Comparison of On-Demand vs Planned Relaparotomy Strategy in Patients With Severe Peritonitis: A Randomized Trial

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SECONDARY PERITONITIS IS NOTORIOUS for its high mortality (20%-60%), long hospital stays, and high morbidity due to the development of sepsis with multiple organ failure.1-4 Secondary peritonitis accounts for approximately 9.3/1000 emergency hospital admissions in the United States.5 In addition, a substantial number of patients (12%-16%) undergoing elective abdominal surgery develop postoperative peritonitis.5,6 Health care utilization due to secondary peritonitis is extensive, with operations to eliminate the source of infection (laparotomy) estimated to occur in 10%-15% of these patients.7 A relaparotomy is necessary in 3%-14% of cases in order to resolve peritonitis.8

Context In patients with severe secondary peritonitis, there are 2 surgical treatment strategies following an initial emergency laparotomy: planned relaparotomy and relaparotomy only when the patient’s condition demands it (“on-demand”). The on-demand strategy may reduce mortality, morbidity, health care utilization, and costs. However, randomized trials have not been performed.

Objective To compare patient outcome, health care utilization, and costs of on-demand and planned relaparotomy.

Design, Setting, and Patients Randomized, nonblinded clinical trial at 2 academic and 5 regional teaching hospitals in the Netherlands from November 2001 through February 2005. Patients had severe secondary peritonitis and an Acute Physiology and Chronic Health Evaluation (APACHE-II) score of 11 or greater.

Intervention Random allocation to on-demand or planned relaparotomy strategy.

Main Outcome Measures The primary end point was death and/or peritonitis-related morbidity within a 12-month follow-up period. Secondary end points included health care utilization and costs.

Results A total of 232 patients (116 on-demand and 116 planned) were randomized. One patient in the on-demand group was excluded due to an operative diagnosis of pancreatitis and 3 in each group withdrew or were lost to follow-up. There was no significant difference in primary end point (57% on-demand [n = 64] vs 65% planned [n = 73]; P = .25) or in mortality alone (29% on-demand [n = 32] vs 36% planned [n = 41]; P = .22) or morbidity alone (40% on-demand [n = 32] vs 44% planned [n = 32]; P = .58). A total of 42% of the on-demand patients had a relaparotomy vs 94% of the planned relaparotomy group. A total of 31% of first relaparotomies were negative in the on-demand group vs 66% in the planned group (P < .001). Patients in the on-demand group had shorter median intensive care unit stays (7 vs 11 days; P = .001) and shorter median hospital stays (27 vs 35 days; P = .008). Direct medical costs per patient were reduced by 23% using the on-demand strategy.

Conclusion Patients in the on-demand relaparotomy group did not have a significantly lower rate of death or major peritonitis-related morbidity compared with the planned relaparotomy group but did have a substantial reduction in relaparotomies, health care utilization, and medical costs.

Trial Registration isrctn.org Identifier: ISRCTN51729393

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The choice of relaparotomy strategy in patients with severe peritonitis is a matter of ongoing debate and practice.

**Design and Eligibility**

In this multicenter study, patients were randomly assigned to either an on-demand or a planned relaparotomy strategy. Patients were eligible if they were diagnosed with secondary peritonitis and required an emergency laparotomy (index laparotomy). Peritonitis was defined as intra-abdominal infection that required an emergency laparotomy, indicating negative findings. That decision was made by the operating surgeon.

An APACHE-II score greater than 10 in the initial 24-hour period was required.

Exclusion criteria were age younger than 18 years or older than 80 years; peritonitis due to bowel perforation after endoscopy operated within 24 hours after perforation; abdominal infection due to continuous ambulatory peritoneal dialysis catheter; peritonitis caused by pancreatitis; expected survival of less than 6 months due to malignancy; severe brain damage due to trauma or anoxia; and imperative relaparotomy (e.g., gauze packing, stapled ends without reanastomosis).

All randomizations were completed only if the clinical diagnosis of peritonitis was confirmed during the index laparotomy. Randomization was performed centrally at the Academic Medical Center, Amsterdam, the Netherlands, using a specialized computer-generated block sequence and stratified per study site according to the APACHE-II score as minimization factor (11-20 vs >20). The operating surgeon was unaware of the allocated treatment strategy while performing the initial emergency laparotomy.

Informed consent was obtained from the patient or the legal representative when patients were temporary incapacitated due to the severity of their illness. The study was approved by the medical ethics committee of all participating centers.

**Surgical Treatment Strategies**

**Planned Relaparotomy.** Relaparotomies were performed every 36 to 48 hours after the index laparotomy to inspect, drain, lavage, and perform other necessary abdominal interventions for residual peritonitis or new infectious foci. The sequence of planned relaparotomies was terminated when a macroscopically clean abdomen was found at relaparotomy, indicating negative findings. That decision was made by the operating surgeon.

**On-Demand Relaparotomy.** Relaparotomy was only performed in patients with clinical deterioration or lack of clinical improvement with a likely intra-abdominal cause. Other (intercurrent) infectious foci (e.g., pneumonia) were ruled out using laboratory tests, imaging modalities, or both. The decision to perform an on-demand relaparotomy was made by the multidisciplinary medical team. To guide the decision for reoperation, the following definitions of deterioration and lack of improvement were specified in the protocol.

Deterioration after the previous operation was considered if there was an increase of more than 4 points in the Multiple Organ Dysfunction Score or prespecified surgical emergencies (i.e., abdominal compartment syndrome; intra-abdominal bleeding with persistent decrease in hemoglobin despite replacement, and hemody-
namic instability; burst abdomen; perforation of visceral organ; anastomotic leakage; intra-abdominal abscess that cannot be drained percutaneously; ischemia/necrosis of a visceral organ.

Lack of improvement of clinical signs of persistent sepsis was considered if the Multiple Organ Dysfunction Score was unchanged (+2 points) for at least 48 hours following the index laparotomy or the previous relaparotomy. Abscess detected at CT imaging with positive fine-needle aspiration results (Gram stain with evidence of bacterial involvement) that could not be drained percutaneously was another reason for relaparotomy.

All participating surgeons and institutions had experience with both strategies. It was not required by protocol to keep patients in the planned relaparotomy group mechanically ventilated between operations. The decision to perform additional procedures during the relaparotomy was left to the discretion of the operating surgeon. Standardized concomitant procedures included direct postoperative care, intensive care unit (ICU) care, use of corticosteroids, postoperative feeding, and antibiotic treatment—all directed by physicians unrelated to the study.

Outcomes and Follow-up
The primary end point was a combination of all-cause mortality and major disease-related morbidity in surviving patients within 12-month follow-up after index laparotomy. A major morbidity end point in survivors was counted only if a prespecified major disease-related morbidity led to a surgical reintervention during index admission or readmission during the 12-month follow-up (with or without the need of surgical intervention) (Box). Additional outcomes included health care utilization and direct medical costs during 12-month follow-up.

Costs
Cost-minimization analysis was used to determine economic differences comparing the on-demand with the planned strategy. Direct medical costs were estimated using primary data on resource utilization and included relaparotomies, percutaneous interventions, diagnostic CT scans, length of hospital stay, ICU stay with and without mechanical ventilation, days in hospital

| Box. Disease-Related Morbidity Needing Nonsurgical Treatment or Surgical Intervention |
| Disease-Related Major Morbidity Needing Readmission and Conservative Treatment but Not Surgery |
| Fistula: nonanatomical connection between hollow organ and cutis or between 2 hollow organs |
| Wound dehiscence/incisional hernia with obstruction: full-thickness discontinuity in abdominal wall with bulging of abdominal content |
| Abscess needing percutaneous drainage: pus-containing non-preexisting cavity confirmed by positive Gram stain or culture |
| Renal failure: urine production <500 mL/24 h with rising level of blood urea nitrogen and creatinine combined with dehydration (decreased circulating volume with elevated hematocrit needing intravenous rehydration) based on inadequate oral intake, nausea/vomiting, or both (only when needing readmission) |
| Myocardial infarction (electrocardiogram and enzyme changes suggestive of myocardial infarction or needing admission to coronary care unit), pulmonary embolus (ventilation-perfusion mismatch on lung scintigraphy), or cerebrovascular accident (ischemic or nonischemic with persistent paresis or paralysis without previous history) |
| Gastric or duodenal bleeding: needing endoscopic treatment or embolization therapy |
| Respiratory failure due to pneumonia, pleural effusion, or pulmonary edema and needing oxygen therapy or mechanical ventilation |
| Urpsepsis: urinary tract infection with positive urine and blood cultures and circulatory shock |
| Disease-Related Major Morbidity Needing Surgical Intervention During First Admission or Readmission |
| Incisional hernia: full-thickness discontinuity in abdominal wall with bulging of abdominal contents with or without obstruction with disabling concerns interfering with daily activities |
| Bowel obstruction or herniation due to intra-abdominal adhesions: diagnosis must be confirmed during surgery |
| Burst abdomen: complete midline or transverse discontinuity in abdominal wall |
| Abdominal compartment syndrome: intra-abdominal hypertension >25 mm Hg with tense abdomen and with increasing respiratory failure, renal failure, or both; measured by the urinary bladder pressure method (modified Burch criteria) |
| Fistula: nonanatomical connection between intestine and cutis or between 2 hollow organs |
| Intra-abdominal bleeding: only when septic bleeding after index laparotomy or relaparotomy or surgical bleeding after relaparotomy but not after index laparotomy |
| Intra-abdominal hematoma needing surgical evacuation |
| Perforation of visceral organ confirmed at surgery |
| Anastomotic leakage: anastomotic leak on contrast imaging needing surgery or contrast-enhanced computed tomography scan, confirmed at relaparotomy |
| Ischemia or necrosis of a visceral organ: critically reduced blood flow to an intra-abdominal organ causing tissue loss, confirmed at pathological examination |
| Enterostomy dysfunction due to prolapse, stenosis, or retraction |
| Gastric or duodenal ulcer bleeding needing intervention of any type |
due to readmissions, administration of antibiotics, elective reoperations, length of stay in rehabilitation centers, health care provided by district nurses, and enterostomy care during 12-month follow-up.

Costs per patient were calculated by multiplying volumes of resource with unit costs. Costs were assessed according to the Dutch guidelines for pharmaco-economic research. Dutch guideline unit costs were used for ICU stay, hospital stay, antibiotic medication, blood products, and visits to primary and outpatient health care clinicians. Unit costs for surgical procedures, enterostomy care, and diagnostic procedures were determined at the Academic Medical Center Amsterdam.

**Statistical Analysis**

The sample size calculation was based on superiority of the on-demand strategy with a 10% absolute reduction of mortality and a 10% absolute reduction of morbidity in survivors, translating into a reduction in risk for the primary combined end point from 44% in the planned group to 28% in the on-demand group at 6 months follow-up. This expected difference of effect size in favor of the on-demand strategy was based on a systematic review and retrospective research performed in preparation of this trial. A sample size of 111 in each group would have a power of 80% to detect such a difference (1-sided α of .05). A dropout rate of 9% (6 patients per group) was expected.

All analyses were performed on the basis of the intention-to-treat principle. We extended the scope of the follow-up to 12 months to ensure capture of all relevant complications and health care utilization related to the initial episode of secondary peritonitis.

We compared the proportion of patients with a primary end point (including analyses of the separate components, mortality and morbidity in survivors) between the 2 strategies and tested for significance using the χ² test. Confidence intervals for the difference between proportions were calculated with the use of a normal approximation of the binomial distribution. The number needed to treat was calculated by taking the reciprocal of the risk difference. Continuous data are presented as median with interquartile range (IQR). Survival curves were constructed with use of the Kaplan-Meier method and tested for differences using the log-rank test.

Differences in health care utilization were tested for significance using the χ² test or Mann-Whitney U test, where appropriate. Confidence intervals for differences in mean costs were based on log-transformed cost data.

Prespecified subgroup analyses were performed for the APACHE-II score at the time of index operation and per including hospital. We used logistic regression models to perform a formal test for interaction to determine whether treatment effects differed significantly between these subgroups.

All statistical analyses were performed using SPSS for Windows version 12.1.2 (SPSS Inc, Chicago, Illinois) or SAS version 9.1 (SAS Institute Inc, Cary, North Carolina). P < .05 was considered statistically significant.

**Data Handling and Trial Monitoring**

Collection and evaluation of all data regarding the initial (index) admission period and follow-up were performed by blinded investigators not involved with patient care. All primary end points were cross-checked with data from primary sources (by an independent data manager blinded for treatment allocation).

An independent data and safety monitoring committee blinded for treatment assignment evaluated progress of the trial and examined safety parameters at regular intervals (every 25 patients).

**RESULTS**

**Patient Enrollment**

All patients with secondary peritonitis were assessed for eligibility between November 2001 and February 2005 and 510 were registered. Of these registered patients, 228 had 1 or more exclusion criteria, the main reasons being an APACHE-II score of 10 or lower and age younger than 18 years or older than 80 years. A total of 232 patients were randomized (116 in each group) (FIGURE 1).

One patient in the on-demand group was diagnosed with pancreatitis during the index laparotomy and excluded after randomization. Furthermore, in both groups 1 patient withdrew consent and 2 patients were lost to follow-up after the initial admission period. Therefore, data were available for the initial admission period from 229 patients and from 225 patients for the follow-up period.

**Baseline Characteristics**

Study groups were comparable for all patient and index laparotomy characteristics (TABLE 1). The median age was 69 years (IQR, 58-75 years), 48% were men, and the median APACHE-II score was 15 (IQR, 13-18). The most common cause for peritonitis was gastrointestinal perforation (58%). Prevalence of major comorbidity was high (60%). Patients with failure of elimination of the infectious focus at index laparotomy were defined as “no infectious focus found and therefore not treated” or “focus not definitively eliminated during the initial laparotomy”; such patients were equally distributed over the 2 study groups.

**Treatment Following Emergency Laparotomy**

Some patients did not receive the treatment to which they were randomized (4, on-demand; 7, planned; Figure 1). The total number of relaparotomies differed between the 2 strategies (TABLE 2): 113 in the on-demand group and 233 in the planned group (P < .001). Forty-two percent of patients in the on-demand group underwent a relaparotomy. The proportion of patients with 3 or more relaparotomies was 9% in the on-demand group compared with 24% in the planned group (P < .001). Regarding the first relaparotomy, negative findings (no signs of persistent peritonitis or new infectious focus) were seen in 31% of the on-
Mortality and Major Morbidity

Combined Primary End Point. The primary end point combining mortality from all causes and major morbidity in survivors within 12 months after index laparotomy occurred in 57% (n = 64) of the patients in the on-demand group and in 65% (n = 73) of the planned group (risk difference, 7.5%; 95% confidence interval [CI], −5% to 20%; P = .58) (Table 2).

Mortality. Cumulative mortality during 12-month follow-up was 29% (32/112) in the on-demand group and 36% (41/113) in the planned group, corresponding with a risk difference of 7.7% (95% CI, −7.5% to 16%; P = .23) (Table 2). The Kaplan-Meier curve for long-term survival shows that most deaths occurred within the first 60 days after the initial emergency operation, with no difference in early mortality between the on-demand and planned strategy (P = .35 for 60 days) (Figure 2).

Major Morbidity. Morbidity in survivors occurred in 40% (32/80) of patients in the on-demand group and in 44% (32/72) of patients in the planned group (risk difference, 4.4%; 95% CI, −11% to 20%; P = .58) (Table 2). During admission, the 2 most frequent causes of morbidity were perforation (on-demand 11/114 [9.6%] vs planned 10/115 [8.7%]; P = .80) and anastomotic leakage (on-demand 7/114 [6.1%] vs planned 11/115 [9.6%]; P = .34), both equally distributed among study groups. Readmission during follow-up was most frequently due to incisional hernia needing surgery (on-demand 13/112 [11.6%] vs planned 15/113 [13.2%]; P = .71).

Health Care Utilization and Direct Medical Costs

The proportion of patients admitted to the ICU was comparable between the 2 strategies (on-demand 90% vs planned 94%). However, patients in the on-demand group had a significantly shorter ICU stay (median, 7 days vs 11 days in planned group; P = .001). The median number of days that patients were mechanically ventilated was shorter for the on-demand group (5 days) vs the planned group (8 days; P = .007). Hospital stay for the initial admission period was also shorter for patients in the on-demand group (median, 27 days) than for patients in the planned group (median, 35 days; P = .008). Forty-six percent of the patients in the on-demand group were readmitted to the hospital compared with 40% of patients in the planned group (P = .39). Patients in the on-demand group were alive and outside the hospital a median of 302 days during the year of follow-up, while patients from the planned group were alive and outside the hospital for a median of 284 days (P = .09; Table 2).

Health care utilization was significantly lower in the on-demand group; in particular, patients in the on-demand group had fewer relaparotomies and fewer days in the ICU and in the hospital (Table 2). ICU stay alone accounted for 35% to 40% of the difference in costs.

The mean direct medical costs per patient after 12 months of follow-up, including index admission period, were 23% lower in the on-demand group: €62 741 (US $86 077) when treated with the on-demand strategy and €81 532 (US $111 858) when treated with the planned strategy, an absolute difference of €18 791 (US $25 780) per patient (95% CI, €68 19 [US $9355] to €31 166 [US $42 758]).

Predefined Subgroup Analyses

Treatment effects with respect to the primary end point were comparable across APACHE-II score subgroups. Treat-
ment effects were also unchanged for the primary end point across the 9 including hospitals. All tests for interactions were not significant (P > .50).

**COMMENT**

This randomized trial found that compared with planned relaparotomy, the on-demand strategy did not result in statistically significant reductions in the primary outcomes of death or major peritonitis-related morbidity but did result in significant reductions in the secondary outcomes of health care utilization, including the number of relaparotomies, the use of percutaneous drainage, and hospital and ICU stay. These are similar to the results of a retrospective study and a systematic review on this topic.4,12 Despite a lack of statistically significant improvement in primary clinical outcome, these substantial reduction in health care utilization and costs with the on-demand strategy suggest that it may be the preferred strategy.

Some studies have described that the planned strategy increases the risk of multiple organ failure due to amplifying the systemic inflammatory response by multiple surgical lavages, leading to increased mortality, ICU stays, and hospital stays.25,26 We also observed that patients treated with the planned strategy had longer ICU stays and had a longer overall hospital stay. The duration of mechanical ventilation was significantly longer for the planned treatment patients. However, this difference in ventilation time may in part be related to the short period between scheduled relaparotomies in the planned strategy, inherent to the planned nature of the procedures, as a result of which some patients could not be weaned off ventilation before the next operation. The number of (minimally invasive) percutaneous interventions was also significantly lower in the on-demand group. Possibly, free abdominal fluids and abscesses were more frequent after multiple surgical interventions due to the reinterventions or a modified inflammatory response. Other potential drawbacks of the planned relaparotomy strategy are the observed strong adherence of microbes residing in the peritoneum making them resistant to peritoneal lavage,21 This reduces the effectiveness of the procedure and the damaging effects of lavage to the mesothelial layer and multiple organ failure due to amplification of the systemic inflammatory response. The observed strong adherence of microbes residing in the peritoneum making them resistant to peritoneal lavage.21 This reduces the effectiveness of the procedure and the damaging effects of lavage to the mesothelial layer may even reduce the innate resistance to infection.26,28

In our trial, the on-demand and planned relaparotomy strategies were equally apt to identify patients with remaining or new intra-abdominal infection after the index laparotomy. This also confirms that patients in the planned group were not more frequently determined to show positive findings due to differential verifica-
tion. In other words, surgeons were not more inclined to determine a planned reoperation as positive, for example, to justify this scheduled intervention.

Although the on-demand strategy reduced the number of relaparotomies, there was still a 31% chance that macroscopic findings were negative in patients selected for relaparotomy. The key challenge in the on-demand strategy is to adequately select patients for relaparotomy and to prevent potentially harmful delay in reintervention by adequate and frequent patient monitoring. A more rigorous use of CT scanning as part of the procedure of selecting patients with abdominal sepsis for relaparotomy may well reduce the proportion of patients with negative findings at relaparotomy even further.

Multiple independent variables and combinations of variables have been described to predict outcome of peritonitis. However, results in the literature are inconclusive and the majority of studies predict disease outcome (mortality) of sepsis rather than positive findings at relaparotomy in secondary peritonitis.

In attempt to guide decision making for relaparotomy and enhance timing of relaparotomy in the on-demand group within this trial, we prespecified the main criteria for necessity of relaparotomy as lack of clinical improvement or clinical deterioration using a quantified method (the Multiple Organ Dysfunction Score). The European Sequential Organ Failure Assessment score may have been an alternative prognostic score for predicting presence of persisting peritonitis. However, although scoring systems were used, the final decision to perform a reoperation on a patient in the on-demand setting was always made within a multidisciplinary team. Therefore, considerations for relaparotomy concerning clinical, laboratory, and imaging parameters were less explicit, but in line with current clinical practice. Future research should focus on optimizing adequate and timely selection of patients for relaparotomy by identification of predictive variables for

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<tr>
<th>Table 2. Primary End Point and Health Care Utilization Among Patients With Secondary Peritonitis Randomly Assigned to On-Demand or Planned Treatment Strategy</th>
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<tr>
<td><strong>On-Demand</strong></td>
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<tr>
<td>Primary end point, No./total (%)</td>
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<tr>
<td>Combined primary end point</td>
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<tr>
<td>Mortality</td>
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<tr>
<td>Major morbidity in survivors (≥1)</td>
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<tr>
<td>Risk difference, % (95% CI)</td>
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<tr>
<td>Number needed to treat (95% CI)</td>
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<tr>
<td>Relative risk</td>
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<tr>
<td>Course of disease and health care utilization</td>
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<tr>
<td>Total No. of relaparotomies (range per patient)</td>
</tr>
<tr>
<td>No. of relaparotomies</td>
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<tr>
<td>1 27/114 (24)</td>
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<td>2 11/114 (10)</td>
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<td>≥3 10/114 (9)</td>
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<tr>
<td>Negative findings when receiving a relaparotomy, No./total (%)</td>
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<td>Positive findings per strategy, No./total (%)</td>
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<tr>
<td>Days in intensive care unit, median (IQR)</td>
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<td>Days of mechanical ventilation, median (IQR)</td>
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<td>Days in hospital, median (IQR)</td>
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<tr>
<td>Percutaneous interventions, No./total (%)</td>
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<td>During index admission</td>
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<td>During entire study period, 12 mo</td>
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<td>Drain placement followed by continuous drainage</td>
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<td>Diagnostic imaging (computed tomography) No./total (%)</td>
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<td>No. of procedures/total (range per patient)</td>
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<tr>
<td>Median (IQR)</td>
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<tr>
<td>No. of patients/total with readmissions (%)</td>
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<td>Days alive and outside hospital, median (IQR)</td>
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<td>Abbreviations: CI, confidence interval; IQR, interquartile range. Data including follow-up (n = 225). Data on the index admission period (n = 229).</td>
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<th>Figure 2. Survival in Patients With Secondary Peritonitis</th>
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<td>Kaplan-Meier curves showing survival of patients assigned to the on-demand or planned relaparotomy strategy over 12 months of follow-up. In both groups 1 patient died on the day of the index laparotomy, leaving 111 and 112 patients at risk at day 0, respectively.</td>
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positive findings at relaparotomy and evaluating the added diagnostic value of diagnostic imaging and potential biomarkers.

One of the difficulties in research on secondary peritonitis is heterogeneity of the study population regarding, eg, severity of disease, etiology, and localization of the infectious focus, which often makes it difficult to extrapolate study results to individual patients in clinical practice. For this reason, we have excluded disease entities with substantially different diagnoses and requiring different treatment strategies, such as pancreatitis, perforation due to endoscopy or perforation due to endovascular therapy.

We also excluded patients with an APACHE-II score of 10 or lower, because the on-demand strategy is already the treatment of choice in mild peritonitis. Within the trial, we examined whether the treatment effect with respect to the combined end point differed with the severity of disease at index laparotomy.

We found no indication that relative treatment effects differed between patients with moderate to severe disease (APACHE-II score 11-20) and those with severe disease (APACHE-II score > 20). Treatment effects were also comparable across including hospitals, translating to the on-demand strategy being a feasible and valid option in both moderately and severely severe peritonitis in every hospital setting.

CONCLUSIONS

In conclusion, this study found that patients in the on-demand relaparotomy group did not have a significantly lower rate of adverse outcomes compared with patients in the planned relaparatomy group but did have a substantial reduction in relaparotomies, health care utilization, and medical costs. On-demand relaparotomy may therefore be considered the preferred surgical strategy in patients with severe peritonitis.

Author Contributions: Dr Boermeester had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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