Percutaneously drained intra-abdominal infections do not require longer duration of antimicrobial therapy

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BACKGROUND: The length of antimicrobial therapy in complicated intra-abdominal infections (CIAIs) is controversial. A recent prospective, multicenter, randomized controlled trial found that 4 days of antimicrobial therapy after source control of CIAI resulted in similar outcomes when compared with longer duration. We sought to examine whether outcomes remain similar in the subpopulation who received percutaneous drainage for source control of CIAI.

METHODS: With the use of the STOP-IT database, patients with a CIAI who received percutaneous drainage were analyzed. Patients were randomized to receive antibiotics until 2 days after the resolution of fever, leukocytosis, and ileus, with a maximum of 10 days of therapy or to receive a fixed course of antibiotics for 4 ± 1 days. Outcomes included incidence of and time to recurrent intra-abdominal infection, *Clostridium difficile* infection, and extra-abdominal infections as well as hospital days and mortality.

RESULTS: Of 518 enrolled patients, 129 met inclusion criteria. Baseline characteristics, including demographics, comorbidities, and severity of illness, were similar. When comparing outcomes of the 4-day group (n = 72) with those of the longer group (n = 57), rates of recurrent intra-abdominal infection (9.7% vs. 10.5%, $p = 1.00$), *C. difficile* infection (0% vs. 1.8%, $p = 0.442$), and hospital days (4.0 [2.0–7.5] vs. 4.0 [3.0–8.0], $p = 0.91$) were similar. Time to recurrent infection was shorter in the 4-day group (12.7 [6.2] days vs. 21.3 [4.2] days, $p = 0.015$). There was no mortality.

CONCLUSION: In this post hoc analysis of a prospective, multicenter, randomized trial, there was no difference in outcome between a shorter and longer duration of antimicrobial therapy in those with percutaneously drained source control of CIAI. (*J Trauma Acute Care Surg.* 2016;81: 108–113. Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Therapeutic/care management study, level IV.

KEY WORDS: Percutaneous drainage; intra-abdominal infection; sepsis; antibiotics.

Complicated intra-abdominal infections (CIAIs) are an important cause of morbidity and mortality worldwide. They include a wide range of disease processes. The most common source is the appendix, accounting for approximately one third of CIAIs regardless of geographic location.[1–3] Despite this diversity in organ involvement, mortality seems to be more dependent on intrinsic factors of the individual than the originating organ.[3]

Nevertheless, principles of treatment remain relatively constant: resuscitation of those with sepsis, removal of the source of the inflammatory response, and systemic antimicrobial therapy. While robust data support the use of antimicrobial therapy in CIAI, the duration of such therapy is less well studied. Joint guidelines from the Surgical Infection Society and the Infectious Diseases Society of America recommend 4 days to 7 days of antimicrobial therapy but are based only on Level B-III evidence.[4] Clinically significant infectious complications arise in approximately 20% of CIAIs.[3] As such, the ideal duration of antimicrobial therapy in CIAI that has undergone source control is still controversial. Recently, the STOP-IT trial, a prospective, randomized, multicenter, international trial on CIAI found that 4 days of antimicrobial therapy resulted in similar outcomes to a longer duration when adequate source control was achieved.[5]

In addition to open surgical drainage for CIAI, percutaneous drainage is an increasingly used intervention for source control.[1,2] Studies demonstrate similar outcomes in surgical and percutaneous approaches for appropriately selected patients with CIAI.[6–16] In addition, in prospective international studies, outcomes seem similar in surgical and percutaneous source control.[1,2] However, given the difference in the ability to remove gross pathologic tissue between surgical and percutaneous drainage, it is unknown if shortening duration of antibiotic therapy is safe is percutaneously drained CIAI. We hypothesized that there is no difference in outcome between shorter and longer antimicrobial therapy in patients with CIAI adequately controlled with percutaneous drainage.

PATIENTS AND METHODS

The STOP-IT trial was conducted between August 2008 and August 2013 at US and Canadian academic medical centers. Its protocol, definitions, and diagnostic criteria for infections have been detailed elsewhere.[5,17] In short, enrolled patients must have been hospitalized with a CIAI, must be 16 years or older, and must have undergone a successful source control procedure. Infection was diagnosed when purulence was noted, organisms were cultured from an intra-abdominal source, an abscess was apparent, or a surgeon or attending physician made a diagnosis of intra-abdominal infection. To be eligible for participation, subjects had either a white blood cell count of greater than 11,000 cells/μL, oral temperature of 38°C or higher, or gastrointestinal dysfunction preventing normal dietary intake within 24 hours of initial intervention. The control group received antibiotics until their temperature remained lower than 38° C, their white blood cell count remained less than 11,000 cells/μL, and they could tolerate oral diet for two calendar days. If antimicrobial duration reached 10 calendar days before achievement of those clinical parameters, administration was

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TABLE 1. Baseline Demographic and Clinical Characteristics, According to Study Group. Per-Protocol Analysis*

	Control Group (n = 57)	Experimental Group (n = 72)
Age, mean (SD), y	50 (15)	52 (17)
Male sex	33 (57.9)	38 (52.8)
Race or ethnic group**		
White	46 (80.7)	54 (75.0)
Black	11 (19.3)	14 (19.4)
Other	0 (0)	2 (3.0)
Characteristics of index infection		
APACHE II score,† mean (SD)	7.8 (3.9)	9.4 (5.6)
Maximum white cell blood count, mean (SD), per microliter	14.0 (6.0)	15.4 (5.6)
Maximum body temperature, mean (SD), °C	37.6 (0.8)	37.7 (0.8)
Organ of origin		
Colon or rectum	11 (19.3)	28 (38.9)
Appendix	4 (7.0)	4 (5.6)
Small bowel	7 (12.3)	13 (18.1)
Pancreas	6 (10.5)	2 (2.8)
Liver/biliary	11 (19.3)	11 (15.3)
Other	18 (31.6)	14 (19.4)

*There were no significant differences between the groups ($p < 0.05$).
**Race and ethnic groups were reported by the patient or surrogate.
†APACHE II scores range from 0 to 71, with higher scores indicating an increased risk of death.

stopped. The experimental group received 4 ± 1 calendar days of antimicrobial therapy. The primary outcome of the original study was a composite incidence of surgical site, recurrent intra-abdominal infection, and mortality within 30 days of the intervention.

In this post hoc subgroup analysis, patients whose treatment adhered to the STOP-IT protocol and who underwent percutaneous drainage for source control of their CIAI were selected. Percutaneous drains were managed according to local practice based on surgeon discretion. Because analysis was performed on a deidentified database, the institutional review board declared this study exempt in accordance with US Health and Human Services federal guidelines.

Patients were divided into short- and long-course groups. Outcome measures included incidence of and days to recurrent intra-abdominal infection, extra-abdominal infection, and *Clostridium difficile* infection (CDI). Because percutaneously drained infections cannot develop superficial surgical site infections (SSIs), these were not recorded. The calendar day of percutaneous drainage was considered Day 0. Recurrent intra-abdominal infection was based on the Centers for Disease Control definition of intra-abdominal organ/space SSIs.[18] The patient must exhibit, related to the operative procedure, purulent drainage from an intra-abdominal drain, organisms on intra-abdominal culture, intra-abdominal abscess, or a diagnosis of an intra-abdominal infection by a surgeon or attending physician within 30 days (or 1 year if an implant was left in place). In this study, recurrent intra-abdominal infection was only diagnosed if an infection met the previously mentioned criteria and required further percutaneous or surgical intervention. Infections that were neither SSIs nor recurrent intra-abdominal infections were categorized as extra-abdominal infections. Hospital days and mortality were also measured.

Parametric data were reported as means with SDs and compared using a two-tailed, independent samples t test. Nonparametric data were reported as medians with interquartile ranges and were compared using independent samples Mann-Whitney U-test. Categorical variables were compared using a Fisher's exact test with significance at $p \leq 0.05$. Data were analyzed using SPSS Statistics for Windows, version 22 (IBM, Armonk, NY).

RESULTS

Of the 519 patients in the STOP-IT database, 399 adhered to the trial protocol. Of those, 129 underwent percutaneous drainage. The short-course group included 72 patients, and the long-course group included 57 patients. There was no difference in baseline characteristics between groups (Table 1). The experimental group received a duration of antimicrobial therapy significantly shorter than that of the control group (4.3 [0.6] days vs. 6.8 [2.7] days, $p < 0.001$).

Results are reported in Table 2. Rate of recurrent intra-abdominal infection in the short-course group was similar to the long-course group (9.7% vs. 10.5%, $p = 1.000$). Days to recurrent intra-abdominal infection were significantly shorter in the short-course group (12.7 [6.2] days vs. 21.3 [4.2] days, $p = 0.015$). Extra-abdominal infection occurred in 5.3% of long-course patients and 2.8% of short-course patients, although this difference was not significant ($p = 0.654$). In total, there

TABLE 2. Primary and Major Secondary Outcomes. Per Protocol Analysis

	Control Group (n = 57)	Experimental Group (n = 72)	p
Primary outcomes			
Recurrent intra-abdominal infection	6 (10.5)	7 (9.7)	1.000
Death	0 (0)	0 (0)	—
Time to event, no. days after index source control procedure			
Diagnosis of recurrent intra-abdominal infection, mean (SD)	21.3 (4.2)	12.7 (6.2)	0.015
Death	—	—	—
Secondary outcome			
Recurrent intra-abdominal infection with resistant pathogen	3 (5.3)	0 (0)	0.084
Any extra-abdominal infection	3 (5.3)	3 (4.2)	0.781
CDI	1 (1.8)	0 (0)	0.442
Duration of outcome, d			
Antimicrobial therapy for index infection, mean (SD)	6.8 (2.7)	4.3 (0.6)	<0.001
Antimicrobial-free days at 30 d	22.0 (20.0–25.0)	26.0 (25.0–26.0)	<0.001
Hospitalization after index procedure	4.0 (3.0–8.0)	4.0 (2.0–7.5)	0.909
Hospital-free days at 30 d	25.0 (21.0–27.0)	26.0 (22.0–27.0)	0.489

TABLE 3. Baseline Demographic and Clinical Characteristics, According to Study Group. Intention-to-Treat Analysis*

	Control Group (n = 86)	Experimental Group (n = 86)
Age, mean (SD), y	49 (16)	52 (16)
Male sex	48 (55.8)	41 (47.7)
Race or ethnic group**		
White	64 (74.4)	66 (76.7)
Black	18 (20.9)	16 (18.6)
Other	4 (4.7)	4 (4.7)
Characteristics of index infection		
APACHE II score,† mean (SD)	8.0 (4.2)	9.6 (5.6)
Maximum white blood cell count, mean (SD), per microliter	14.5 (6.5)	15.6 (5.7)
Maximum body temperature, mean (SD), °C	37.7 (0.9)	37.6 (0.8)
Organ of origin		
Colon or rectum	22 (25.6)	34 (39.5)
Appendix	7 (8.1)	6 (7.0)
Small bowel	12 (14.0)	15 (17.4)
Pancreas	7 (8.1)	2 (2.3)
Liver/biliary	16 (18.6)	12 (14.0)
Other	22 (25.6)	17 (19.8)

*There were no significant differences between the groups ($p < 0.05$) unless noted.
**Race and ethnic groups were reported by the patient or surrogate.
†$p = 0.038$. APACHE II scores range from 0 to 71, with higher scores indicating an increased risk of death.

were six extra-abdominal infections in this subgroup, three in the control group, and three in the experimental group. In the control group, there was one bloodstream infection, no lung infection, no skin or soft tissue infection unrelated to the surgical site, no vascular catheter infection, one urine infection, and one infection recorded as other. Two of these infections were caused by multidrug-resistant pathogens. In the treatment arm, there were two bloodstream infections and one vascular catheter infection, all of which were fungal. None of the fungal infecions involved a multidrug-resistant pathogen. Days to extra-abdominal infection were similar in the short- and long-course groups (19.5 [6.4] vs. 19.3 [4], $p = 0.973$). CDI incidence was 1.8% in the control group, and there were no cases of CDI in the experimental group, but this difference was not significant ($p = 0.442$). The CDI was diagnosed 23 days after the index source control procedure. Hospital days were not significantly different between the experimental and control groups (4.0 [3.0–8.0] vs. 4.0 [2.0–7.5], $p = 0.909$). There were no deaths in either group.

An intention-to-treat approach was also used to analyze the control (n = 86) and experimental (n = 86) groups and found no significant difference in baseline characteristics except for Acute Physiology and Chronic Health Evaluation II (APACHE II) score, which was higher in the experimental group (9.6 [5.6] vs. 8.0 [4.2], $p = 0.038$) (Table 3). Outcomes were similar to the per-protocol analysis (Table 4). When comparing the control group with the experimental groups, median days to a normal white blood cell count (3.0 [1.0–4.0] vs. 2.0 [1.0–4.0], $p = 0.510$), a normal temperature (1.0 [1.0–1.0] vs. 1.0 [1.0–2.0], $p = 0.687$), and toleration of enteral nutrition (2.0 [1.0–4.0] vs. 1.0 [1.0–3.0], $p = 0.057$) were similar. However, in both the control and experimental groups, only 16.3% met all control group criteria to stop antibiotics on the fourth calendar day.

DISCUSSION

Outcomes seemed to be similar in this post hoc subgroup analysis of the STOP-IT trial, comparing whether infection rates were similar between CIAIs treated with percutaneous drainage and 4 ± 1 days of antimicrobial therapy or a longer course. Short-course patients who did experience a recurrent intra-abdominal infection, however, were diagnosed approximately 1 week earlier compared with long-course patients. Nevertheless, length of stay and mortality did not seem to be significantly different between groups. Although our data do not allow elucidation as to why this difference was present, it is possible that prolonged antibiotic administration suppressed an inflammatory response that could be recognized clinically without actually preventing recurrent infection. It is worth noting that only approximately

TABLE 4. Primary and Major Secondary Outcomes. Intention-to-Treat Analysis

	Control Group (n = 86)	Experimental Group (n = 86)	p
Primary outcomes			
Recurrent intra-abdominal infection	14 (16.3)	14 (16.3)	1.000
Death	0 (0)	0 (0)	—
Time to event, no. days after index source control procedure			
Diagnosis of recurrent intra-abdominal infection, mean (SD)	18.1 (8.0)	11.4 (5.6)	0.018
Death	—	—	—
Secondary outcome			
Recurrent intra-abdominal infection with resistant pathogen	5 (5.8)	2 (2.3)	0.443
Any extra-abdominal infection	6 (7.0)	6 (7.0)	1.000
CDI	1 (1.2)	0 (0)	1.000
Duration of outcome, d			
Antimicrobial therapy for index infection	8.0 (5.0–10.0)	4.0 (4.0–5.0)	<0.001
Antimicrobial-free days at 30 d	21.0 (19.0–25.0)	25.0 (23.0–26.0)	<0.001
Hospitalization after index procedure	4.5 (3.0–8.0)	5.0 (3.0–8.0)	0.583
Hospital-free days at 30 d	25.0 (21.0–27.0)	24.0 (20.0–27.0)	0.784

one in six patients normalized their white blood cell count, temperature, and enteral intake by Day 4, when it seems to be safe to stop antibiotic therapy. This would suggest that using clinical parameters to determine end points of successful treatment of CIAI lags behind adequate treatment length. Thus, caution should be used only when using abnormalities in those variables as a justification to prolong antimicrobial therapy.

CIAI includes a broad variety of disease processes. However, management is unified by three principles regardless of originating organ. First, source control is fundamental, in that failure to achieve early and adequate source control is almost uniformly fatal.[19–21] Second, management of sepsis codified by the evidence-based Surviving Sepsis Campaign Guidelines serves as a guideline for resuscitation.[22] Third, antimicrobial therapy is an important adjunct. Current guidelines recommending 4 days to 7 days of antibiotic administration are based on case-control studies. Data have existed for several decades, however, suggesting a shorter duration of therapy leads to acceptable outcomes in the contaminated abdomen.[23] Reticence to shorten duration, though has been based on the notable recurrent infection rate. However, a recent prospective, observational cohort study found that there was no difference in infectious complications after appendectomy for complicated appendicitis when postoperative antibiotic therapy was reduced from 5 days to 3 days.[24] Similarly, the STOP-IT trial comparing 4 days of antimicrobial therapy to a longer a course for CIAI demonstrated similar outcomes.[5]

For most CIAIs, only 10% to 15% of patients undergo percutaneous drainage to achieve source control.[1,2] In diverticular disease, the percutaneous approach is used in closer to one third of patients.[2] Furthermore, its use can vary based on disease process or type of patient. Sometimes, as is the case with periappendiceal or diverticular abscesses, percutaneous drainage is selected based on the presence or size of a well-formed abscess. However, high-risk patients are sometimes selected for percutaneous drainage given their inability to tolerate open or laparoscopic drainage, such as in acute cholecystitis. Given the increasing reliance on minimally invasive methods of source control in intra-abdominal infection, it is incumbent upon the clinician to ensure that he or she is using appropriately extrapolated evidence. Percutaneous drainage and open surgical drainage have previously been shown to have similar outcomes when treated with a longer course of antibiotics. It is unclear, however, whether such similarity is because open surgical drainage and percutaneous drainage are physiologically similar despite the inability to remove all gross pathologic tissue in a percutaneous intervention or because prolonged antibiotic administration serves to compensate for the difference in tissue removal. If the latter were the case, shortening the duration of antibiotic therapy in percutaneously drained CIAI would demonstrate different outcomes. In contrast, unnecessary antimicrobial therapy has its own attendant risks, most notably, morbidity and mortality from CDI. Our data were unable to detect a difference in infectious complications between 4 days of antimicrobial therapy and a longer duration in patients with CIAI undergoing percutaneous source control, suggesting that shortening duration of antimicrobial therapy may be safe.

Strengths of this study include the fact that it was conducted at multiple institutions internationally and encompassed a broad array of organ sources of CIAI. This analysis was based on a robust, prospectively collected database. There was a minimal dropout rate after enrollment. Taken together, these strengths contribute to the external validity of this study. Furthermore, the per-protocol results were validated by an intention-to-treat analysis.

This study is limited by the fact that the set of patients were not a priori randomized based on the method of source control as part of a planned subgroup analysis, thus introducing bias. Similar to the original STOP-IT trial, this study is also limited by sample size. Based on previous data suggesting a complication rate of 30% in CIAI treated with source control and antimicrobial therapy, the original investigators calculated that 1,010 patients were required to detect a 10% difference between control and experimental groups with 90% power, an α of 0.05, and an assumed dropout rate of 10%. After interim analysis of the 518 patients, funding was discontinued for futility because outcomes seemed identical.[5] Nevertheless, given the power calculation conducted, the limitation of the STOP-IT trial and thus this subsequent study includes Type 2 error. It is worth noting, however, that the cumulative complication rate in the original STOP-IT trial was greater than 30% and that the dropout rate was 0.2%, suggesting the sample size required was overestimated. An additional limitation of the external validity is that all patients were required to have source control. Source control is unable to be achieved in CIAI in up to 10% of the cases.[2]

The findings of this study suggest that regardless of the method of source control for CIAI, a shorter duration of antimicrobial therapy seems to result in similar rates of infectious morbidity and mortality when compared with longer duration therapy. In other words, the inability to remove all gross pathologic tissue when the majority can be drained percutaneously does not seem to be a valid reason to prolong antibiotic therapy duration when adequate source control has been achieved in CIAI. In other studies on CIAI, adjusting antibiotic duration, even in severe illness, does not seem to affect outcome.[17] However, the majority of these analyses are post hoc subgroup analysis, and as such, conclusions are limited. Nevertheless, implementation of these results may have significant economic and resource use effects.

To determine equivalence or even superiority, for example, with regard to CDI, a larger study of patients with CIAI randomized to different groups based on source control method would be necessary. Such a study would also need to perform prespecified subgroup analyses on higher-risk populations, such as the elderly or immunocompromised, who tend to have higher rates of percutaneous drainage. Indeed, the clinician may note that the average patient in the STOP-IT trial was not severely ill and any conclusions cannot be extrapolated to a critically ill patient who is receiving percutaneous drainage because they cannot tolerate an open surgical procedure. A prospective study of CIAI with a shorter duration of antimicrobial therapy in a more severely ill population may help elucidate such questions. Finally, this study's design and sample size does not allow conclusions to be drawn about the clinical, economic, resource use, and quality-of-life consequences of a longer period before diagnosis of recurrent intra-abdominal infection when administering a longer duration of antimicrobial therapy. These are also areas for future research. For now, while more definitive conclusions await further studies, it seems that as long as adequate source control is achieved, 4 days of antimicrobial therapy may result in similar outcomes in the treatment of CIAI.

AUTHORSHIP

R.R. and C.J.A. contributed to the study design, data analysis, data interpretation, writing, and critical revision. N.N., T.M.D., O.D.R., R.G.S., R. A., K.L.B., R.C., C.H.C., and P.J.O. contributed to the data collection, data interpretation, writing, and critical revision.

DISCLOSURE

The authors declare no conflicts of interest.

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