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Factors Affecting Mortality in Generalized Postoperative Peritonitis: Multivariate Analysis in 96 Patients

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Abstract. Mortality of generalized postoperative peritonitis remains high at 22% to 55%. The aim of the present study was to identify prognostic factors by means of univariate and multivariate analysis in a consecutive series of 96 patients. Mortality was 30%. Inability to clear the abdominal infection or to control the septic source, older age, and unconsciousness were significant factors related to mortality in the multivariate analysis. Failure to control the peritoneal infection (15%) was always fatal and correlated with failed septic source control, high Acute Physiology and Chronic Health Evaluation (APACHE) II score, and male gender. Failure to control the septic source (8%) also was always fatal and correlated with high APACHE II score and therapeutic delay. In patients with immediate source control, residual peritonitis occurred in 9% after purulent or biliary peritonitis and in 41% after fecal peritonitis ($p = 0.002$). In patients without immediate control of the septic source, delayed control was still achieved in 100% after a planned relaparotomy (PR) strategy versus 43% after an on-demand relaparotomy (ODR) strategy ($p = 0.018$). In the same patients, mortality was 0% in the PR group versus 64% in the ODR group ($p = 0.007$). Early relaparotomy is related to improved septic source control. After relaparotomy for generalized postoperative peritonitis, a PR strategy is indicated whenever source control is uncertain. It also might decrease mortality in fecal peritonitis. An ODR approach is adequate for purulent and biliary peritonitis with safe septic source control.

The mortality of postoperative peritonitis is 22% to 55% and remains higher than the mortality of perforation peritonitis (11% to 29%) in studies published since 1990 [1–8]. Several studies analyzed prognostic factors in peritonitis in general [1–8] or in postoperative abdominal infection including abscesses and localized peritonitis [9, 10], but, to our knowledge, no study exclusively looked at prognostic factors in postoperative generalized peritonitis. The aim of our study was to perform a univariate and multivariate analysis of these factors in order to explore how mortality could be decreased.

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Materials and Methods

Definitions, Selection Criteria, and Patients

Generalized postoperative peritonitis was defined as the presence of pus with positive cultures, bile or bowel contents in the four abdominal quadrants, occurring in the first month after an abdominal operation which had not been performed because of peritonitis or abdominal trauma. Children under the age of 1 year were excluded.

The timing of the first signs and symptoms of postoperative peritonitis was based on the onset of one or more of the following: abnormal pain, drain production, fever ≥ 38.5°C measured axillary, hypoxemia ($Pa_{O_2} < 65$ mmHg), hypotension (systolic blood pressure < 100 mmHg), or oliguria (urinary output < 500 ml/day). Therapeutic delay was defined as the interval between the first sign of peritonitis and the first relaparotomy. Early relaparotomy was defined as a delay of < 24 hours, late relaparotomy or therapeutic delay as a delay of ≥ 24 hours. The Acute Physiology and Chronic Health Evaluation (APACHE) II score [11] was calculated on the day of the first relaparotomy. Control of the septic source was defined as the effective termination of continuing contamination of the abdominal cavity. Clearance of the abdominal infection was defined as the macroscopic elimination of all abdominal exudate and purulent pseudomembranes. Residual peritonitis was defined as an abdominal cavity that was still contaminated by exudate or purulent pseudomembranes at relaparotomy or autopsy. Mortality was defined as death during hospitalization. Resident surgeons (first year after specialization) were considered as junior surgeons, in contrast to the senior staff surgeons.

Factors submitted for statistical analysis were: age, sex, the Chronic Health Evaluation component of the APACHE II score, chronic use of corticosteroids, type of first operation (gastrointestinal, vascular, urological, gynecological, kidney transplantation), elective versus urgent nature of primary surgery, presence of malignancy at first operation, first operation in our hospital versus another hospital, interval between first operation and first signs of peritonitis, therapeutic delay, interval between first operation and

relaparotomy, signs and symptoms at relaparotomy (temperature, abnormal pain, productive drainage, ileus, hypotension, oliguria, hypoxemia, consciousness, white blood cell count), scheduled (versus on-demand) use of opioids, APACHE II score and Acute Physiology component of the APACHE II score at the first relaparotomy, organ location of the septic source, compartment location of the septic source (upper or lower abdomen), nature of the septic source—i.e., cause of peritoneal contamination, nature of peritoneal exudate (purulent, biliary or faecal)—planned relaparotomy (PR) versus on-demand relaparotomy (ODR) strategy, number of relaparotomies, treatment of septic source (closure of a leak or reconstruction of an anastomosis, resection and stoma, drainage only), control of the septic source, number of relaparotomies needed to obtain control of the septic source, clearance of the abdomen, number of relaparotomies needed to obtain clearance of the abdomen, complications of relaparotomies, type of surgeon at the first relaparotomy, length of ICU stay, length of stay on the ward, total hospital stay.

Between January 1986 and December 1995, 96 consecutive patients with generalized postoperative peritonitis underwent their first or following relaparotomies in our department. Fourteen patients were referred from other hospitals. There were 55 men and 41 women. Mean age was 57.1 years ± 18.3 SD (range 14 to 90 years). Primary surgery had always been performed for noninfectious pathology. It was an emergency procedure in 46% of the patients. Original pathology was as follows: gastroduodenal 14, biliary 11, hepatic 4, pancreatic 5, small intestinal 10, colorectal 38, vascular 7, urologic 3, gynecologic 2, kidney transplantation 2. Four senior surgeons and ten junior surgeons were involved in the first relaparotomies for peritonitis. Causes of the diffuse postoperative peritonitis were anastomotic leaks and stump leaks (56 cases); unrecognized iatrogenic lesion leaks—e.g., bowel laceration (16 cases); secondary perforations—e.g., ischemic, peptic or due to diverticulitis (15 cases); infected fluid (6 cases); and drain leaks—i.e., dislodged T tube or gastrostomy tube (3 cases). The peritoneal fluid was purulent in 19 cases, biliary in 22 cases, and fecal in 55 cases.

Methods

At all relaparotomies the surgical treatment aimed to control the septic source. In the upper gastrointestinal (GI) tract, this was done by closure of a leak or reconstruction of an anastomosis (14/33 patients); if this was technically impossible, drainage alone was used (19/33 patients). Small intestinal leaks were treated by closure of a leak or reconstruction of an anastomosis (10/14 patients), resection and stoma (3), or drainage only (1). Colorectal leaks were treated by resection and stoma (34/43 patients), proximal derivative stoma and drainage (7 patients), or reconstruction of the anastomosis (2 patients). Finally, in 6 patients, only infected peritoneal fluid was found.

To clear the abdominal infection, the peritoneal cavity was cleaned at each relaparotomy. A complete abdominal exploration was performed, with aspiration of the exudate and gentle removal of as much as possible of the fibrino-purulent pseudomembranes without causing bleeding, followed by repeat peritoneal lavage with several liters of physiologic saline. At the end of each relaparotomy a choice was made between a PR or an ODR strategy. The PR strategy was chosen if adequate peritoneal debridement and cleansing could not be achieved by the end of the operation in more than one abdominal quadrant. Relaparotomies were scheduled every 48 hours with temporary abdominal closure using Velcro or zipper until the peritoneal contamination disappeared macroscopically [1]. These PR were performed in 24 of 55 patients with fecal peritonitis, and in 5 of 41 patients with purulent or biliary peritonitis. In the ODR approach no further relaparotomy was considered unless signs of sepsis reappeared or persisted.

All patients were treated in the intensive care unit (ICU). Broad-spectrum antibiotics were initiated at the latest at the time of the first relaparotomy and adapted to the results of cultures in the postoperative period.

Statistical Methodology

Fisher tests were used to analyze the relation of mortality with categorical covariates in a univariate setting. For continuous covariates, the results of a univariate logistic regression are reported. Because the univariate analysis has only an exploratory character, no correction was used for multiple testing and two-sided p values are reported. All p values are based on exact tests. Because all patients without clearance of the abdomen and all patients without control of the septic source died, there exists no maximum likelihood estimator for the effect of control of the septic source. Analyses involving these covariates, therefore, use the median unbiased estimator instead of the classical maximum likelihood estimator. A procedure to obtain these estimates is available in logXact. The results of the univariate analysis were used as a guideline in the construction of a multivariate model for mortality (because the number of covariates is large with reference to the number of patients). Because all patients without control of septic source also had no clearance of the abdomen (but not vice versa), both covariates could not be estimated in the same multivariate model. Therefore, we only used clearance of the abdomen in the multivariate analysis. All analyses were performed with StatXact 4 and LogXact 4.

Results

Mortality

The mortality was 30% (29 patients). Twenty-four patients died in the ICU: in 8 patients the septic source could not be controlled; in 7 patients the peritoneal infection could not be controlled; 6 patients died of septic shock and multiple organ failure despite a clean peritoneum; and 3 patients died of other complications (pulmonary embolism, bronchopneumonia, and vegetative coma). Five patients died on the ward because of respiratory complications (2 aspiration pneumonitis, 2 respiratory tract infection, 1 progressive respiratory insufficiency); they were significantly older than the other ICU surviving patients: 80 ± 8.1 years (range 69 to 90 years) versus 51 ± 18.1 years (range 14 to 87 years) ($p < 0.001$). The global hospital stay per patient was 30.9 days (range 1 to 151 days): 11.6 days (range 1 to 49 days) for those who died, and 39.2 days (range 1 to 151 days) for surviving patients. The mean number of ICU days per patient was 11.8 (range 1 to 99 days): 10.5 (1 to 49) days for deceased patients and 12.3 (1 to 99) days for surviving patients. Death occurred within 2 weeks after the first relaparotomy in 69% of the patients who died.

Factors related to mortality in a univariate and multivariate analysis are listed in Tables 1 and 2. Inability to clear the abdominal infection or to control the septic source, older age, and uncon-

Table 1. Factors related to mortality in univariate analysis.

	Mortality		
Dichotomic variables	If variable absent	If variable present	*p*-Value
Control of septic source	100% (8/8)	23.9% (21/88)	< 0.0001
Clearance of abdomen	100% (15/15)	17.3% (14/81)	< 0.0001
Hypotension	18.3% (13/71)	64% (16/25)	< 0.0001
Dyspnea	20.6% (14/68)	53.6% (15/28)	0.0028
Normal consciousness	64.3% (9/14)	24.4% (20/82)	0.005
Use of corticoids	36.4% (28/77)	5.3% (1/19)	0.010
Oliguria	25.3% (21/83)	61.5% (8/13)	0.019
Primary surgery vascular	27% (24/89)	71.4% (5/7)	0.025
Planned relaparotomy	37.3% (25/67)	13.8% (4/29)	0.029
Continuous variables[a]	Alive	Dead	*p*-Value
Age (years)	51.03 ± 18.11	71.14 ± 8.57	< 0.0001
APACHE II score	10.41 ± 6.48	20.11 ± 8.25	< 0.0001
Acute physiology component of APACHE II score	6.41 ± 6.06	14.26 ± 8.17	< 0.0001

APACHE: Acute Physiology and Chronic Health Evaluation.
[a]Data are presented as mean ± standard deviation.

Table 2. Factors related to mortality in multivariate analysis.

	Odds ratio	95% CI	*p*-Value
Failed clearance of abdomen (including failed control of septic source)[a]	76,923	10.417–+∝	< 0.0001
Age	1.125[b]	1.057–1.213	< 0.0001
Unconsciousness	11,765	1.527–142.857	0.013

[a]Because all patients without control of the septic source also lacked clearance of the abdomen, the effect of control of the septic source could not be estimated independently.
[b]For each added year of age.
CI: confidence interval.

sciousness were significant factors related to mortality in the multivariate analysis. A PR approach was associated with a lower mortality than an ODR approach (14% vs. 37%, $p = 0.029$), but this was significant in the univariate analysis only. The PR and ODR groups were comparable for APACHE II score: 12.56 ± 6.48 versus 13.55 ± 8.96 ($p = 0.98$). The median and mean delay between the first signs of postoperative peritonitis and the first relaparotomy were 1 and 1.8 days, respectively. A therapeutic delay (observed in 55 patients) was not associated with a higher APACHE II score or with increased mortality: 38% (21/55) versus 23% (8/35) ($p = 0.167$). However, it seriously decreased the ability to achieve immediate control over the septic source.

Septic Source Control

The mortality in 88 patients with immediate or delayed source control was 24%, whereas all 8 patients in whom no source control could be obtained died ($p < 0.001$). Examples of uncontrollable sources in these 8 patients were a releaking duodenal stump or releaking anastomoses such as a pancreaticojejunostomy, a choledochoduodenostomy, or a gastroenterostomy, as well as a postoperative perforation peritonitis from irresectable total small bowel ischemia. The results of univariate and multivariate analysis of the factors related to failed septic source control are shown in Table 3. A high initial APACHE II score and therapeutic delay were identified as independent prognostic factors. The impact of therapeutic delay can be illustrated as follows: immediate control was achieved in 95% (35/37 patients) after early relaparotomy versus 66% (31/47) after late relaparotomy ($p = 0.001$). In the group of 21 patients without immediate control of the septic source, delayed control was still achieved in 100% (7/7) after a PR strategy with a mean of 5.0 relaparotomies *versus* in 43% (6/14) after an ODR strategy ($p = 0.018$). In the same patients, mortality was 0% (0/7) and 64% (9/14), respectively ($p = 0.007$). Both groups were comparable for APACHE II score: 13.43 ± 4.58 versus 16.86 ± 10.65 ($p = 0.60$).

Clearance of the Peritoneal Infection

The mortality in a group of 81 patients with control of the abdominal septic source and clearance of the abdominal cavity was 17%, whereas all 7 patients in whom no clean abdomen could be obtained despite source control died ($p < 0.001$). A univariate and multivariate analysis of factors related to failed clearance of the abdomen is shown in Table 4. Failure to control the peritoneal infection correlated with failed septic source control, high initial APACHE II score, and male gender. In the subgroup of 75 patients with immediate control of the septic source, residual peritonitis occurred in 9% (3/34) after purulent or biliary peritonitis and in 41% (17/41) after fecal peritonitis ($p = 0.002$). In the former group, mortality was 0% after PR (0/5) versus 14% after ODR (4/29) ($p > 0.999$). In the latter group, mortality was 24% (4/17) in the PR group after a mean of 3 relaparotomies vs. 50% (12/24, $p = 0.113$) in the ODR group. Groups were comparable for APACHE II score: 13.3 ± 7.42 versus 14.4 ± 9.2 ($p = 0.88$).

Discussion

This article is a retrospective audit of all types of postoperative peritonitis as they occurred in a consecutive series in a tertiary referral center.

The audit was performed to identify independent prognostic factors. The mortality in our series was 30% despite considerable therapeutic efforts. Analysis of all types of primary surgery might be considered inappropriate. Indeed, a vascular procedure as com-

Table 3. Factors related to failed control of the septic source.

Univariate analysis			
	Control		
Dichotomic variables	If variable absent	If variable present	*p*-Value
Therapeutic delay	0% (0/35)	14.6% (8/55)	0.021
Pancreatic leak	6.5% (6/92)	50% (2/4)	0.034
Dyspnea	4.4% (3/68)	17.9% (5/28)	0.044
Continuous variables	Control	No control	*p*-Value
APACHE II score	12.5 ± 7.99	21.4 ± 7.40	0.009
Acute physiology component of APACHE II score	8.03 ± 7.33	15.6 ± 7.21	0.001
Multivariate analysis	Odds ratio	95% CI	*p*-Value
APACHE II score	1.12[a]	1.03–1.25	0.01

[a]For each added point of the score.

Table 4. Factors related to failed clearance of the abdomen.

Univariate analysis			
	Clearance		
Dichotomic variables	If variable absent	If variable present	*p*-Value
Control of septic source	100% (8/8)	8% (7/88)	< 0.001
Male gender	2.4% (1/41)	25.5% (14/55)	0.002
Hypotension	8.5% (6/71)	36% (9/25)	0.003
Oliguria	10.8% (6/68)	46.2% (6/13)	0.005
Dyspnea	8.8% (6/68)	32.1% (9/28)	0.01
Primary surgery vascular	12.4% (11/89)	57.1% (4/7)	0.011
Secondary perforation	12.5% (11/88)	50% (4/8)	0.019
Planned relaparotomy	20.9% (14/67)	3.5% (1/29)	0.034
Use of corticoids	19.5% (15/77)	0% (0/19)	0.037
Continuous variables	Clearance	No clearance	*p*-Value
APACHE II score	11.9 ± 7.4	21.1 ± 9	0.0006
Acute physiology component of APACHE II score	7.5 ± 6.7	15.5 ± 9.1	0.001
Age (years)	54.9 ± 19.03	68.9 ± 5.6	0.010
Multivariate analysis	Odds ratio	95% CI	*p*-Value
Failed control of septic source	74.9	7.5–+∝	< 0.0001
Male gender	8.24	1.05–+∝	0.044
APACHE II score	1.12[a]	1.00–1.29	0.047

[a]For each added point of the score.

pared with other types of primary surgery was found to be related to increased mortality and to failed clearance of the abdominal infection in univariate analysis. However, it was not identified as an independent prognostic factor in multivariate analysis. Multivariate analysis revealed that mortality is determined by four factors: inability to control the septic source or to clear the abdominal infection, older age, and unconsciousness. The APACHE II score was not retained as an additional independent factor in the multivariate analysis. However, starting from a model with only age and unconsciousness as predicting factors, the APACHE II score as well as its acute physiology component had an additive value: odds ratio, lower–upper 95% confidence interval and p value of 1.151, 1.052–1.259, $p = 0.002$ and 1.165, 1.06–1.28, $p = 0.0018$, respectively. Cause, localization, and nature (purulent, biliary, or fecal) of postoperative peritonitis or therapeutic delay, technique used for septic source control, or relaparotomy strategy were not identified as relevant and independent factors related to mortality.

A relationship between delay, organ failure, and mortality has been reported in most studies [4, 12–16]. In our series, however, the influence of delay on mortality did not reach a statistically significant level. We also found a comparable acute physiology component of the APACHE II score in patients undergoing late and early relaparotomies. A plausible explanation is that the mean delay was relatively short (1.8 days), so that not much organ function deterioration was allowed. Delay, however, seriously decreased the ability to achieve immediate or delayed control over the septic source.

If the septic source cannot be controlled, the patient will die inevitably [2, 12, 17]. Such patients should be excluded from analysis when comparing different treatment strategies in peritonitis. Control of the septic source should be obtained at the first relaparotomy in order to avoid increasing mortality [2, 3]. Thus, the surgeon has to choose the safest technique to clear the source immediately. When control of the septic source is uncertain, a PR strategy is strongly advised [18]. In our study, 7/7 patients with an

initially failed source control eventually were cured and survived while undergoing planned relaparotomies. This contrasts with the poor results after an ODR strategy in identical circumstances.

Methods to reduce bacterial contamination at the first laparotomy for peritonitis have been reviewed recently [19]. Two surgical strategies can be adopted: ODR or PR. The ODR approach is still largely in use, even for severe peritonitis [20, 21]. With this approach, the difficult detection of recurrent or persisting signs of peritonitis [22] leads to therapeutic delay, with multiple organ failure and a high associated mortality [1–3, 13, 23–26]. To improve outcome, we and others have advocated PR as the correct approach in patients with severe advanced peritonitis [18, 24, 27, 28]. Our retrospective studies [24–26], as well as the results of this series and those of a nonrandomised prospective study [1] comparing PR with ODR, found a clinically and statistically significant survival benefit for the PR approach after univariate analysis. In contrast, two studies that compared PR with ODR in mixed series of mild and severe peritonitis did not observe a better survival after PR [21, 29]. It is possible that in the latter studies, the disadvantages of PR in mild cases—damage to edematous viscera [30] and enhanced systemic inflammatory response [31]—neutralized its advantages in severe cases. Indeed, a PR approach should be restricted to the subgroup of patients with a high risk of persisting intra-abdominal infection. Based on our findings, we recommend PR for postoperative generalized fecal peritonitis, which carries a 41% risk of ongoing peritonitis, as well as for patients with uncertain or insecure septic source control. We do not agree with the recommendation that all patients with postoperative peritonitis [5] or all patients with severe purulent peritonitis [32] should have a PR: after immediate septic source control, only 9% of our patients with postoperative generalized purulent or biliary peritonitis had recurrent sepsis.

Résumé. La mortalité due à la péritonite postopératoire généralisée reste élevée: 22%–55%. Le but de cette étude a été d'identifier les facteurs pronostiques par analyse uni- et multifactorielle dans une série consécutive de 96 patients. La mortalité a été de 30%. L'impossibilité d'enlever toute trace d'infection, de contrôler la source de l'infection, un âge avancé et le coma étaient tous des facteurs indépendants significatifs de mortalité en analyse multifactorielle. L'impossibilité de contrôler l'infection péritonéale (15%) a toujours été fatale et corrélait avec l'absence de contrôle de la source, un score APACHE II élevé et le sexe male. L'impossibilité d'éliminer la source de l'infection (8%) a également toujours été fatale et corrélait avec un score APACHE II élevé et un délai dans la prise en charge thérapeutique. Chez les patients ayant eu un contrôle immédiat de la source de l'infection, on a observé une péritonite résiduelle chez 9% des patients après péritonite purulente ou biliaire et chez 41% des patients après péritonite fécale ($p = 0.002$). Lorsque le contrôle initial, immédiat de la source septique a été difficile, il a quand même été obtenu chez 100% des patients après une stratégie de relaparotomie programmée (PR) vs. 43% après une relaparotomie à la demande (ODR) ($p = 0.018$). Chez les mêmes patients, la mortalité a été de 0% dans le groupe PR vs. 64% dans le groupe ODR ($p = 0.007$). Le taux de relaparotomie précoce est en rapport avec une amélioration du contrôle de la source de l'infection. Après relaparotomie pour péritonite postopératoire généralisée, une stratégie PR est indiquée dès lors que le contrôle de la source est incertain. Ce principe pourrait également diminuer la mortalité de la péritonite fécale. L'approche ODR, associée à un contrôle de la source septique, convient bien à la péritonite purulente et biliaire.

Resumen. La mortalidad en la peritonitis generalizada es alta oscilando entre el 22 al 55%. Este trabajo intenta, mediante análisis uni y multivariantes, identificar los factores pronósticos estudiando una serie de 96 pacientes con peritonitis generalizada. La mortalidad fue del 30%. En el análisis multivariante los factores más significativos en relación a la mortalidad fueron: incapacidad de eliminar la infección abdominal o de controlar el origen de la sepsis, la edad avanzada y el déficit de conciencia del enfermo. Si el control de la infección peritoneal (15%) es ineficaz el desenlace es siempre fatal y se correlaciona con la falta de erradicación del foco séptico y puntuación alta en la escala APACHE II, siendo más frecuente en el hombre. Si el control del origen de la sepsis fracasa (8%) el desenlace es también fatal correlacionándose con una puntuación APACHE II elevada e instauración tardía del tratamiento oportuno. Si se controla precozmente el origen de foco séptico se observa en el 9% de los casos una peritonitis residual tras peritonitis purulenta o biliar, desarrollándose hasta un 41% de peritonitis residuales secundarias a una peritonitis fecaloidea ($p = 0.002$). En pacientes sin control inmediato del foco séptico, se consiguió un control tardío en el 100% de los casos de relaparotomía planificada (PR) vs. el 43% con relaparotomía a demanda (ODR) ($p = 0.018$). En el mismo tipo de pacientes la mortalidad fue 0% en el grupo PR frente al 64% en el grupo ODR ($p = 0.007$). La relaparotomía precoz constituye la medida más adecuada para controlar definitivamente el foco séptico. Tras una relaparotomía por peritonitis generalizada postoperatoria la PR está formalmente indicada cuando el control del foco séptico es incierto, disminuyendo además la mortalidad en casos de peritonitis fecaloidea. La relaparotomía a demanda está indicada en peritonitis biliares y purulentas en las que el foco séptico ha sido erradicado con toda seguridad.

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