Trial of short-course antimicrobial therapy for intraabdominal infection

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Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection


BACKGROUND

The successful treatment of intraabdominal infection requires a combination of anatomical source control and antibiotics. The appropriate duration of antimicrobial therapy remains unclear.

METHODS

We randomly assigned 518 patients with complicated intraabdominal infection and adequate source control to receive antibiotics until 2 days after the resolution of fever, leukocytosis, and ileus, with a maximum of 10 days of therapy (control group), or to receive a fixed course of antibiotics (experimental group) for 4±1 calendar days. The primary outcome was a composite of surgical-site infection, recurrent intraabdominal infection, or death within 30 days after the index source-control procedure, according to treatment group. Secondary outcomes included the duration of therapy and rates of subsequent infections.

RESULTS

Surgical-site infection, recurrent intraabdominal infection, or death occurred in 56 of 257 patients in the experimental group (21.8%), as compared with 58 of 260 patients in the control group (22.3%) (absolute difference, −0.5 percentage point; 95% confidence interval [CI], −7.0 to 8.0; P=0.92). The median duration of antibiotic therapy was 4.0 days (interquartile range, 4.0 to 5.0) in the experimental group, as compared with 8.0 days (interquartile range, 5.0 to 10.0) in the control group (absolute difference, −4.0 days; 95% CI, −4.7 to −3.3; P<0.001). No significant between-group differences were found in the individual rates of the components of the primary outcome or in other secondary outcomes.

CONCLUSIONS

In patients with intraabdominal infections who had undergone an adequate source-control procedure, the outcomes after fixed-duration antibiotic therapy (approximately 4 days) were similar to those after a longer course of antibiotics (approximately 8 days) that extended until after the resolution of physiological abnormalities. ( Funded by the National Institutes of Health; STOP-IT ClinicalTrials.gov number, NCT00657566.)
Compl icated intra ab domi nal in fection con tinues to be a common problem world wide. Approx imately 300,000 cases of appendicitis occur each year in the United States,1 and at least twice that many cases of non-appen
diceal infection require management.2 Morbid ity ranges from 5% among patients evaluated in broad observational studies2–4 to close to 50% in some cohorts, such as the elderly or critically ill.5,6 De
spite the diversity of specific processes in these infections, the basic tenets of management are similar: resuscitate patients who have the systemic infl am matory response syndrome (SIRS), control the source of contamination, remove most of the infected or necrotic material, and administer anti
microbial agents to eradicate residual pathogens.7,8
Antimicrobial therapy for the management of intra abdominal infections continues to evolve. Published guidelines include recommendations for appropriate antimicrobial agents on the basis of high-quality evidence.7,8 The appropriate dura
tion of therapy, however, remains unclear. Traditionally, practitioners have treated patients until all evidence of SIRS has resolved, typically for 7 to 14 days. More recently, it has been suggested that with adequate source control, a shorter course of 3 to 5 days should suffice for cure9 and could de
crease the risk of antimicrobial resistance. Cur
rently used guidelines, including those published jointly by the Surgical Infection Society (SIS) and the Infectious Diseases Society of America (IDSA), recommend a treatment course of 4 to 7 days de
pending on the clinical response.7,8
Despite these recommendations, observational studies show that therapy is typically administered for 10 to 14 days.4,10,11 One reason that shortening therapy has been difficult is the 20% rate of clini
cally significant infectious complications after treatment.3 These subsequent complications, how
ever, are often due to progression of the original disease or inadequate original source control and may not be preventable with antimicrobial therapy alone.

We conducted the randomized Study to Opti
mize Peritoneal Infection Therapy (STOP-IT) trial to compare two strategies guiding the duration of antimicrobial therapy for the management of complicated intraabdominal infection. We hypo
thesized that the administration of fixed-duration antibiotic therapy (4 days) after source control would lead to equivalent outcomes and a shorter duration of therapy as compared with the tradi
tional strategy of administration of antibiotics until 2 days after the resolution of the physiological abnormalities related to SIRS.

METH ODS

STUDY POPULATION
Patients were eligible for enrollment in the study if they were 16 years of age or older; if they pre
sented with a complicated intraabdominal infec
tion with either fever (temperature ≥38.0°C), leukocytosis (≥11,000 peripheral white cells per cubic millimeter), or gastrointestinal dysfunction due to peritonitis precluding intake of more than half their normal diet; and if they had undergone an intervention to achieve source control.

Source control, defined as procedures that eliminate infectious foci, control factors that pro
mote ongoing infection, and correct or control anatomical derangements to restore normal phys
iological function, is critical to the management of any infection.12 The adequacy of source control was confirmed by the local investigator and the principal investigator of the overall study (see the full protocol, available with the full text of this article at NEJM.org).

STUDY DESIGN AND OVERSIGHT
In this investigator-initiated, open-label, multi
center trial, we randomly assigned participants in a 1:1 ratio to receive 4 full days of antimicrobial therapy after their index source-control procedure (experimental group) or to receive antimicrobial therapy until 2 days after the resolution of the physiological abnormalities related to SIRS (control group). This resolution was defined as a body temperature of less than 38.0°C for 1 entire calendar day, normalization of the peripheral white-cell count to less than 11,000 per cubic millimeter, and the patient’s ability to consume more than half of his or her regular diet without adverse effects.

All the patients or their legal surrogates provided written informed consent. The specific choice of antimicrobial agents was not dictated by the protocol but rather was considered to be acceptable if it was consistent with published SIS–IDSA guidelines.7,8

Randomization was performed with the use of a Web-based data system managed by Merge Healthcare, an independent contract research or
organization paid by the sponsor. Each study site...
used a unique randomization sequence. Only 20 patients with appendiceal disease were permitted in each sequential block of 200 randomly assigned patients. Patients were enrolled at 23 sites throughout the United States and Canada, and the study was coordinated through the SIS and managed by the University of Virginia team. The protocol was approved by the institutional review board at each site. All the authors vouch for the accuracy and completeness of the data, the analyses reported here, and the fidelity of the study to the protocol.

**Duration of Therapy and Adherence to the Protocol**
After randomization, patients were followed to assess their clinical course and adherence to the protocol. In the control group, adherence to the protocol was defined as the receipt of appropriate antimicrobial agents until 2 ± 1 calendar days after the first day that the patient had a maximum temperature of less than 38.0°C for 1 whole calendar day, less than 11,000 peripheral white cells per cubic millimeter, and the ability to meet more than half their nutritional needs enterally. A maximum of 10 days of therapy was allowed for treatment of the initial intraabdominal infection.

In the experimental group, adherence to the protocol was defined as the receipt of effective antimicrobial agents for 4 ± 1 calendar days after the index source-control procedure. Patients were followed for 30 days after the initial source-control procedure and assessed for infectious complications, use of antimicrobial therapy, and death from any cause. Patients hospitalized for more than 30 days were followed to determine hospital length of stay. A resistant pathogen was defined as methicillin-resistant *Staphylococcus aureus*, any vancomycin-resistant enterococcus species, or a gram-negative organism that was resistant to all members of a major class of antimicrobial agents.

**Statistical Analysis**
The primary analysis compared the proportion of patients in each group in whom a surgical-site infection or recurrent intraabdominal infection developed or in whom death occurred within 30 days after the index source-control procedure. Analyses were performed with the use of the chi-square test with Yates’ correction, Student’s t-test, or Wilcoxon signed-rank test, where applicable, in the intention-to-treat population, which consisted of all patients who provided consent and underwent randomization. Kaplan-Meier curves for time to an event were constructed and compared with the use of the log-rank test.

Secondary analyses assessed the duration of antimicrobial therapy for the index infection, overall exposure to antimicrobial agents, rates of subsequent extraabdominal infection, and adherence to the protocol. Prespecified subgroups for analysis included patients with an Acute Physiology and Chronic Health Evaluation (APACHE) II score of 10 or higher (on a scale of 0 to 71, with higher scores indicating an increased risk of death), patients with a health care–associated infection, patients with an appendiceal source of index infection and those with a non-appendiceal source of index infection, and patients with an index infection treated by surgical drainage and those whose index infection was treated by percutaneous drainage. Multivariate logistic regression was performed to determine associations with the composite outcome, including key demographic variables and treatment-group assignments.

According to the original sample-size calculation to define equivalence between the two groups, we calculated that a sample of 505 patients per group would be required to give the study 90% power to detect a 10% difference in complication rates, assuming a 30% complication rate among controls and assuming a dropout rate of 10%, at an alpha level of 0.05. After the first interim analysis showed nearly identical outcomes in the two cohorts, a competitive renewal request for continued support to reach the targeted enrollment levels was not funded owing largely to a concern for futility.

**RESULTS**

**Patient Characteristics and Index Infections**
From August 2008 through August 2013, a total of 518 patients underwent randomization. One patient withdrew consent after randomization. Thirty-day follow-up was completed in 99.8% of the patients (Fig. 1).

The mean (±SE) age of the patients was 52.2 ± 1.0 years (range, 16 to 88); most of the patients were male, and the composition of racial and ethnic groups was similar in the two groups.
The mean APACHE II score for the index infection was 10.1±0.3 (range, 0 to 29), the most common origin of the infection was the colon or rectum, and one third of the infections were treated with a percutaneous procedure (Table 1). Complete demographic data are provided in Table S1 in the Supplementary Appendix, available at NEJM.org. There were no differences between the two study groups, at a significance level of less than 0.05, with respect to any demographic variable.

### ADHERENCE TO THE PROTOCOL

A total of 211 of 258 patients in the experimental group (81.8%), as compared with 189 of 260 patients in the control group (72.7%), ultimately received antimicrobial therapy for the protocol-specified duration (P=0.02) (Fig. 1). In the control group, 10 patients received therapy for too few days for no identifiable reason, 26 received therapy for more than required on basis of physiological findings, but for <10 days total, 35 received treatment for >10 days, 6 had new surgical-site infection, 8 had recurrent intraabdominal infection, 1 had infectious disease owing to extra-abdominal infection, 20 had no identifiable reason to receive >10 days of treatment, and 10 received therapy for too few days for no identifiable reason.

In the experimental group, all 47 patients who did not adhere to the protocol received a treatment totaling 6 days, including 7 patients who continued to have an elevated white-cell count and 4 patients who had ongoing gastrointestinal dysfunction when therapy was discontinued. Among the other patients who did not receive the assigned therapy, 26 received therapy for less than 10 days (but longer than required according to their physiological findings) and 35 received therapy for more than 10 days. In some patients in the control group, the initial course of antimicrobial therapy was extended owing to a second infection, and they were considered to be in violation of the protocol; 6 of these patients had a surgical-site infection, 8 had a recurrent intraabdominal infection, and 1 had an infectious disease owing to extra-abdominal infection.

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The composite primary end point of surgical-site infection, recurrent intraabdominal infection, or death occurred in 56 of 257 patients in the experimental group (21.8%), as compared with 58 of 260 patients in the control group (22.3%) (absolute difference, −0.5 percentage point; 95% confidence interval [CI], −7.0 to 8.0; P = 0.92) (Table 2). Kaplan–Meier analysis showed no significant between-group difference in the time to the composite primary outcome (Fig. 2).

No significant between-group differences were seen in the rates of the individual primary-endpoint components of surgical-site infection (absolute difference, −2.2 percentage points; 95% CI, −2.4 to 7.0; P=0.43), recurrent intraabdominal infection (absolute difference, 1.8 percentage points; 95% CI, −4.5 to 7.8; P = 0.67), and death (absolute difference, 0.4 percentage point; 95% CI, −1.7 to 2.7; P=0.99). Diagnosis of surgical-site infection and recurrent intraabdominal infection, but not death, occurred significantly later in the control group than in the experimental group (Table 2). Death occurred in 5 of the 518 patients in the two groups combined (1.0%, 2 patients in the control group and 3 patients in the experimental group) at a mean of 18.7±0.4 days after the index source-control procedure. All the deaths were judged by the site principal investigator and the study principal investigator to be related to underlying coexisting diseases (principally cancer and cardiovascular disease) and not to the initial intraabdominal infection.

The median duration of antimicrobial treatment for the index intraabdominal infection was 4.0 days (interquartile range, 4.0 to 5.0) in the experimental group, as compared with 8.0 days (interquartile range, 5.0 to 10.0) in the control group (absolute difference, −4.0 days; 95% CI, −4.7 to −3.3; P<0.001). There were significantly fewer median antimicrobial-free days at 30 days (including all antimicrobial therapy) in the control group (absolute difference, −3.0 days; 95% CI, −3.4 to −2.6; P<0.001). The occurrence of the primary composite outcome was similar in the two study groups in all prespecified subgroups, including patients who were.
treated per protocol (33 of 189 patients in the control group [17.5%] and 37 of 211 patients in the experimental group [17.5%]; absolute difference, 0.1 percentage point; 95% CI, −7.4 to 7.6; P = 0.72) (Fig. 3, and Table S2 in the Supplementary Appendix). Differences in the duration of therapy among patients in all subgroups were similar to those seen in the intention-to-treat analysis, with the exception of the subgroup of patients who were not treated according to the

### Table 2. Primary and Major Secondary Outcomes. *

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group (N = 260)</th>
<th>Experimental Group (N = 257)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome: surgical-site infection, recurrent intraabdominal infection, or death — no. (%)</strong></td>
<td>58 (22.3)</td>
<td>56 (21.8)</td>
<td>0.92</td>
</tr>
<tr>
<td>Surgical-site infection</td>
<td>23 (8.8)</td>
<td>17 (6.6)</td>
<td>0.43</td>
</tr>
<tr>
<td>Recurrent intraabdominal infection</td>
<td>36 (13.8)</td>
<td>40 (15.6)</td>
<td>0.67</td>
</tr>
<tr>
<td>Death</td>
<td>2 (0.8)</td>
<td>3 (1.2)</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>Time to event — no. of days after index source-control procedure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis of surgical-site infection</td>
<td>15.1±0.6</td>
<td>8.8±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diagnosis of recurrent intraabdominal infection</td>
<td>15.1±0.5</td>
<td>10.8±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death</td>
<td>19.0±1.0</td>
<td>18.5±0.5</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>Secondary outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical-site infection or recurrent intraabdominal infection with resistant pathogen — no. (%)</td>
<td>9 (3.5)</td>
<td>6 (2.3)</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>Site of extraabdominal infection — no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any site†</td>
<td>13 (5.0)</td>
<td>23 (8.9)</td>
<td>0.11</td>
</tr>
<tr>
<td>Urine</td>
<td>10 (3.8)</td>
<td>13 (5.1)</td>
<td>0.65</td>
</tr>
<tr>
<td>Blood</td>
<td>3 (1.2)</td>
<td>5 (1.9)</td>
<td>0.71</td>
</tr>
<tr>
<td>Lung</td>
<td>3 (1.2)</td>
<td>3 (1.2)</td>
<td>0.99</td>
</tr>
<tr>
<td>Area of skin other than surgical site</td>
<td>1 (0.4)</td>
<td>4 (1.6)</td>
<td>0.36</td>
</tr>
<tr>
<td>Vascular catheter</td>
<td>0 (0)</td>
<td>2 (0.8)</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>Clostridium difficile infection — no. (%)</strong></td>
<td>3 (1.2)</td>
<td>5 (1.9)</td>
<td>0.71</td>
</tr>
<tr>
<td>Extraabdominal infection with resistant pathogen — no. (%)</td>
<td>6 (2.3)</td>
<td>2 (0.8)</td>
<td>0.29</td>
</tr>
<tr>
<td><strong>Duration of outcome — days</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimicrobial therapy for index infection</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median</td>
<td>8</td>
<td>4</td>
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</tr>
<tr>
<td>Interquartile range</td>
<td>5–10</td>
<td>4–5</td>
<td></td>
</tr>
<tr>
<td>Antimicrobial-free days at 30 days</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median</td>
<td>21</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>18–25</td>
<td>21–26</td>
<td></td>
</tr>
<tr>
<td>Hospitalization after index procedure</td>
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<td></td>
<td>0.48</td>
</tr>
<tr>
<td>Median</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>4–11</td>
<td>4–11</td>
<td></td>
</tr>
<tr>
<td>Hospital-free days at 30 days</td>
<td></td>
<td></td>
<td>0.22</td>
</tr>
<tr>
<td>Median</td>
<td>23</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>18–26</td>
<td>16–26</td>
<td></td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SE.
† Some patients had extraabdominal infections at more than one site.
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Discussion

In this randomized study involving patients with complicated intraabdominal infections, a fixed duration of 4 days of antibiotic treatment resulted in outcomes that were similar to those of a traditional, longer course that was based on resolution of physiological abnormalities, and the shorter course was associated with significantly fewer days of antibiotic exposure. These data provide support for the concept that after an adequate source-control procedure, the beneficial effects of systemic antimicrobial therapy are limited to the first few days after intervention. In addition, it might be argued that the delay in manifestation of infectious complications in the control group was itself an adverse outcome, since the time to recognition of these events and, therefore, the overall time to resolution of all infections was prolonged.

Traditionally, physicians have administered antimicrobial therapy in patients who have intraabdominal infections until clinical and laboratory evidence suggests that the infection has resolved. They reasoned that ongoing sepsis was indicative of ongoing replication of pathogens. More recent experimental data, however, suggest that a prolonged SIRS may be more a reflection of host immune activity than an indication of the presence of viable microorganisms. As such, efforts have begun to shorten the duration of antimicrobial therapy in the presence of traditional markers of sepsis. These efforts have already been successful in other severe infections such as ventilator-associated pneumonia.

Currently, the average duration of antibiotic therapy for intraabdominal infection is 10 to 14 days. The results of smaller studies of the effect of an abbreviated course of antimicrobial therapy have been published. Schein et al. reported on an uncontrolled study in which 23 consecutive patients with diffuse peritonitis were assigned to receive 3 to 5 days of antibiotics. Infections developed in 22% of these patients; these rates were similar to those seen in a historical cohort. Basoli et al., who randomly assigned 90 patients with mild-to-moderate intraabdominal infection to either 3 days or 5 or more days of ertapenem therapy, found no between-group difference in infectious outcomes. Those findings, however, are not generalizable to the majority of patients with intraabdominal infection, since half the patients had appendiceal disease and the overall rate of infectious complications was less than 10%. As compared with these studies, the STOP-IT trial had several advantages, including a larger sample size, randomized design, and enrollment of patients with a broader range of severity of illness.

The rate of infectious complications was more than 20% in both groups of our study, and most of these complications were recurrent intraabdominal infections. Given the large difference in the number of days of treatment in the two study groups, neither shortening nor lengthening the duration of antimicrobial therapy appears likely to affect infectious outcomes. Truly clinically significant improvement in the management of this disease, therefore, probably awaits more effective technical or immune response–modifying interventions. However, the observed mortality in our study was only 1%; this is better than anticipated among patients with a mean APACHE II score...
of 10 and is perhaps related to the reduction in mortality from many serious infections noted after the initiation of the Surviving Sepsis Campaign.\textsuperscript{18}

Strengths of the trial include the inclusion of 23 centers and the similarity in outcomes between the control group and the experimental group in a wide variety of important, prespecified subgroups. For example, although rates of complications differed according to the severity of illness and the method of source control (percutaneous vs. surgical drainage), the effect size was similar in the two study groups. These findings suggest that the results may well be generalizable across a wide array of patient populations, care settings, and interventions, as long as adequate source control is first achieved.

Several limitations to the interpretation of these data are worth noting. First, patients without adequate source control were excluded, and only a small number of patients with immunosuppression were included; it remains unclear whether these populations would benefit from a longer duration of therapy. Second, the rate of nonadherence to the protocol was moderately high, including 18\% of patients in the experimental group; this created bias toward the null hypothesis of no difference in therapy, though the fact that the per-protocol population had similar complication rates between the experimental and control groups is reassuring. Finally, the original calculated sample size to assert equivalence between groups was not achieved and proof of equivalence cannot be claimed, although the 95\% confidence interval for the difference in event rates was $-7.0$ to $8.0$ and provides encouraging evidence that the true difference is less than 10\%. In other words, the null hypothesis of equal efficacy cannot be rejected.

In conclusion, outcomes in patients with intraabdominal infections who have undergone a successful source-control procedure and receive a fixed, 4-day course of antimicrobial therapy appear to be generally similar to outcomes in pa-
tients in whom systemic antimicrobial agents are administered until after the resolution of signs and symptoms of sepsis.


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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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