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ORIGINAL ARTICLE

Retrospective Study

Risk factors for mortality in postoperative peritonitis in critically ill patients

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Abstract

AIM

To identify the risk factors for mortality in intensive care patients with postoperative peritonitis (POP).

METHODS

This was a retrospective analysis using a prospective database that includes all patients hospitalized in a surgical intensive care unit for POP from September 2006 to August 2011. The data collected included demographics, comorbidities, postoperative severity parameters, bacteriological findings, adequacy of antimicrobial therapy and surgical treatments. Adequate source control was defined based on a midline laparotomy, infection source control and intraoperative peritoneal lavage. The number of reoperations needed was also recorded.

RESULTS

A total of 201 patients were included. The overall mortality rate was 31%. Three independent risk factors for mortality were identified: The Simplified Acute Physiological Ⅱ Score (OR = 1.03; 95%CI: 1.02-1.05, $P < 0.001$), postoperative medical complications (OR = 6.02; 95%CI: 1.95-18.55, $P < 0.001$) and the number of reoperations (OR = 2.45; 95%CI: 1.16-5.17, $P = 0.015$). Surgery was considered as optimal in 69% of the cases, but without any significant effect on mortality.

CONCLUSION

The results from the large cohort in this study emphasize the role of the initial postoperative severity parameters in

the prognosis of POP. No predefined criteria for optimal surgery were significantly associated with increased mortality, although the number of reoperations appeared as an independent risk factor of mortality.

Key words: Mortality; Postoperative peritonitis; Risk factors; Surgery

Core tip: This retrospective study performed from a prospective data base analysed the risk factor for mortality in 201 patients admitted for postoperative peritonitis (POP) in a surgical intensive care unit. Three independent risk factors for mortality were identified: The Simplified Acute Physiological Ⅱ Score, postoperative medical complications and the number of reoperations. This study emphasizes the role of the initial postoperative severity parameters in the prognosis of POP. No predefined criteria for optimal surgery were significantly associated with increased mortality, although the number of reoperations appeared as an independent risk factor of mortality.

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INTRODUCTION

Postoperative peritonitis (POP), defined as peritonitis occurring after a planned or urgent abdominal surgery, is an infrequent (occurring in approximately equal to the 2%-3% of laparotomies)[1,2], but serious event, with a mortality rate ranging from 30% to 35%[3-5]. The principles of POP management are based on an early diagnosis, optimized surgical source control, adequate antimicrobial therapy and the control of organ failure(s), if necessary[6,7]. Despite clinical, biological and radiological tools, the diagnosis of POP in the postoperative period remains challenging and the surgical source control is not always easy to perform in recently operated abdomens[8-10]. Moreover, multi-drug resistant (MDR) bacteria are frequently isolated in cases of POP, potentially leading to an inadequate antimicrobial therapy and a worsening prognosis[3,5]. Finally, peritonitis is shown to be a frequent condition related to death due to multiple organ failure. In this context, reoperation and postoperative immune depression may favour sepsis and the development of organ failure[11-14].

All of these factors may explain the high mortality observed in association with POP and illustrate the need to evaluate POP separately from other types of intra-abdominal infections. Nevertheless, few studies have evaluated the risk factors for mortality in POP, especially in critically ill patients[8,15,16].

We hypothesized that POP may have specific characteristics and risk factors for mortality that could help physician in the care of the patients with POP. Accordingly, we performed an analysis using a prospective database to determine the risk factors for mortality associated with POP in patients who required intensive care.

MATERIALS AND METHODS

We performed a retrospective analysis from a prospective database that aimed to include all patients with POP. This database was completed from September 2006 to August 2011 in a surgical critical care unit of a university hospital (Rennes - France). All patients older than 18 years of age who were admitted for POP were included. POP was defined as a peritoneal infection developing after intra-abdominal surgery. Only the first episode of POP was taken into account. Patients who had focal abscess(es) drained under computed tomography (CT)-scan guidance and/or who had more than one previous episode of POP before intensive care unit (ICU) admission were excluded. Infections were confirmed macroscopically and/or based on the identification of one or several pathogens in peritoneal sample. Patients were followed up from the first day of hospitalization until their discharge from the hospital or death if it occurred during hospitalization. This study was reviewed and approved by the ethics committee of Rennes University hospital which waived informed consent according to the retrospective design (Avis n° 16-129).

The following data were prospectively collected in the first 24 h: Age, sex, origin of patient (Rennes University hospital or another hospital), hospitalization over the previous 3-mo, antibiotic therapy in the 3 mo previous to the current hospital admission, immunocompromised status (defined based on systemic treatments with corticosteroids or other immunosuppressive drugs, chemotherapy or radiotherapy in the 3 mo previous to the admission), co-morbidities (assessed based on MacCabe score and the following severity scores: Simplified Acute Physiological Score Ⅱ (SAPS Ⅱ), Acute Physiology and Chronic Health Evaluation Ⅱ (APACHE Ⅱ) and Sequential Organ Failure Assessment (SOFA)[17-19]. The status (urgent or non-urgent) of the first intra-abdominal surgery was also recorded.

Surgery assessment included the cause of POP and the delay between the first surgery and the reoperation. An optimal surgical treatment was qualified as adequate when the 3 following criteria were met: (1) middle laparotomy; (2) ileostomy or colostomy in cases of injury/perforation below the transverse mesocolon injury or drainage above the transverse mesocolon injury; and (3) careful peritoneal washing of the entire peritoneal cavity with at least 6 L of warm physiological serum and until obtaining a macroscopically clean cavity. Coelioscopy and/or a primary anastomosis were considered as inadequate because their roles in the current recommendations are not well-established[6,7]. The number of

reoperations and the surgical complications, including abdominal wall abscesses, intra-abdominal abscesses, CT-guided drainage of abdominal abscesses and the need for subsequent reoperation, were also reported. Moreover, in our unit, relaparotomies were not planned and were only performed on-demand.

If required, antibiotic prophylaxis for the first surgery was prescribed according to the recommendations of the French Society of Anesthesia and Critical Care (Recommandations pour la pratique de l'antibioprophylaxie en chirurgie. Actualisation 1999. www.sfar.org). Antimicrobial therapies applied between the first surgery and reoperations beginning at least 24 h before the reoperation and lasting more than 24 h were noted. Empirical antimicrobial treatment for the first episode of POP was administered according to the local protocol and included cefotaxime and metronidazole for early POP (< 5 d from the initial surgery) and ticarcillin-clavulanate and amikacin for late POP (≥ 5 d from the initial surgery). Because of the low frequency of methicillin resistant *Staphylococcus aureus* and *Enterococcus faecium*, the use of vancomycin was not considered. Effects of antimicrobial therapy on *Enterococcus* species for ongoing POP and the rates of escalation or de-escalation of antimicrobial therapy were reported. Empirical antimicrobial therapies were re-evaluated based on microbiological data and the susceptibility of the isolated microorganisms. Treatments against fungi were only administered in cases of positive, direct examinations of the peritoneal liquid or positive cultures and included the use of fluconazole or an echinocandin. Bacteremia was recorded and defined based on at least one positive blood culture (2 positive samples in cases of coagulase-negative *Staphylococcus*) and were linked to the intra-abdominal infection if the same microorganisms were recovered in each sample. The duration of antimicrobial therapy ranged from 7 to 10 d.

The isolated microorganisms and the presence of multidrug resistance strains were reported. For each bacterium, the antibiotic sensitivity was determined using the disk-diffusion method. Bacteria were matched into 3 categories: Sensitive, intermediate and resistant. MDR bacteria were defined as follows: Methicillin-resistant *Staphylococcus aureus; Enterococcus* spp. resistant to vancomycin and to high concentrations of gentamycin; *Enterobacteriaceae* producing extended-spectrum beta-lactamase or overexpressing third-generation cephalosporinase; *Pseudomonas aeruginosa* resistant to ticarcillin, ceftazidime, carbapenem or ciprofloxacin; *Acinetobacter* spp. resistant to carbapenem and/or ticarcillin and/or aminoglycosides[5].

Medical complications included septic shock, acute respiratory distress syndrome (ARDS), and acute renal failure. Septic shock was defined based on the Bone criteria[20] and ARDS according to international recommendations[21]. Acute renal failure was defined based on a serum creatinine level and uraemia and/or a urine output and/or a need for dialysis[22]. In cases of chronic renal failure, acute renal failure was defined as an increase of serum creatinine or uraemia and/or urine output and/or the need for dialysis[22]. Lengths of ICU and hospital stays and mortality rates were reported.

Statistical analysis

All statistical analysis were performed with SAS software version 9.2 (SAS Institute, Cary, NC, United States). Mean values and standard deviations were used to describe quantitative data, and a *t*-test or Wilcoxon test were used as needed. Numbers, ranges, and percentages were used to describe qualitative data, and a χ^2 test or Fisher's test was used as needed. The multivariate analysis was designed by selecting variables with a *P*-value < 0.20 in the univariate analysis to build a logistic regression model. The results are expressed with ORs and 95% confidence intervals (95%CI). Results were considered significant at a *P*-value < 0.05.

RESULTS

A total of 201 patients were included in this study. The overall mortality rate was 31% (63/201). The patients' baseline characteristics, severity scores and the determinants of the initial surgery are detailed in Table 1. In a univariate analysis, age, comorbidity evaluated based on McCabe scores and severity at admission in ICU (based on SOFA, APACHE Ⅱ and SAPS Ⅱ scores) were significantly associated with mortality.

The causes of POP were anastomosis leakage (40%), necrosis/ischaemia (20%), traumatic perforation (12%) and miscellaneous (28%) and were not different between the non-survivors and survivors. Surgical procedures were deemed optimal in 69% of the cases (140/201) and the rate did not differ between non-survivors and survivors [71% (45/63) *vs* 69% (95/138); *P* = 0.743]. Details of surgical source control and the number reoperations are provided in Table 2. No significant influence of surgical parameters on the prognoses was found between non-survivors and survivors (Table 2).

Antimicrobial treatment prior to POP (prophylaxis and/or therapy) and changes during the postoperative period (escalation or de-escalation) are provided in Table 3. The microorganisms isolated from the peritoneal fluid (Table 4) and the mean number of microorganisms isolated per patient did not differ between non-survivors and survivors (Table 4). A total of 440 microorganisms were identified in 196 patients [non-survivors, *n* = 139 (61 patients, 2 had no growth) and survivors, *n* = 301 (135 patients, 3 had no growth)]. A total of 46 patients had at least one MDR bacteria recovered from their peritoneal fluid [non-survivors = 28% (17/61) and survivors = 21% (29/135), *P* = 0.378]. Bacteremia did not differ between the 2 groups [non-survivors = 33% (21/63) and survivors = 26% (36/138); *P* = 0.268].

The occurrence of medical complications was identified as a potential risk factor for mortality in the univariate analysis, and the length of hospital stay was significantly shorter for non-survivors (Table 3).

In the multivariate analysis, three independent risk

Table 1 Baseline characteristics, severity scores and initial surgery *n* (%)

	All patients (*n* = 201)	Non-survivors (*n* = 63)	Survivors (*n* = 138)	*P*
Age (yr)	63 ± 15	69 ± 12	61 ± 16	< 0.001
Sex, male	133 (66)	46 (73)	87 (63)	0.199
Origin of patients				
Rennes University Hospital	132 (66)	44 (70)	88 (64)	0.4
Other hospitals	69 (34)	19 (30)	50 (36)	
Hospitalization in the previous 3 mo, yes	78 (39)	24 (38)	54 (39)	1
Immunosuppression, yes	33 (16)	9 (14)	24 (17)	0.581
Antimicrobial therapy in the past 3 mo, yes	54 (26)	16 (25)	38 (28)	0.751
MacCabe score				
Class A	57 (28)	11 (18)	46 (34)	0.036
Class B	107 (53)	36 (57)	71 (51)	
Class C	37 (19)	16 (25)	21 (15)	
SAPS Ⅱ	48 ± 19	60 ± 25	43 ± 14	< 0.001
APACHE Ⅱ	20 ± 8	24 ± 11	18 ± 6	< 0.001
SOFA	7 ± 4	8 ± 5	6 ± 4	< 0.001
Urgent initial surgery	69 (34)	22	47	0.905
Site of the initial surgery				
Colorectal	82 (41)	25 (40)	57 (41)	0.363
Liver - biliary - pancreas	48 (24)	15 (24)	33 (24)	
Oesophagus - gastro-duodenal - small bowel	60 (30)	22 (35)	38 (28)	
Others	11 (5)	1 (1)	10 (7)	

Data are expressed as the mean ± SD or as the number of patients (percentages). SAPS Ⅱ: Simplified acute physiological score Ⅱ; APACHE Ⅱ: Acute physiology and chronic health evaluation Ⅱ; SOFA: Sequential organ failure assessment.

Table 2 Surgical considerations *n* (%)

	Total (*n* = 201)	Non-survivors (*n* = 63)	Survivors (*n* = 138)	*P*
Delay between first operation and surgical reintervention (d)	9.9 ± 7.5	10.4 ± 9.6	9.9 ± 6.2	0.718
Complete surgical source control	140 (69)	45 (71)	95 (69)	0.743
Large way of laparotomy	181 (90)	56 (89)	125 (91)	0.71
Per-operative management of lesions[1]	184 (92)	57 (89)	127 (92)	0.713
Peritoneal washing (at least 6 L) and clear peritoneal cavity	175 (87)	55 (89)	120 (87)	0.946
Reoperation after the first episode of postoperative peritonitis (number)	59 (29)	23 (37)	36 (29)	0.132
No. of reoperations after the first episode of postoperative peritonitis	1.3 ± 0.6	1.4 ± 0.7	1.2 ± 0.5	0.121
Surgical complications				
Parietal abscess	23 (11)	11 (17)	12 (10)	0.095
Intra-abdominal abscess	36 (18)	11 (17)	25 (20)	0.875
Computed tomography-scan guided drainage	30 (15)	7 (11)	23 (19)	0.287

[1]The per-operative management of lesions was defined as the realization of ileostomy or colostomy in cases of injured/perforated infra-mesocolic bowel injury or drainage in cases of supra-mesocolic bowel injury. Data are expressed as the mean ± SD or as the number of patients (percentages).

factors for mortality were identified: SAPS Ⅱ score, the occurrence of medical complications and the number of subsequent reoperations (Table 5).

DISCUSSION

Using a large cohort of ICU patients, we explored the risk factors for mortality associated with POP and found that SAPS Ⅱ score, medical complications and the number of reoperations were independent risk factors for hospital mortality.

Few studies have assessed risk factors for mortality in patients with POP, and most of the studies that have examined this topic included patients hospitalized both in ICUs and surgical wards or included a mix of community and nosocomial peritonitis (including post- and/or non-postoperative) and did not focused on POP in ICU-patients requiring high levels of care[15,16,23]. Mulier *et al*[15] reported a mortality of 30% in 96 POP patients and found that the inability to control the septic source or to clear the abdominal cavity, older age and unconsciousness were independent risk factors for mortality. In this retrospective study, which was not specifically focused on ICU patients, disease severity, measured based on the APACHE Ⅱ score and its acute physiological component, did not appear as an independent risk factor and was only significant when age and unconsciousness were also included in the multivariate model[15]. In another retrospective study performed in 56 POP patients, Torer *et al*[16] found a 32% mortality rate and that sex (female), malignancy, organ failure, a lack of source control and the time period between symptom onset and the 2nd operation were independent risk factors for mortality. Nevertheless, the small cohort of patients in this study

Table 3 Antimicrobial therapies and medical complications *n* (%)

	Total (*n* = 201)	Non-survivors (*n* = 63)	Survivors (*n* = 138)	*P*
Antibiotic prophylaxis for the first surgery	165 (82)	53 (84)	112 (81)	0.38
Antimicrobial treatment prior to the first reintervention	132 (66)	40 (63)	93 (67)	0.564
Empirical antibiotic therapy for POP effective against *Enterococcus* spp.	104 (52)	35 (56)	69 (50)	0.466
Change in empirical antimicrobial POP treatment	130 (65)	33 (52)	97 (70)	0.005
Escalation	60 (46)	20 (32)	40 (29)	
De-escalation	70 (54)	13 (21)	57 (41)	
Medical complications				0.001
Septic shock	125 (62)	58 (92)	67 (49)	
Acute renal failure	79 (39)	39 (62)	40 (29)	
ARDS	54 (27)	28 (44)	26 (19)	
Lengths of stay, d				
ICU	17 ± 17	17 ± 18	17 ± 17	0.2
Hospital	48 ± 44	31 ± 27	57 ± 48	< 0.001

Data are expressed as the mean ± SD or as the number of patients (percentages). POP: Postoperative peritonitis; ARDS: Acute respiratory distress syndrome; ICU: Intensive care unit.

Table 4 Microorganisms recovered from the peritoneal liquid and number per patients in which they were found

	Total[1] (*n* = 440)	Non-survivors[1] (*n* = 63)	Survivors[1] (*n* = 138)	*P*
Gram-negative bacilli	206	62	144	0.959
Escherichia coli	97	26	71	0.213
Enterobacter spp.	32	13	19	0.079
Pseudomonas aeruginosa	24	7	17	0.700
Klebsiella spp.	15	3	12	0.066
Proteus spp.	9	3	6	1.000
Citrobacter spp.	8	4	4	0.255
Other gram-negative bacilli	21	6	15	1.000
Gram-positive cocci	161	48	113	0.989
Enterococcus spp.	107	35	72	0.429
E. faecalis	70	25	45	0.328
E. faecium	18	2	16	0.053
Other enterococci	19	8	11	0.279
Streptococcus spp.	23	6	17	0.504
Staphylococcus aureus				
Methicillin sensitive	7	1	6	0.580
Other gram-positive cocci	24	6	18	0.625
Anaerobes	47	17	30	0.979
Bacteroides spp.	39	13	26	0.889
Clostridium spp.	4	2	2	1.000
Other anaerobes	3	2	1	1.000
Fungi	26	12	14	0.938
Candida albicans	17	7	10	0.715
Other fungi	8	4	4	0.317
Number of microorganism types recovered per patient	2.2 ± 1.2	2.2 ± 1.2	2.2 ± 1.2	0.998

[1]Methicillin resistant Staphylococcus aureus was not recovered. Data are expressed as the number of microorganisms (percentage) and the mean ± SD until otherwise.

clearly lacks statistical power, as shown by the wide confidence intervals, and it did not specifically address ICU patients[16]. More recently, in a retrospective study including 102 POP patients, a mortality rate of 39.2% was reported and 4 independent risk factors for mortality were identified (age ⩾ 60, multiple organ failure, inadequate antimicrobial treatment and a stercoral aspect of the peritoneal fluid)[24]. In a selected population of 27 obese patients who required re-operation after initial bariatric surgery and ICU admission, a preoperative BMI > 50 kg/m^2 and multiple reoperations were associated with a poor prognosis and the number of organ failures[8].

Our results generally support the findings of these previous reports. The mortality rate in the cohort studied here was 31%, which is similar to the rates reported in previous related studies, although the patients in the present study were older than those in previous studies. Nevertheless, none of our pre-defined factors for surgical source control were found to significantly impact the mortality rate, and surgical postoperative complications did not appear as a risk factor for mortality. However, the number of reoperations was significantly associated with mortality and, in some patients, surgical source control was not effectively achieved. Indeed, the need

Table 5 Multivariate analysis for the risk factors for mortality

	Odds ratio	95%CI	*P*
Simplified acute physiological score Ⅱ	1.03	1.02-1.05	< 0.0001
Medical postoperative complications	6.02	1.95-18.55	< 0.0001
Number of subsequent reoperations	2.45	1.16-5.17	0.0154

to re-operate after the first episode of POP was 29%, and among these patients, 27% had persistent intra-abdominal infections. Moreover, surgical reoperation under septic peritoneal conditions and inflammation, along with the inherent risk of new bowel injuries, was sometimes associated with difficulties in closing the abdominal wall, which may have played a role in worsening the mortality rate of these patients.

We found a significant influence of the initial severity scores in predicting mortality. Indeed, the SAPS Ⅱ score and medical complications were independently associated with mortality. This confirms the need for the early identification of patients at risk and who have severe symptom to avoid delays in reoperations, which favours the occurrence of organ failure and bacterial growth in the peritoneal cavity and worsens their prognosis for survival[15]. Our results emphasize that the initial hours following POP diagnosis are crucial in the prognosis of POP. Thus, a rapid control of organ failure is required to achieve a better outcome. POP management is based on 3 goals: Supportive care of septic shock, early and adequate antibiotic treatment and the early surgery. Previous reports have shown that a failure to achieve these goals increases the mortality rate[3,25,26].

For initial antimicrobial treatments, we found that patients who survived had a greater rate of secondary adaptation to antibiotics, as reflected by treatment de-escalation. In the cases of antibiotic escalation, the bacteria recovered were resistant and/or not covered by the initial antimicrobial treatment, consequently leading to a potentially higher risk of mortality, although in our study, this parameter was included in the multivariate analysis[3,25,26]. In cases of de-escalation, we assumed that the bacteria recovered were completely targeted by the empirical antimicrobial treatment. In addition, MDR bacteria were found in 23% of patients, which is a lower rate than previously reported, but this did not influence the mortality rate[3,27]. Riché *et al*[28], in a prospective cohort of 68 POP patients admitted to a surgical ICU, found that yeasts recovered in POP patients were associated with an increased risk of death at day 30 after surgery, whereas *Enterococcus* spp. and anaerobes recovered were not. In our study, no bacterial (notably *Enterococcus* spp.) or fungal species were found to impact the mortality rate. The impact of the *Enterococcus* spp. recovered from POP patients on mortality is controversial, and we did not find a relationship between *Enterococcus* spp. and mortality[29-31]. Finally, we did not find that age influenced mortality, but the population we studied was older than that of other studies[15,32,33]. Controversies exist regarding age as a risk factor for mortality in ICUs, and factors other than age itself, such as previous comorbidities and/or frailty, may have a better prognostic significance[34,35]. This issue has been poorly studied in ICU patients with peritonitis. In 163 patients with secondary peritonitis, excluding patients with POP, Hynninen *et al*[32] showed that previous functional status was an independent risk factor for mortality overall but not in the ICU patients.

Several limitations to the interpretation of our data are worth noting. First, this is a retrospective and monocentric study, but data were prospectively collected, and one third of the patients came from another hospital. Moreover, the management of POP was standardized regardless of whether it was for surgical procedures or postoperative ICU management. Second, we assessed only 3 surgical criteria (the type of laparotomy, the intra-operative management of the lesions and the quality of washing), but many other surgical factors not reported in our database may affect outcomes, such as the experience of the surgeon, the duration of the surgery, the quality of the drainage and the stitching of abdominal wall. Third, our inclusion criteria were stringent because we excluded POP that had been operated on using coelioscopy because we believe that the coelioscopy does not have a sufficiently well-defined role in the surgical management of peritonitis[6,7,36]. Fourth, biological markers of inflammation have not been recorded in our database. It might have allowed a better stratification of the peritonitis severity, but were not recommended in usual practice in a recent guideline[36].

This study confirms the negative role of the initial severity criteria and the deleterious role of multiple reoperations, which constitute an indirect sign of inadequate source control, in assessing mortality in patients with POP. An early and successful first surgery is required to increase the chances of a definitive and efficient treatment of POP.

COMMENTS

Background

Postoperative peritonitis (POP) is a rare but severe disease, associated with a challenging diagnosis and a high mortality rate. Multiple organ-failure is a predominant explanation of this burden. But, in addition to supportive care, surgery represents the cornerstone of peritonitis treatment. The timing and adequacy of surgical source control are paramount concerns. Suboptimal surgery may lead to an overwhelmingly negative effect on outcome. In this study, the authors focused on a more refined peritonitis patient's population to better precise the risk factors of mortality especially the impact of surgical parameters.

Research frontiers

Whereas several data exist on the risk factors of mortality in secondary peritonitis, large sample specific studies on POP are scarce. Moreover, surgery has a central role in the management of POP. Identifying more accurately the role of surgical parameters in POP management could affect the way of peritonitis treatment.

Innovations and breakthroughs

This paper is the larger sample size study of selected patients with POP, in which the authors investigated the risk factors of mortality, especially the impact of surgical parameters but also the medical complications. This study confirms

the prominent role of medical complications in the poor outcome of POP, however, it found out no surgical risk factor of mortality.

Applications

These data confirm and recall the prominent negative role of severity parameters in POP outcome. No surgical factor has been found to impact negatively the mortality but larger sample size study with more surgical parameters is needed. Moreover, no patient was treated with laparoscopy but new investigations could be drawn in this perspective.

Terminology

POP belongs to the usual group of secondary peritonitis. More precisely, it includes broadly postoperative abdominal abscesses or diffuse peritoneal infection following abdominal surgery. POP is usually caused by leakage of gut contents, but also by spreading of residual infection or by the occurrence gut ischemia. The severity of POP relies on the associated multiple organ failure.

Peer-review

This is a well written paper with a very relevant topic. It is well researched.

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