therapy for 3 days for IAIs with mild severity, such as perforated acute appendicitis, is reasonable and acceptable by most attending surgeons. However, the duration of antibiotic therapy for IAIs with moderate to high severity should be determined.

2) IAIs with moderate severity

Sawyer et al.[6] conducted an RCT named "STOP-IT" to evaluate short-course antibiotic therapy in patients who underwent adequate source control. The mean APACHE II score was 10.1 (83.9% of patients had an APACHE II score of <15), indicating moderate severity, and the number of patients with complicated appendicitis was restricted to 15%. The primary endpoint of SSI, recurrent IAI, or death occurred in 21.8% of patients with a fixed 4-day duration of therapy compared with 22.3% of patients who received antibiotics until 2 days after the resolution of infection ($p = 0.92$). They concluded that 4 full days (96 h) of therapy is non-inferior to a traditional and long-course therapy. The study revealed significantly fewer median antimicrobial-free days at 30 days in patients who received the 4-day therapy than those who received the long-course antibiotic therapy, indicating that additional antibiotic therapy for recurrent infections did not impair the beneficial effect of limited use of antibiotics in patients who received the 4-day therapy.

Although the incidence of SSI and recurrent IAI did not differ between the two study groups, these infections were diagnosed significantly later in patients who received the long-course therapy than in those who received the 4-day therapy[6]. Early discontinuation of antibiotic therapy might facilitate early recognition of these postoperative infections. As a practical consequence, clinicians may be reluctant to try new strategies tested only by non-inferiority trials. The desirability of outcome ranking (DOOR) and response adjusted for duration of antibiotic risk (RADAR) analyses were recently introduced as innovative approaches. Celestin et al.[21] retrospectively applied these methods (DOOR/RADAR) to STOP-IT data, and the results suggested that a short-duration therapy is "superior" to a long-course therapy for complicated IAIs.

Several factors should be taken into consideration before introducing short-course antibiotic therapy into clinical practice in patients with complicated IAIs. In the above-mentioned RCT, the rate of nonadherence to the protocol was 18% in patients who received the 4-day therapy, and percutaneous drainage was performed as a source control procedure in one-third of the patients who were studied[6]. The optimal duration of therapy might differ between interventional radiology for well-encapsulated intra-abdominal abscesses and surgical approaches for diffuse peritonitis. The SSI rate is 38.5% in dirty and infected wounds in colorectal surgery[22], and tertiary peritonitis may occur after surgery for bacterial secondary peritonitis. In contrast, these risks are uncommon with a percutaneous catheter drainage procedure.

The process of percutaneous drainage is a continuum that starts with the first catheter placement. Further, this is followed by drainage of infected liquid over several days because of the inability to remove all gross pathologic tissue in a percutaneous intervention. Successful source control using percutaneous catheter drainage is generally achieved within 4 days[5], and antimicrobial treatment is theoretically unnecessary thereafter. Rattan et al.[23] confirmed that patients who underwent percutaneous drainage of IAIs did not require a long-course antimicrobial therapy, and the rate of mortality and recurrent IAI was 0% and 10%, respectively, in patients who received the 4-day therapy. With regard to source control with a surgical procedure, the high postoperative infection rate and the impact of the surgical insult should be considered before implementation of the 4-day therapy, especially in patients who are critically ill.

c. Duration of antimicrobial therapy in patients who are critically ill

Data regarding the optimal duration of antibiotic therapy for complicated IAIs in patients who are critically ill in the intensive care unit are lacking. Considering the poor prognosis and lack of clear evidence available for shortening the duration of antibiotic therapy[24-27], the duration of therapy for complicated IAIs should be individually determined according to the clinical course in patients who are critically ill or those with ongoing signs of sepsis[2]. Limiting therapy to no more than 7 days, as recommended in previous guidelines[1], seems to be warranted in patients who are critically ill with a good clinical course. If progressive organ dysfunction develops within the first 24-48 hours after source control or if no clinical improvement in organ dysfunction has occurred after 48 hours, patients should be assessed for source control failure[2]. If signs of infection persist for 4-7 days, imaging tests should be performed to determine the requirement of additional source control rather than prolonging antimicrobial treatment[1].

1) Secondary bacteremia from IAI

In a systematic review and meta-analysis[28] involving 155 patients with bacteremia, including 40 patients with IAIs receiving short-course (5-7 days) versus long-course (7-21 days) antibiotic therapy, no significant differences were found in the clinical cure and survival rates. In the revised SIS guidelines[2], the committee suggested that most patients with secondary bacteremia caused by IAI and patients who are no longer bacteremic can discontinue antibiotic therapy after 7 days as long as an adequate source control has been achieved. However, no study has yet been conducted to evaluate the duration of antibiotic therapy only in patients with secondary bacteremia from an abdominal source. Alqarni et al.[29] analyzed 64 (19%) patients with bacteremia among 343 patients with postoperative IAI. The factors associated with bacteremia were the presence of immunosuppression, ongoing cancer, and a high Sepsis-related Organ Failure Assessment (SOFA) score, and the mortality rate was 41%. Antibiotic therapy for postoperative IAI in patients with bacteremia was administered for 11 ± 6 days.

2) High severity score

High severity of illness (APACHE II score of ≥15) is one of the predictive factors for failure of therapy[1]. Although Rattan et al.[30] demonstrated that short-course (4-day) and long-course antimicrobial therapy had similar incidence of complications among patients with an APACHE II score of ≥15, the conclusions are limited by bias because of the post hoc analysis nature of this study and the fact that the sample sizes were too small (48 and 35, respectively) to evaluate the efficacy of 4-day therapy in patients with highly severe illness. Montravers et al.[31] randomly assigned patients who are critically ill with postoperative IAIs to either immediately stop antimicrobial therapy on day 8 or to continue antimicrobial therapy until day 15. The median Simplified Acute Physiology Score (SAPS) II was 45, indicating a high severity of illness in their cohort. The most common source of infection was the colon, rectum, or small bowel, and no patients with complicated appendicitis were included in the study. Percutaneous drainage was conducted in only 2.5% of patients. On day 8, 27% of patients received mechanical ventilation, and the 45-day mortality rate was 11.2%. The number of antibiotic-free days between days 8 and 28 was higher in the 8-day therapy group than in the 15-day therapy group. No difference was found in the mortality rate or reoperation rate between the two treatment groups. However, the issues of a higher number of patients requiring subsequent drainage and the increased rate of bacteremia following 8-day therapy require clarification.

Maseda et al.[32] conducted a study to evaluate the efficacy of a procalcitonin (PCT)-guided antibiotic therapy in patients who are critically ill with secondary peritonitis. The severity of their patients' illnesses, with a mean SAPS II score of 43.4, was comparable with that reported by Montravers et al.[31]. The duration of treatment was significantly shorter in the PCT-guided group than in the non-PCT-guided group (5.1 ± 2.1 vs. 10.2 ± 3.7 days, respectively) without affecting the outcome. This study suggests that the duration of antibiotic therapy may be shorter than the 8-day regimen proposed by Montravers et al.[31] after adequate source control surgery in patients who are critically ill.

3) Sepsis and septic shock

Rattan et al.[32] evaluated the efficacy of a 4-day antibiotic therapy regimen in a subset of patients of STOP-IT with complicated IAIs presenting with sepsis diagnosed according to an old definition [two or more systemic inflammatory response syndrome (SIRS) criteria]. Because the SIRS criteria do not indicate a dysregulated or life-threatening response, relatively few patients who were severely ill with organ dysfunction or shock were enrolled in the trial, and the mortality rate was only 1.5% and 0.0% in each group. In contrast, the new definition emphasizes that sepsis is organ dysfunction caused by a dysregulated host response to infection and that organ dysfunction is identified as an acute change of ≥2 points in the total SOFA score[24]. Patients with a SOFA score of ≥2 points had an overall mortality risk of approximately 10% in a general hospital population of patients with presumed infections[25].

One study showed that the risk-adjusted hospital mortality rate was 42.3% in patients with septic shock defined as fluid-resistant hypotension requiring vasopressors and hyperlactatemia (>2 mmol/L)[24]. Among patients with secondary generalized peritonitis, a significantly higher mortality rate was demonstrated in patients presenting with than without septic shock (35% vs. 8%, respectively)[26]. Visser et al.[27] reported that antimicrobial treatment should not be discontin-

Table 1. Optimal Duration of Therapy in Patients with IAIs Who Underwent an Adequate Source Control Procedure.

Intra-abdominal infection and contamination	Indication	Optimal duration of therapy
Contamination of the abdominal cavity	Patients with intraoperative significant slippage of intestinal contents and gastroduodenal perforations underwent surgery within 24 hours. With traumatic and iatrogenic perforations, they underwent surgery within 12 hours	24 hours or less (prophylactic use)
Uncomplicated IAI in which infected focus was completely eradicated at the time of surgery	Patients with non-perforated appendicitis, non-perforated acute cholecystitis, or bowel necrosis without perforation	24 hours or less (prophylactic use)
Uncomplicated IAI without a definitive source control intervention	Patients with uncomplicated acute diverticulitis or uncomplicated acute appendicitis	There are insufficient data, and antimicrobial therapy could be continued until the resolution of clinical abnormalities. Patients with persistent infection after 5-7 days should be reassessed for a potential source control intervention
Complicated IAIs with mild severity	Patients with perforated acute appendicitis	3 days
Complicated IAIs with moderate severity	Patients with APACHE II score of <15. Patients with percutaneous drainage for a localized abscess are good candidates	4 days
Complicated IAIs in critically ill patients	Patients with transient secondary bacteremia	7 days
	Patients with a high severity score	Although one study demonstrated usefulness of 8-day therapy, there are insufficient data
	Patients with sepsis and septic shock	Duration should be determined individually according to the clinical course. Limiting therapy to no more than 7 days seems to be warranted in patients with a good clinical response
Complicated IAIs in patients with immunosuppression	Patients receiving immunosuppressive medication	There are insufficient data, and the duration should be determined individually

IAI: intra-abdominal infection; APACHE II: Acute Physiology and Chronic Health Evaluation II

ued in patients with a high score in a scoring system that predicts recurrence of fulminant IAI. Based on these findings, whether a short-course (4-day) therapy can be used in patients with sepsis and septic shock remains uncertain.

Conclusions

In Table 1, we have summarized the optimal duration of antibiotic therapy in patients with IAIs. The outcome in patients with complicated IAIs is heavily dependent on several factors other than antibiotics[1,2,29,34]. These include patient-related factors (immunosuppression or a dysregulated host response to infection), the type of IAI (secondary or tertiary peritonitis, community-acquired, or healthcare and hospital-associated infection), local disease factors (organ of origin, diffuse peritonitis or localized abscess, single or multiple abscesses, or adequacy of source control), and concomitant secondary bacteremia. The aforementioned risk factors should be considered when short-course antimicrobial therapy is being contemplated. In the revised SIS guidelines[2], the committee suggested caution when applying the short-course therapy rule to patients who are immunosuppressed or those who are critically ill with severe sepsis and septic shock. Further investigation is required to confirm the efficacy of short-course antibiotic therapy in these patients who are high-risk with complicated IAIs.

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Conflicts of Interest

Yoshio Takesue received speaker's honoraria from Taisho Toyama Pharmaceutical Co., Ltd., MSD K.K., and Astellas Pharma Inc., and received donations from Sumitomo Dainippon Pharma Co., Ltd., and Shionogi & Co., Ltd. The other authors declare that there are no conflicts of interest.

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