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# RE-OPERATION FOR COMPLICATED SECONDARY PERITONITIS – HOW TO IDENTIFY PATIENTS AT RISK FOR PERSISTENT SEPSIS

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*Abstract:*
*Introduction:* There is an ongoing dispute on the benefit of planned relaparotomy for patients with diffuse peritonitis.
*Setting:* Surgery Department, university hospital
Patients: 145 patients with diffuse peritonitis treated with planned relaparotomy were analysed for APACHE II, MOF- and MODS-score (Goris and Marshall), complications, outcome and clinical/laboratory factors indicating intra-abdominal compartment syndrome (positive endexpiratory pressure (PEEP), central venous pressure (CVP), creatinine, blood urea nitrogen (BUN)) after termination of planned relaparotomy. Statistical analysis of data (mean and standard deviation) was performed using Mann-Whitney, chi-square, ANOVA and multiple regression analysis.
*Results:* The overall mortality was 29.7% and APACHE II score on admission 16.7 ± 8.3 . In 107 patients (mortality 17.8%) closure of the abdomen was achieved at termination of planned relaparotomy. 20 patients (mortality 30%) were treated with mesh closure and in 18 patients (mortality 100%) closure of the abdomen was not feasible. After closure of the abdomen 39 patients showed signs of persistent sepsis. Patients who were explored had a mortality of 37.5% and without re-exploration a mortality of 67%. BUN, PEEP and CVP were significantly different in survivors and non-survivors. Independent predictors of outcome were closure of the abdomen, complications, APACHE II and MOF scores.
*Conclusion:* Patients with planned relaparotomy for diffuse peritonitis are not a uniform group and differ in mortality depending on source control and closure of the abdomen. Patients with persistent sepsis after termination of planned relaparotomy may be recognized by clinical and laboratory parameters and benefit from a timely reexploration. The decision when to close the abdomen may not only be based on intraperitoneal findings but also on the existence and level of organ failure.

*Key words:* Peritonitis; intra-abdominal infection; planned relaparotomy; multi-organ-failure; intra-abdominal compartment syndrome; closure of the abdomen; mesh; immune response; laparotomy on demand; risk factors

## INTRODUCTION

Therapeutic success in the management of intra-abdominal infection translates into mortality. Most patients die from infection if not operated upon in a timely fashion. Standard treatment includes source control and intra-abdominal lavage. (Kirschner 1926) Adhering exclusively to standard principles may not adequately treat a subset of patients with advanced disease. In advanced peritonitis, the source of infection may be difficult to eliminate with one single operation, and there may be excessive pus, necroses, and spoilage of the peritoneum. Adequate cleansing may not be achieved with the classical single operation standard in these cases. Additionally, peritonitis may have produced inflammatory oedema that increases intra-abdominal pressure, and closure of the abdominal incision over the commonly dilated bowels will not be possible without creating undue tension to the fasciae and increasing intra-abdominal pressure upon forced closure (Holzheimer and Dralle 2001). For such conditions, planned relaparotomies (Teichmann et al. 1986) or STaged Abdominal Repair (STAR) (Wittmann et al. 1990) have been proposed. It has been suggested that these strategies allow a better elimination of the source of infection, decompress the intra-abdominal pressure, offsetting the liabilities (adverse pathological consequences) of the abdominal compartment syndrome on renal, hepatic, cardiovascular, and intestinal perfusion (Schein et al. 1995). Other options are leaving the abdomen open or covering the gap with a mesh (Steinberg 1979; Hedderich et al. 1986). However, in recent years the dispute on which technique is better - planned relaparotomy or laparotomy on demand - has been taken up again without solving the problem (Hau et al. 1995). Some of the problems reported with planned relaparotomy may be associated with technical errors or human factor, which are always difficult to discuss. In this study an analysis of the patients with complicated secondary peritonitis treated with planned relaparotomy was performed with regard to clinical and laboratory parameters indicating increased intra-abdominal pressure after closure of the abdomen. To our knowledge this is the first time that a sub-group of

patients with complicated secondary peritonitis who failed after termination of planned relaparotomy is presented and further analysed.

## Patients and Methods

A total of 145 patients treated with planned relaparotomy for severe intra-abdominal infection at a University Surgery Department (1992-1997) were included in the analysis. In all patients, the abdomen was not closed at the end of the initial operation and subsequent abdominal exploration (-planned relaparotomy) was planned when source control was not secured, the patient was not hemodynamically stable to close the abdomen, or the abdomen could not be closed due to increased intra-abdominal pressure. The abdomen was then temporarily closed, bridging the gap between the fascial edges with an artificial burr. Once the fascial gap had become sufficiently narrow to allow for final closure without leaving undue abdominal pressure, the abdominal wall was closed fascia to fascia, whenever possible with closure of the skin. If sepsis persisted or had progressed to tertiary peritonitis, and further abdominal intervention appeared to do harm, no further re-entries were done, and the abdomen was closed either with a Vicryl™ mesh or by leaving it totally open, in the presence of increased intra-abdominal pressure. Re-exploration in patients with closed abdomen was necessary when signs of persistent intra-abdominal sepsis were present. Patient demographics were recorded and analysed with regard to operative technique (planned relaparotomy with closure of the abdomen, mesh closure, no closure) and post-operative complication and mortality. The APACHE II severity of diseases score (Knaus et al. 1985), the Goris multi-organ failure (MOF) score (Goris et al. 1985) and the Marshall multi-organ dysfunction (MODS) score (Marshall et al. 1995) were assessed on admission, during the planned relaparotomy procedure, and after closure of the abdomen. At the day of closure of the abdomen and the two consecutive days data were collected, which were considered to correlate with increased intra-abdominal pressure, e.g., positive end-expiratory pressure (PEEP), urine output, blood urea nitrogen (BUN), creatinine, central venous pressure (VCP) (Sugerman et al. 1999). Statistical evaluation of the data and distribution pattern was performed with the Instat statistical package (Santa Monica Ca USA) and with the Mann-Whitney and ANOVA test for quantitative analysis. Multi regression analysis was performed to identify risk factors for death using the SPSS program.

## Results

A total of 145 patients (75 men and 70 women, age 57± 18 years) were entered into the study. 43 (29.7%) of the patients died 2 to 179 days after the first operation for peritonitis, either from sepsis or tertiary peritonitis. All patients underwent an abdominal operation for intra-abdominal infection (index operation) followed by 4 ± 5.8 abdominal re-entries. The median age of all 145 patients was 61 years and the mean APACHE II score was 16.7 ± 8.3, median 16 (1-26). The source of peritonitis was located in the following organs: stomach n = 9, duodenum n = 8 , biliary tree n = 10 , small bowel n = 45 , appendix n = 17 , large bowel n = 48 . 11 patients were treated with cortisol. 9 patients received chemotherapy and radiation for malignant tumour, and 26 patients had diabetes. 40 patients had a malignant tumour as underlying disease. Patients stayed for 20 ± 27 days (mean; range 0-176) in the intensive care unit and for 42 ± 47 days (mean; range 2-280) in the hospital.

There are three types of patients in this study: patients with primary abdominal closure after presumed source control (n = 107), patients with mesh secondary closure (n = 20), and patients where no abdominal closure could be performed (n = 18). (Table 1)

After the index operation, the abdomen was explored daily for a total of 508 days in all 145 patients. The final abdominal closure was performed after 4 days (mean; median 2.0; range 0-37). During the index operation, the source of infection was resected in 84 cases (58%) or closed by suture in 37 (26%) cases. 9 cholecystectomies were performed and 15 cases required simple drainage only. During planned relaparotomy, additional problems and complications were observed in 36 (25%) patients. Problems encountered and treated during planned relaparotomy included intra-abdominal haemorrhage (n = 16), intra-abdominal abscess formation (n = 6), persistent intestinal leak (n = 3) and anastomotic leakage (n = 1). Abdominal wall infection (n = 7), the burr sheet torn out of the abdominal wall fascia (n = 2) and surgical haemorrhage (n = 1) were considered complications of the operative technique. Ongoing sepsis that could not be controlled perpetuated multi-organ failure in n = 16 cases, and led to pneumonia in 9 cases during planned relaparotomy. Source control was thought to be achieved by resection of the diseased bowel in 83, suture closure of the perforated bowel in 42 cases. 46 colostomies were thought to be necessary to exteriorise the infectious source or as protective colostomy.

The abdomen was closed primarily at the termination of planned relaparotomy in 107 (74%) of patients. 19 (17.8%) patients in this group died from tertiary peritonitis (ongoing inflammatory response) without any further re-exploration (n = 10), and from sepsis after a re-exploration has been performed despite termination of the planned relaparotomy (n = 9). These 19 patients were further analysed. In 20 patients, after a mean of 11.2 ± 8.1 re-entries, the abdominal wall could not be closed because of persisting inflammatory oedema. The abdominal fascial gap was bridged by Vicryl mesh when planned relaparotomy was terminated. These patients spent 51 ± 40 days in the intensive care unit; six (30%) of them died.

*Table 1.* Patients with primary closure after termination of planned relaparotomy, mesh closure and no abdominal closure in peritonitis treatment.

| Clinical parameters | A) Primary abdominal closure * n = 107 | B) Mesh closure * n = 20 | C) No abdominal closure * n = 18 | p-value by ANOVA | |
|---|---|---|---|---|---|
| APACHE II | 15.43 ± 7.56 | 17.95 ± 7.75 | 23.11 ± 10.20 | 0.001 | A vs C |
| Goris-Score | 3.36 ± 2.91 | 6.35 ± 3.28 | 8.11 ± 2.37 | 0.000 | A vs B vs C |
| MODS-Score | 5.11 ± 4.93 | 5.80 ± 6.06 | 13.27 ± 3.17 | 0.000 | A vs B vs C |
| Age ± years) | 57.68 ± 18.35 | 53.75 ± 16.40 | 57.66 ± 16.74 | 0.661 | A vs B vs C |
| Duration of symptoms ± days) | 3.83 ± 4.21 | 3.65 ± 2.20 | 4.50 ± 3.16 | 0.763 | A vs B vs C |
| Goris-Score at admission | 1.50 ± 1.49 | 2.50 ± 2.41 | 2.88 ± 2.74 | 0.003 | A vs B vs C |
| Intensive care stay ± days) | 15.48 ± 22.49 | 50.75 ± 39.54 | 14.88 ± 12.84 | 0.000 | A vs B |
| Hospitalization period ± days) | 40.48 ± 45.68 | 77.00 ± 57.01 | 14.88 ± 12.84 | 0.000 | A vs B vs C |
| Time until closure of the abdomen ± days) | 2.66 ± 4.17 | 11.20 ± 8.06 | | 0.000 | A vs B |

* Data are given as mean and standard deviation

*Table 2.* Severity of disease scores and indicators of increased abdominal pressure at the completion of planned re-laparotomies ± after fascial closure comparing patients with recovery versus ongoing sepsis/SIRS.

| Parameter | Unit | Recovery group | Ongoing sepsis or SIRS group | Difference at $p < 0.05$ |
|---|---|---|---|---|
| Number of cases | | N = 68 | N = 39 | |
| Age ± years) | mean ± SD | 55.1 ± 19.2 | 62.2 ± 15.9 | No |
| APACHE II | mean ± SD | 13.3 ± 7 | 19.3 ± 7.1 | Yes |
| Number of abdominal reentries | | 2.7 ± 4.4 | 2.5 ± 3.8 | No |
| CVP after closure | $CmH_2O$ | 12.5 | 10.3 | Yes |
| Serum creatinine after closure | mg/dl | 1.5 | 1.8 | Yes |
| BUN after closure | mg/dl | 16.7 | 33 | Yes |
| PEEP after closure | Torr | 8.8 | 11.5 | Yes |
| MOF score after closure | mean ± SD | 2.2 ± 2.3 | 5.4 ± 2.8 | Yes |
| MODS score after closure | mean ± SD | 3.3 ± 4 | 8.2 ± 4.8 | Yes |
| Mortality | | 0 (0%) | 19 (48.7%) | Yes |
| ICU stay | Days | 8.9 ± 12 | 27 ± 30.7 | Yes |

MOF = Multi-Organ Failure score (Goris)
MODS = Multi-Organ-Dysfunction (Marshall) score
APACHE II = acute physiology and chronic health evaluation (APACHE) II score
CVP = central venous pressure
BUN = blood urea nitrogen
PEEP = positive end expiratory pressure

*Table 3.* Severity of disease and outcome of patients with ongoing sepsis and SIRS stratified for post-planned re-laparotomy re-explorations.

| | Without reexploration n = 15 | With re-exploration n = 24 | Difference significant |
|---|---|---|---|
| Mortality | n = 10 (66.7%) | n = 9 (37.5%) | P < 0.001 |
| Age (years) | 66.7 ± 15.9 | 59.4 ± 15.6 | ns |
| Lag-phase (days) | 3.4 ± 4 | 5.4 ± 5.6 | Ns |
| APACHE II | 18.9 ± 7.3 | 19.5 ± 7.2 | Ns |
| PR time until closure | 1.7 ± 3.1 | 3.1 ± 4.2 | Ns |
| MOF score | 5.2 ± 2.6 | 5.5 ± 2.9 | Ns |
| MODS score | 8.4 ± 3.8 | 8.1 ± 2.9 | Ns |
| ICU stay (days) | 10.6 ± 9.6 | 37.2 ± 34.9 | P < 0.05 |

MOF = Multi-Organ Failure score (Goris)
MODS = Multi-Organ-Dysfunction (Marshall) score
APACHE II = acute physiology and chronic health evaluation (APACHE) II score
PR = planned re-laparotomy
data indicated as mean ± standard deviation

Hemodynamic parameters and organ failure scores of 14 patients indicated ongoing inflammatory reaction or sepsis, requiring a significantly prolonged intensive care treatment (60 versus 30 days; $p < 0.05$ when compared to patients without ongoing sepsis/inflammation). In 18 patients the abdomen was never closed because of ongoing sepsis; all patients died after 16 ± 12 days (mean). All patients in this group presented with advanced disease at the time of the index operation indicated by significantly higher APACHE II scores (average 23; $p < 0.05$) when compared to patients with primary closure of the abdomen (average 15) or mesh closure (average 18).

39 patients in the first group with closure of the abdomen who demonstrated signs of ongoing sepsis/inflammation after closure of the abdomen were analysed in comparison to the 68 patients who were cured. Patients with ongoing sepsis/inflammation had significantly higher APACHE II scores (average 19 ± 7) versus patients who were cured (average 13 ± 7; $p < 0.001$). These patients also had significantly higher organ failure scores and stayed longer in the intensive care unit (27 ± 30.7 days versus 8.9(12 days; $p < 0.01$). The length of surgical treatment (planned relaparotomy) was not different in both groups (3 days). (Table 2)

Patients with presumed successful termination of planned relaparotomy and abdominal closure (n = 107 total) had to be re-explored due to symptoms of abdominal compartment syndrome and/or ongoing sepsis in n = 24 cases of whom n = 9 (37.5%) died and 15 patients survived. The mortality rate of patients with ongoing sepsis/inflammation who were not re-explored was 67% and significantly higher (10/15) (Chi-square = 3.1431; $p < 0.05$). This difference in outcome was not indicated by a difference in the APACHE II score at the index operation nor did the number of explorations before closure of the abdomen (n = 5 in patients with re-exploration after closure of the abdomen versus n = 3 in patients without re-exploration; n.s.) reveal a possible association with the disease severity or ongoing sepsis/inflammation. Non-surviving patients who were re-explored after closure of the abdomen for ongoing sepsis/inflammation had significantly higher APACHE II scores (23.88 ± 26), MOF scores (7.67 ± 7) and MODS scores (12.4 ± 11) than survivors (17.13 ± 17; 4.2 ± 5; 5.53 ± 7, respectively). However, the scores were not different in patients who were re-explored when compared to patients without re-exploration after closure of the abdomen and ongoing sepsis/inflammation. (Table 3)

Blood urea nitrogen (BUN), creatinine, and central venous pressure (CVP) were significantly different in surviving patients after termination of planned relaparotomy and closure of the abdomen when compared to non-survivors. (Table 4) An increase of 20% in creatinine levels (positive prediction 91.6%, sensitivity 83.4%, specificity 56.3%) as well as increased creatinine levels at the second day after closure of the abdomen and increased blood urea nitrogen levels at the first day after closure of the abdomen were associated with detrimental outcome. (Table 5)

The closure of the abdomen (positive predictive value 100%, sensitivity 80.3%, specificity 66.7%), complications during surgical treatment, e.g., bleeding or pneumonia, (positive predictive value 95.1%, sensitivity 84.2%, specificity 83.2%), anastomotic leakage and translocation (positive predictive value 93.1%, sensitivity 74%, specificity 58.7%) were associated with poor outcome. Isolation of pathogens, the classification of the exudate, the origin of peritonitis, pre-treatment, pre-existing malignancy did not seem to have an influence on the outcome. Co-existing liver disease (positive predictive value 97.1%, sensitivity 75%, specificity 76.8%), organ failure at the time of the index oper-

*Table 4.* Blood urea nitrogen (BUN), creatinine (CR), positive end expiratory pressure (PEEP), and central venous pressure (CVP) of survivors and non-survivors at the day of abdominal closure and termination of the planned relaparotomy, first and second postoperative day (ANOVA analysis). mean ± standard deviation

| | | n | Survivors | n | Non-survivors | p-value |
|---|---|---|---|---|---|---|
| BUN 0 | mg/dl | 96 | 16.97 ± 20.19 | 24 | 43.38 ± 42.74 | 0.000 |
| BUN 1 | mg/dl | 96 | 17.47 ± 21.40 | 24 | 45.25 ± 40.27 | 0.000 |
| BUN 2 | mg/dl | 96 | 17.87 ± 22.40 | 22 | 43.42 ± 38.52 | 0.000 |
| CR 0 | mg/dl | 101 | 1.47 ± 1.98 | 24 | 2.57 ± 1.75 | 0.015 |
| CR 1 | mg/dl | 102 | 1.36 ± 1.39 | 24 | 3.03 ± 2.08 | 0.000 |
| CR 2 | mg/dl | 102 | 1.31 ± 1.56 | 22 | 3.16 ± 1.79 | 0.000 |
| PEEP 0 | Torr | 86 | 9.19 ± 1.99 | 24 | 9.75 ± 2.38 | 0.253 |
| PEEP 1 | Torr | 82 | 8.86 ± 1.93 | 22 | 9.83 ± 2.18 | 0.039 |
| PEEP 2 | Torr | 81 | 8.19 ± 2.25 | 22 | 9.59 ± 2.34 | 0.012 |
| CVP 0 | cm $H_2O$ | 95 | 10.65 ± 3.67 | 24 | 13.20 ± 2.99 | 0.002 |
| CVP 1 | cm $H_2O$ | 94 | 9.85 ± 3.72 | 24 | 13.62 ± 3.10 | 0.000 |
| CVP 2 | cm $H_2O$ | 94 | 8.96 ± 3.91 | 22 | 13.22 ± 3.89 | 0.000 |

*Table 5.* Creatinine (CR) and blood urea nitrogen (BUN) after abdominal closure and termination of planned relaparotomy (Multivariate analysis).

| Parameter | β | S.E. | Wald | Df | Sig | R | Exp (β) |
|---|---|---|---|---|---|---|---|
| CR (20%) | 2.2422 | 0.6100 | 13.5087 | 1 | 0.0002 | 0.3179 | 9.4139 |
| CR 2 | 3.0162 | 1.1230 | 7.2141 | 1 | 0.0072 | 0.2230 | 20.4128 |
| BUN 1 | 0.1794 | 0.0805 | 4.9684 | 1 | 0.0258 | 0.1682 | 1.1965 |

CR 20% : 20% increase of creatinine
CR 2 : creatinine level on day 2 after closure of the abdomen
BUN 1: blood urea nitrogen on day 1 after closure of the abdomen

*Table 6.* Multivariate analysis of risk factors in peritonitis for death.

| | β | S.E. | Wald | df | Sig | R | Exp (β) |
|---|---|---|---|---|---|---|---|
| Abdominal closure | -1.9474 | 0.4828 | 16.2709 | 1 | 0.0001 | -.2845 | 0.1426 |
| Hemorrhage | 2.5717 | 0.8664 | 8.8107 | 1 | 0.0030 | 0.1966 | 13.0884 |
| Pneumonia | 1.7413 | 0.7135 | 5.955 | 1 | 0.0147 | 0.1498 | 5.7046 |
| Insufficiency | 1.4538 | 0.6653 | 4.7754 | 1 | 0.0289 | 0.1257 | 4.2798 |
| Translocation | 1.4018 | 0.6948 | 4.0706 | 1 | 0.0436 | 0.1086 | 4.0626 |
| Liver | 2.6674 | 1.2371 | 4.6492 | 1 | 0.0311 | 0.1226 | 14.4020 |
| MOF score | 0.4896 | 0.0831 | 34.7278 | 1 | 0.0000 | 0.4317 | 1.6317 |
| APACHE II | 0.1182 | 0.0272 | 18.8591 | 1 | 0.0000 | 0.3092 | 1.1255 |
| MODS score | 0.3575 | 0.0585 | 37.3931 | 1 | 0.0000 | 0.4490 | 1.4297 |

ation (MOF score: positive predicitive value 90.1%, sensitivity 85.7%, specificity 73.7%; MODS score: positive predictive value 91.1%, sensitivity 88.5%, specificity 77.5%) and severity of disease at the time of the index operation (APACHE II score: positive predictive value 93.0%, sensitivity 86.4%, specificity 68.2%) were identified as significant predictors for outcome in peritonitis (Table 6).

## Discussion

In our study 145 patients with severe peritonitis and treated with planned relaparotomy were analysed with regard to closure of the abdomen - primary closure after planned relaparotomy, secondary closure with mesh, and no closure at all - and complications after termination of planned relaparotomy and closure of the abdomen. The mean mortality of 29.7% in all patients is comparable to the mortality rate reported in other studies. (Schein et al. 1988). Patients in whom closure of the abdomen was successfully done had a similar severity of disease score (APACHE II) and mortality rate compared to results in recent studies. (Wacha et al. 1999; Koperna and Schulz 2000)

### Planned Relaparotomy Versus Laparotomy on Demand and Source Control

Yet, there is an unresolved dispute over the benefit of planned relaparotomy. Several reports have demonstrated that planned relaparotomy may help to control the intra-abdominal infection (Teichmann et al. 1986; Wittmann et al. 1990; Penninckx et al. 1990; Hubens et al. 1994). Open management of the septic abdomen with mesh has been advocated by others (Hedderich et al. 1986; Bose et al. 1991; Hakkiluoto and Hannukainnen 1992). It has been stated that planned relaparotomy is associated with increased frequency of infectious complications, e.g. suture leaks, recurrent intra-abdominal sepsis, septicaemia and that more patients with a Goris score above 5 are in this group when compared to laparotomy on demand (Hau et al. 1995). The authors of this study have compared 38 patients in each group. The study protocol did not include a clear definition of successful source control. This decision was left to the personal discretion of each participating and/or operating surgeon. The missing definition of source control is not just a problem of this study but of most published studies on peritonitis (Holzheimer and Dralle 2001). In other studies the patients treated with planned relaparotomy had more complications due to primary disease or sepsis which may reflect a different patient group (Demmel et al. 1993). In large studies there was no significant difference detectable in mortality in patients treated with planned relaparotomy or laparotomy on demand (Christou et al. 1993; Gotzinger et al. 1996; Koperna and Schulz 2000) The dilemma is obviously also not resolved by meta-analysis (Lamme et al. 2002).

### Comparability of Studies - What is the Reason for the Differences in Outcome: Human Factor, Operative Technique or Different Patients?

Despite the introduction of disease severity und multi-organ failure/dysfunction scores into clinical studies in order to make studies comparable (Dellinger et al. 1985; Bohnen et al. 1988; Ohmann et al. 1993) we still have a problem when we analyse clinical studies with regard to complications and outcome. It is well accepted that none of the existing scores can be trusted enough for individual therapeutic decisions in peritonitis patients (Ohmann et al. 1997). It has been suggested to combine several scores (Bosscha et al. 1997) or to measure inflammatory cytokines as surrogate parameters (Holzheimer et al. 1991). Despite promising results of a recently published European multi-centre trial with regard to the combination of scores and cytokine analysis in critically ill surgical patients, the measurement of scores and cytokines does not relieve the surgeons dilemma to re-explore or not a patient with suspected persistent sepsis nor does it characterize the individual patient perfectly (Holzheimer et al. 2000) The benefit of doing sophisticated analysis in critically ill surgical patients remains to be clarified with regard to the high cost in intensive care treatment (Welcker et al. 2002).

There are obvious differences between some studies on peritonitis. A conservative surgical treatment concept supplemented with extensive intraoperative lavage in just one surgical intervention in almost 90% of patients was said to reduce the reoperation rate and to translate into a low mortality rate of just 14% in patients with diffuse peritonitis (Seiler et al. 2000). What is responsible for differences in peritonitis studies: is it the human factor, the operative technique or do we investigate different patients? The surgeon may have positive as well as negative effects on outcome, which may not be recognized precisely and with validity in studies (de Leval et al. 2000; Bruce et al. 2001; Healey et al. 2002).

There is an argument that the surgical technique treating peritonitis is responsible for outcome. Planned relaparotomy has been criticized to cause intra-operative complications and to be unable to reverse organ dysfunction (van Goor et al. 1997). Intra-abdominal complications were more common among the non-survivors than the survivors, but the non-survivors had higher MOF scores than the survivors at the beginning of treatment. Patients with advanced disease may have in reality more complications no matter what kind of treatment is started. We, in contrast, observed no significant increase in intra-abdominal complications during planned relaparotomy.

### Host Response in Peritonitis - Is it Increased or Decreased by the Surgical Treatment?

Peritonitis can cause an increased intra-peritoneal inflammatory response, which may lead to organ failure and death (Holzheimer et al. 1995). Planned relaparotomy has been accused to further increase the inflammatory response causing a need for more blood products and to harm the patients (Sautner et al. 1997; Zugel et al. 2002). However, other factors, e.g., source control, circadian rhythm, antibiotic-induced endotoxin release, may be involved (Holzheimer 2001; Holzheimer

et al. 2002). Another recent study demonstrated the significant dominance of host-related factors over type, source of infection and other factors on the prognosis of patients with intra-abdominal infection (Pacelli et al. 1996), but this has been challenged by others (Burger et al. 1995).

### Organ Failure and Source Control - Decisive Factors at the Start of Treatment

Organ failure and failure in source control may have implications early in the treatment process and this may not be recognized at the index operation. In our study 39 patients who were diagnosed to have ongoing sepsis/inflammation after termination of planned relaparotomy had significantly higher APACHE II scores at the index operation and higher MOF scores after closure of the abdomen pointing into the direction of a failure in source control. Preoperative organ impairment has been identified as independent predictor of death in intra-abdominal infection (Pacelli et al. 1996). Koperna and Schulz observed in 105 patients in whom standard surgical treatment of secondary peritonitis failed and who had to undergo relaparotomy for persisting abdominal sepsis that aggressive surgical treatment has reached its limit in patients whose source of infection could not be controlled at the initial operation (Koperna and Schulz 2000) Gotzinger et al. stated that regardless of the type of operation - planned relaparotomy or laparotomy on demand - the crucial point is that the elimination of the infectious source is achieved as soon as possible (Gotzinger et al. 1996).

### Can We Identify Patients that Will Fail or who Will Develop Persistent Sepsis?

Can we recognize patients who do not profit from standard treatment or who may develop tertiary peritonitis/ persistent sepsis after closure of the abdomen? Poorly localized intra-abdominal infection, altered microbial flora, progressive organ dysfunction and significantly higher mortality have been associated with tertiary peritonitis (Rotstein and Meakins 1990), which describes the clinical situation of most patients with ongoing sepsis after termination of planned relaparotomy in this study. The type of surgery may not have a relationship to tertiary peritonitis and it may not be possible to predict the development of tertiary peritonitis by scores (Nathens et al. 1998). A recent retrospective study revealed that while increasing APACHE II score independently predicted progression from secondary to tertiary peritonitis but tertiary peritonitis was not an independent predictor of mortality. The authors concluded that the high mortality associated with tertiary peritonitis is more a function of the patient population in which it occurs than the severity of the pathological process itself (Evans et al. 2001). The evaluation of scores may not be of help since it does not provide any therapeutic alternative to the surgeon who has to perform a relaparotomy as soon as possible and the impossibility of definitive operative resolution of the intra-abdominal pathologic findings at initial operation may have no significant effect on mortality (Koperna and Schulz 1996). In our study we found some evidence that organ failure, clinical and laboratory parameters reflecting the development of intra-abdominal compartment syndrome may be clinically useful to identify patients at risk. This is also supported by others who investigated the scores in patients with or without persistent sepsis (Paugam-Burtz et al. 2002).

### When to Close the Abdomen and Stop the Planned Relaparotomy?

When to close the abdomen and to stop planned laparotomy is another important aspect of peritonitis treatment. It is not yet clear which clinical parameters do definitely allow us to decide on the termination of planned relaparotomy. The colonization of the upper gastrointestinal tract with Pseudomonas, Staphylococcus epidermidis and Candida has been associated with the development of invasive infection and may progress into organ failure (Marshall et al. 1993). Intra-abdominal cultures have been advocated by some authors and rejected by others (Sawyer et al. 1992; Schoeffel et al. 1995; van Goor et al. 1997) The isolation of Candida in peritoneal fluid has been associated with mortality (Dupont et al. 2002).

### Does Relaparotomy Affect the Outcome?

Re-operation in peritonitis has been considered to be harmful (Sautner et al. 1997) and to have no benefit for the clinical course of disease (van Goor et al. 1997). A higher mortality rate (42%) in patients with reoperation versus 27% without reoperation has been observed (Christou et al. 1993). Others have reported a 27% reduction of mortality in patients with persisting or relapsing sepsis (Billing et al. 1992) In several studies organ failure was not reversed by relaparotomy even when adequate therapy has been accomplished (Norton 1985; Marshall et al. 1988). However, the development of tertiary peritonitis or persistent intra-abdominal sepsis may reflect inadequate therapy of peritonitis leading to multi organ failure which then may be considered to be an indication for re-exploration of the abdomen (Fry et al. 1980; Ferraris et al. 1983; Hinsdale and Jaffe 1984; Polk and Shields 1977; Nathens et al. 1998). In difference to most of these studies we have analysed patients with ongoing sepsis after termination of planned relaparotomy. We observed that clinical and laboratory signs of abdominal compartment syndrome and organ failure may be present at the time of closure of the abdomen. An increased compartmentalized intraperitoneal inflammatory response may be followed by an increase in intra-abdominal pressure with consecutive renal failure (BUN, creatinine), ventilatory disturbances re-

flected by high peak inspiratory pressure and impaired gas exchange, and increased central venous pressure (Burch et al. 1996; Sugerman et al. 1999). The role of abdominal compartment syndrome in trauma victims is well recognized (Meldrum et al. 1997; Ivatury et al. 1998; Maxwell et al. 1999). Peritonitis patients, especially patients after cessation of planned relaparotomy, have not been studied comparably. In our study we observed significant alterations in the renal function, which have been observed as consequence of increased intra-abdominal pressure and predictor of fatal outcome in patients undergoing reoperation for sepsis (Sugrue et al. 1999; Machiedo et al. 1985). Re-exploration of some of these patients resulted in a better survival rate (37.5% versus 67%) when compared to the survival rate of patients who were not re-explored again. Intra-abdominal compartment syndrome is not in any case the reason for increased mortality - at least in this study. Despite leaving the abdomen open or secondary closure with mesh, which is known to avoid abdominal compartment syndrome in trauma patients (Ciresi et al. 1999; Mayberry et al. 1997), the mortality rate was unacceptable high (30% and 100%, respectively) in this group of patients and mostly the failure in source control accounted for this mortality. The concept of timely re-exploration is supported by several other studies, although they have not investigated the subgroup of patients after cessation of planned relaparotomy (Hinsdale and Jaffe 1984; Koperna and Schulz 2000).

In conclusion, we observed a different mortality in sub-groups of patients treated with planned relaparotomy with regard to closure of the abdomen. Patients in whom organ failure is present at the index operation or where source control is impossible are at risk for death. Sub-group analysis of patients with ongoing sepsis after cessation of planned relaparotomy revealed that most of these patients had indicators (MOF scores, renal failure) of intra-abdominal compartment syndrome mostly due to failure in source control and that re-exploration reduced the mortality when compared to patients who were not re-explored. There is still a problem to compare clinical studies despite powerful scores. Especially in subgroups of patients who may benefit from early detection of complications the characterization of these patients could be improved. The decision to close the abdomen may not only be influenced by the intra-abdominal findings, but also by the existence and level of organ failure.

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## References

Bartels H, Barthlen W, Siewert JR. The therapeutic results of programmed relaparotomy in diffuse peritonitis. Chirurg 1992;63(3):174-80

Billing A, Frohlich D, Mialkowskyi O, Stokstad P, Schildberg FW. Treatment of peritonitis with staged lavage: prognostic criteria and course of treatment. Langenbecks Arch Chir 1992;377(5):305-13

Bohnen JM, Mustard RA, Oxholm SE, Schouten BD. APACHE II score and abdominal sepsis. A prospective study. Arch Surg 1988;123(2):225-9

Bose SM, Kalra M, Sandhu NP. Open management of septic abdomen by Marlex mesh zipper. Aust N Z J Surg 1991;61(5):385-8

Bosscha K, Reijnders K, Hulstaert PF, Algra A, van der Werken C. Prognostic scoring systems to predict outcome in peritonitis and intra-abdominal sepsis. Br J Surg 1997;84(11):1532-4

Bruce J, Russell EM, Mollison J, Krukowski ZH. The measurement and monitoring of surgical adverse events. Health Technol Assess 2001;5(2):1-194

Burch JM, Moore EE, Moore FA, Franciose R. The abdominal compartment syndrome. Surg Clin North Am 1996;76:833-42

Burger JA, Schoffel U, Sach M, Jacobs E, Kownatzki E, von Specht BU, Farthmann EH. Effects of peritonitis exudates on chemotaxis and phagocytosis of human neutrophils. Eur J Surg 1995;161(9):647-53

Christou NV, Barie PS, Dellinger EP, Waymack JP, Stone HH. Surgical Infection Society intra-abdominal infection study. Prospective evaluation of management techniques and outcome. Arch Surg 1993;128(2):193-8

Ciresi DL, Cali RF, Senagore AJ. Abdominal closure using nonabsorbable mesh after massive resuscitation prevents abdominal compartment syndrome and gastrointestinal fistula. Am Surg 1999;65:720-4

De Leval MR, Carthey J, Wright DJ, Farewell VT, Reason JT. Human factors and cardiac surgery: a multicenter study. J Thorac Cardiovasc Surg 2000; 119(4 Pt 1):661-72

Dellinger EP, Wertz MJ, Meakins JL, Solomkin JS, Allo MD, Howard RJ, Simmons RL. Surgical infection stratification system for intra-abdominal infection. Multicenter trial. Arch Surg 1985;120(1):21-9

Demmel N, Osterholzer G, Gunther B. Differentiated treatment strategy for peritonitis: single stage closure with drainage or open with programmed reintervention/lavage ?. Zentralbl Chir 1993;118(7):395-400

Dupont H, Paugam-Burtz C, Muller-Serieys C, Fierobe L, Chosidow D, Marmuse JP, Mantz J, Desmonts JM. Predicitive factors of mortality due to polymicrobial peritonitis with Candida isolation in peritoneal fluid in critically ill patients. Arch Surg 2002;137(12):1341-6

Evans HL, Raymond DP, Pelletier SJ, Crabtree TD, Pruett TL, Sawyer RG. Tertiary peritonitis (Recurrent diffuse or localized disease) is not an independent predictor of mortality in surgical patients with intraabdominal infection. Surg Infect (Larchmt) 2001;2(4):255-65

Ferraris VA. Exploratory laparotomy for potential abdominal sepsis in patients with multiple-organ failure. Arch Surg 1983;118:1130-3

Fry DE, Pearlstein L, Fulton RL, Polk HC. Multiple system organ failure: the role of uncontrolled infection. Arch Surg 1980;115:136-40

Goris RJA, te Boekhorst TPA, Nuytinck JKS, Gimbrere JSF. Multiple-organ failure: generalized autodestructive inflammation? Arch Surg 1985;120:1109-1115

Gotzinger P, Gebhard B, Wamser P, Sautner T, Huemer G, Fugger R. Revision of diffuse peritonitis: planned versus on demand. Langenbecks Arch Chir 1996; 381(6):343-7

Hakkiluoto A, Hannukainen J. Open management with mesh and zipper of patients with intra-abdominal abscesses or diffuse peritonitis. Eur J Surg 1992;158(8): 403-5

Hau T, Ohmann C, Wolmershauser A, Wacha H, Yang Q. Planned relaparotomy vs relaparotomy on demand in the treatment of intra-abdominal infections. The peritonitis study group of the Surgical Infection Society-Europe. Arch Surg 1995;130(11):1193-6

Healey MA, Shackford SR, Osler TM, Rogers FB, Burns E. Complications in surgical patients. Arch Surg 2002;137(5):611-7

Hedderich GS, Wexler MJ, McLean AP, Meakins JL. The septic abdomen: open management with Marlex mesh with a zipper. Surgery 1986;99(4):399-408

Hinsdale JG, Jaffe BM. Re-operation for intra-abdominal sepsis. Indications and results in modern critical care setting. Ann Surg 1984;199(1):31-6

Holzheimer RG, Muhrer KH, L'Allemand N, Schmidt T, Henneking K. Intraabdominal infections: classification, mortality, scoring and pathophysiology. Infection 1991;19(6):447-52

Holzheimer RG, Schein M, Wittmann DL. Inflammatory response in peritoneal exudate and plasma of patients undergoing planned relaparotomy for severe secondary peritonitis. Arch Surg 1995;130(12):1314-9

Holzheimer RG, Capel P, Cavaillon JM, Cainzos M, Frileux P, Haupt W, Marie C, Muller E, Ohmann C, Schoffel U, Lopez-Boado MA, Sganga G, Stefani A, Kronberger L. Immunological surrogate parameters in a prognostic model for multi-organ failure and death. Eur J Med Res 2000; 5(7):283-94

Holzheimer RG. Antibiotic induced endotoxin release and clinical sepsis: a review. J Chemother 2001;Spec No 1 (1):159-72

Holzheimer RG, Dralle H. Paradigm change in 30 years peritonitis treatment - a review on source control. Eur J Med Res 2001;6(4):161-8

Holzheimer RG, Curley P, Saporoschetz IB, Doherty JM, Mannick JA, Rodrick ML. Circadian rhythm of cytokine secretion following thermal injury in mice: implications for burn and trauma research. Shock 2002;17(6):527-9

Hubens G, Lafaire C, De Praeter M, Ysebaert D, Vaneerdeweg W, Heytens L, Eyskens E. Staged peritoneal lavages with the aid of a Zipper system in the treatment of diffuse peritonitis. Acta Chir Belg 1994;94(3):176-9

Ivatury RR, Porter JM, Simon RJ, Islam S, John R, Stahl WM. Intra-abdominal hypertension after life-threatening penetrating abdominal trauma: prophylaxis, incidence, and clinical relevance to gastric mucosal pH and abdominal compartment syndrome. J Trauma 1998;44:1016-21

Kirschner M. Die Behandlung der akuten eitrigen freien Bauchfellentzündung. Langenbecks Arch Chir 1926; 142:53-267

Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29

Koperna T, Schulz F. Prognosis and treamtent of peritonitis. Do we need new scoring systems? Arch Surg 1996;131(2):180-6

Koperna T, Schulz F. Relaparotomy in peritonitis: prognosis and treatment of patients with persisting intra-abdominal infection.World J Surg 2000;24(1):32-7

Lamme B, Boermeester MA, Reitsma JB, Mahler CW, Obertop H, Gouma DJ. Meta-analysis of relaparotomy for secondary peritonitis. Br J Surg 2002; 89(12): 1516-24

Machiedo GW, Tikellis J, Suval W, Lee BC, Blackwood JM, Rush BF. Reoperation for sepsis. Ann Surg 1985;51:149-54

Marshall JC, Christou NV, Horn R, Meakins JL. The microbiology of multiple organ failure. The proximal gastrointestinal tract as an occult reservoir of pathogens. Arch Surg 1988;123:309-15

Marshall JC, Christou NV, Meakins JL. The gastrointestinal tract. The undrained abscess of multiple organ failure. Ann Surg 1993;218(2):111-9

Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex outcome. Crit Care Med 1995;23:1638-1652

Maxwell RA, Fabian TC, Croce MA, Davis KA. Secondary abdominal compartment syndrome: an underappreciated manifestation of severe hemorrhagic shock. J Trauma 1999;47:995-9

Mayberry JC, Mullins RJ, Crass RA, Trunckey DD. Prevention of abdominal compartment syndrome by absorbable mesh prosthetic closure. Arch Surg 1997; 132(9):957-61

Meldrum DR, Moore FA, Moore EE, Franciose RJ, Sauaia A, Burch JM. Prospective characterization and selective management of the abdominal compartment syndrome. Am J Surg 1997;174:667-72

Nathens AB, Rotstein OD, Marshall JC. Tertiary peritonitis: clinical features of a complex nosocomial infection. World J Surg 1998;22:158-63

Norton LW. Does drainage of intraabdominal pus reverse multiple organ failure? Am J Surg 1985;149: 347-50

Ohmann C, Wittmann DH, Wacha H. Prospective evaluation of prognostic scoring systems in peritonitis. Peritonitis study group. Eur J Surg 1993;159(5):267-74

Ohmann C, Yang Q, Haut T, Wacha H. Prognostic modelling in peritonitis. Peritonitis Study Group of the Surgical Infection Society Europe. Eur J Surg 1997;163(1):53-60

Pacelli F, Doglietto GB, Alfieri S, Piccioni E, Sgadari A, Gui D, Crucitti F. Prognosis in intra-abdominal infections. Multivariate analysis on 604 patients. Arch Surg 1996;131(6):641-5

Paugam-Burtz C, Dupont H, Marmuse JP, Chosidow D, Malek L, Desmonts JM, Mantz J. Daily organ-system failure for diagnosis of persistent intra-abdominal sepsis after postoperative peritonitis. Intensive Care Med 2002;28(5):594-8

Penninckx F, Kerremans R, Filez L, Ferdinande P, Schets M, Lauwers P. Planned relaparotomies for advanced, established peritonitis from colonic origin. Acta Chir Belg 1990;90(5):269-74

Polk HC, Shields CL. Remote organ failure: a valid sign of occult intra-abdominal infection. Surgery 1977; 81:310-3

Rotstein OD, Meakins JL. Diagnostic and therapeutic challenges of intraabdominal infections. World J Surg 1990;14:159-66

Sautner T, Gotzinger P, Redl-Wenzel EM, Dittrich K, Felfernig M, Sporn P, Roth E, Fugger R. Does reoperation for abdominal sepsis enhance the inflammatory host response? Arch Surg 1997;132:250-5

Sawyer RG, Rosenhof LK, Adams RB, May AK, Spengler MD, Pruett TL. Peritonitis into the 1990s: changing pathogens and changing strategies in the critically ill. Am Surg 1992;58(2):82-7

Schein M, Saadia R, Decker G. Intraoperative peritoneal lavage. Surg Gynecol Obstet 1988;166:187-95
Schein M, Wittmann DH, Aprahamian C, et al. The abdominal compartment syndrome. The physiological and clinical consequences of elevated intraabdominal pressure. J Am Coll Surg 1995;180:745-753
Schoeffel U, Jacobs E, Ruf G, Mierswa F, von Specht BU, Farthmann EH. Intraperitoneal micro-organisms and the severity of peritonitis. Eur J Surg 1995; 161(7):501-8
Seiler CA, Brugger L, Forssmann U, Baer HU, Buchler MW. Conservative surgical treatment of diffuse peritonitis. Surgery 2000;127(2):178-84
Steinberg D. On leaving the peritoneal cavity open in acute, generalized peritonitis. Am J Surg 1979;137: 216-20
Sugerman HJ, Bloomfiled GL, Saggi BW. Multisystem organ failure secondary to increased intraabdominal pressure. Infection 1999;27:61-6
Sugrue M, Jones F, Deane SA, Bishop G, Bauman A, Hillman K. Intra-abdominal hypertension is an independent cause of postoperative renal impairment. Arch Surg 1999;134:1082-5
Teichmann W, Wittmann DH, Andreone PA. Scheduled reoperations (planned relaparotomy) for diffuse peritonitis. Arch Surg 1986;121(2):147-52
Van Goor H, Hulsebos RG, Bleichrodt RP. Complications of planned relaparotomy in patients with severe general peritonitis. Eur J Surg 1997;163(1):61-6
Wacha H, Hau T, Dittmer R, Ohmann C and the Peritonitis study group. Risk factors associated with intraabdominal infections: a prospective multicenter study. Langenbeck's Arch Surg 1999;384:24-32
Welcker K, Lederle J, Schorr M, Siebeck M. Surgery and adjuvant therapy in patients with diffuse peritonitis: cost analysis. World J Surg 2002;26(3):307-13
Wittmann DH, Aprahamian C, Bergstein JM. Planned relaparotomy: advanced diffuse peritonitis managed by planned multiple laparotomies utilizing zippers, slide fastener, and Velcro analogue for temporary abdominal closure. World J Surg 1990;14(2):218-26
Zugel N, Siebeck M, geissler B, Lichtwark-Aschoff M, Gippner-Steppert C, Witte J, Jochum M. Circulating mediators and organ function in patients undergoing planned relaparotomy vs conventional trherapy in severe secondary peritonitis. Arch Surg 2002;137(5): 590-9

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