Risk factors for multidrug-resistant bacteria in patients with post-operative peritonitis requiring intensive care

Philippe Seguin1*, Yannick Fédun1, Bruno Laviolle2, Nicolas Nessler1, Pierre-Yves Donnio3 and Yannick Malléant1

1Service de Réanimation Chirurgicale, Université Rennes 1, INSERM U991, Hôpital de Pontchaillou, 2 rue Henri Le Guilloux, 35033 Rennes Cedex 9, Rennes, France; 2Service de Pharmacologie Clinique, and Centre d’investigation Clinique-INSERM 0203, Hôpital de Pontchaillou, 2 rue Henri Le Guilloux, 35033 Rennes Cedex 9, Rennes, France; 3Laboratoire de Bactériologie-Virologie, Hôpital de Pontchaillou, 2 rue Henri Le Guilloux, 35033 Rennes Cedex 9, Rennes, France

*Corresponding author. Service de Réanimation Chirurgicale, Hôpital de Pontchaillou, 2 rue Henri Le Guilloux, 35033 Rennes Cedex 9, France. Tel: +33-2-99-28-42-46; Fax: +33-2-99-28-24-21; E-mail: philippe.seguin@chu-rennes.fr

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Objectives: This prospective non-interventional study investigated the risk factors for multidrug-resistant bacteria (MDRB) in patients with post-operative peritonitis (POP), to provide guidance for empirical antimicrobial therapy.

Methods: All consecutive patients, >15 years old, admitted to a surgical intensive care unit (ICU) between September 2006 and January 2009 for a first episode of POP were included. Antibiotic susceptibilities of microorganisms recovered from blood cultures and peritoneal fluid were determined by disc diffusion. Amoxicillin/clavulanic acid, ticarcillin/clavulanic acid, piperacillin/tazobactam, cefotaxime, ceftazidime, cefepime, imipenem, gentamicin, amikacin and ciprofloxacin were tested against Gram-negative bacteria, and oxacillin, amoxicillin, vancomycin, gentamicin and erythromycin were tested against aerobic Gram-positive bacteria. Results were reported as susceptible or resistant.

Results: MDRB were isolated from 20/115 (17%) patients. In univariate analysis, use of antimicrobial therapy during the 3 months prior to hospitalization and a long duration between hospital admission or first operation and relaparotomy were significantly associated with MDRB recovery. In multivariate analysis, only antimicrobial treatment in the 3 months preceding hospitalization and duration between first operation and relaparotomy were independent risk factors for MDRB [odds ratio (OR) = 5.80, 95% confidence interval (95% CI) = 1.99–16.91 and OR = 1.10, 95% CI = 1.02–1.19, respectively]. No MDRB were found when the delay between the first operation and relaparotomy was <5 days. POP severity, non-surgical and surgical complications, hospital and ICU length of stay, and mortality were similar in patients with and without MDRB.

Conclusions: Our results suggest that broad-spectrum antibiotics should be used in ICU patients with POP who have received antimicrobial therapy in the 3 months prior to hospitalization, or with >5 days between the first operation and relaparotomy.

Keywords: antimicrobial therapy, empirical therapy, in vitro susceptibility, surgery

Introduction

Post-operative peritonitis (POP) is the consequence of previous surgery, and has a mortality rate of nearly 40%.1,2 Treatment usually consists of a combination of surgical or radiological drainage, and antibiotics. Antimicrobial therapy is initially empirical, and the possible types of bacteria involved and levels of resistance to antimicrobial agents should therefore be considered. Escherichia coli is recovered less frequently from POP than from secondary community-acquired peritonitis, whereas other Enterobacteriaceae are more common, notably Enterobacter spp. and Enterococcus spp.3,4 Multidrug-resistant bacteria (MDRB) are frequently recovered from POP.4,5 As inadequate antimicrobial therapy is associated with increased mortality,3 recommendations for empirical antimicrobial therapy in POP are based on a combination of broad-spectrum antibiotics.5,6 Nevertheless, the use of broad-spectrum antibiotics has been associated with the appearance of MDRB.7–9 Any efforts that contribute to a decrease in prescription of costly, broad-spectrum antibiotics in the intensive care unit (ICU) are

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warranted. However, the microbiological profile of POP does not systematically imply MDRB, and this idea is supported by the fact that MDRB are preferentially recovered when there is a long duration of antimicrobial therapy before reoperation and a long time lapse until reoperation.

In this context, we carried out a prospective, non-interventional study to determine the risk factors for MDRB infections in a critically ill population of patients with POP. The identification of specific risk factors for MDRB could provide guidance for empirical antimicrobial therapy.

**Methods**

This prospective observational study was performed in a surgical ICU of a university hospital between September 2006 and January 2009. This unit acts as a referral centre and receives patients from local and regional institutions when a high level of care is required. The local ethics committee waived informed consent as it was a non-interventional study.

All consecutive patients, >15 years old, admitted for a first episode of POP during the study period were included. Only the first episode of POP was taken into account in the analysis of risk factors for MDRB. Exclusion criteria were limited to infected pancreatitis, gynaecological infections, intra-abdominal abscess alone and the absence of microbiological samples.

The following data were recorded within 24 h of hospitalization in the ICU: age; sex; immunosuppression; prior antimicrobial therapy and/or hospitalization in the previous 3 months; origin of patients (in hospital or transferred patients); MacCabe score; severity assessed by Acute Physiology and Chronic Health Evaluation II (APACHE II), Simplified Acute Physiology Score II (SAPS II) and Sequential Organ Failure Assessment (SOFA); and origin of POP. During hospitalization in the ICU, the occurrence of bacteraemia, septic shock, acute respiratory distress syndrome (ARDS), acute renal failure and surgical post-operative complications (parietal and/or intra-abdominal abscess and/or relaparotomy and/or radiological percutaneous drainage) were also noted. The use of antimicrobial therapy between first surgery and relaparotomy, and all modifications performed subsequently in the post-operative period taking into account the susceptibility of the bacteria recovered (escalation or de-escalation therapy) were recorded. The duration (days) between hospital admission and first surgery and relaparotomy was also noted, as well as the length of ICU and hospital stay, and hospital mortality.

**Microbiological data**

At least two blood cultures (aerobic and anaerobic) were performed in the perioperative period. One or more peritoneal fluid sample(s) were taken during the operation and these were incubated at 37°C in two aerobic media (trypticase soy agar and trypticase soy broth) and two anaerobic media (horse blood agar and Schadler broth). The number of microorganisms recovered per patient was recorded.

Antibiotic susceptibilities were determined by the disc diffusion method (Bio-Rad, Marnes la Coquettes, France) according to the recommendations of the Antibiogram Committee of the French Microbiology Society (CA-SFM). The bacteria were then classified as susceptible or resistant (susceptible and intermediate). The susceptibility of aerobic Gram-negative bacteria to 10 antibiotics (amoxicillin/clavulanic acid, ticarcillin/clavulanic acid, piperacillin/tazobactam, cefotaxime, cefazidime, cefepime, imipenem, gentamicin, amikacin and ciprofloxacin) was reported.

The susceptibilities of three aerobic Gram-positive bacteria (Enterococcus spp., Staphylococcus aureus and Streptococcus spp.) to the following antibiotics were reported: oxacillin (S. aureus and Streptococcus spp.); amoxicillin (Enterococcus spp.); vancomycin (Enterococcus spp., S. aureus and Streptococcus spp.); gentamicin (Enterococcus spp. and Streptococcus spp.); and erythromycin (Streptococcus spp.). The susceptibility of anaerobic bacteria was not reported. The evaluation of resistance to antibiotics when a second or third episode of intra-abdominal infection occurred, and the impact of inadequate initial empirical antimicrobial therapy on mortality were also studied.

**Definitions**

POP was defined as the presence of pus in the abdominal cavity with positive cultures in the first month after abdominal surgery. Immunosuppression was defined as patients receiving immunosuppressive agents (including corticosteroid whatever the dosage), irrespective of the reason (cancer, vasculitis or transplantation) and HIV-positive patients with a CD4 count <200/mm³. Prior antimicrobial therapy was defined as the administration of at least one antimicrobial agent for three or more consecutive days in the 3 months before hospital admission. Antimicrobial therapy between first surgery and relaparotomy for POP was defined as the administration of at least one antimicrobial agent for >1 day during this period. Bloodstream infection was defined as at least one positive blood culture (two positives in the case of coagulase-negative staphylococci) reported to be secondary to the intra-abdominal infection (unless another source of systemic infection was found). Septic shock was defined according to the Bone criteria, and ARDS as persistent and bilateral opacities on chest X-ray associated with a PaO₂/FiO₂ ratio <200 without cardiac failure or left atrial hypertension. Acute renal failure was defined as a serum creatinine concentration >240 μmol/L and serum urea >16 mmol/L, and/or a urine output <400 mL/24 h, and/or the need for dialysis. In the case of chronic renal failure, acute renal failure was defined as an increase in serum creatinine >120 μmol/L or serum urea >8 mmol/L, and/or a urine output <400 mL/24 h, and/or the need for dialysis.

MDRB were classified as follows: methicillin-resistant S. aureus (MRSA); Enterococcus spp. resistant to vancomycin and to high concentrations of gentamicin (CA-SFM breakpoint = 128 mg/L); Enterobacteriaceae producing an extended-spectrum β-lactamase (ESBL) (Klebsiella spp., Enterobacter spp., E. coli and Proteus mirabilis) or producing a cephalosporinase to a high level (Enterobacter spp., Serratia spp. and members of Citrobacter freundii group); Pseudomonas aeruginosa resistant to ticarcillin, ceftazidime, imipenem or ciprofloxacin, or producing an ESBL; and Acinetobacter spp. resistant to imipenem and/or ticarcillin and/or aminoglycosides.

**Statistical analysis**

Statistical analysis was performed using SAS software version 9.1 (SAS Institute, Cary, NC, USA). Data are presented as means ± SD for continuous variables, and number and corresponding percentage for qualitative variables. The characteristics of patients infected with MDRB and those who were not were compared using the Student’s t-test or Wilcoxon’s rank sum test, as appropriate, for continuous variables, and the χ² or Fisher’s exact test, as appropriate, for categorical variables. To identify independent risk factors for the occurrence of MDRB, variables found to be significantly different (P < 0.05) between the two groups were entered into a forward stepwise logistic regression model. A complementary analysis was performed for continuous variables identified by the model, using a cut-off that could best predict the risk of developing MDRB. For all analyses, P = 0.05 was considered to be significant.

**Results**

Among 115 patients included in the study, a total of 244 microorganisms were recovered from peritoneal fluid samples (Table 1). The mean number of microorganisms recovered per
patient was two (range 1–5). This was similar in patients with MDRB and those without [mean=2 (range 1–5) versus 2 (range 1–5), respectively; \(P=0.371\)]. Twenty MDRB were isolated from 20/115 patients (17%) and resistance patterns are summarized in Table 2. We did not observe vancomycin-resistant enterococci.

The baseline characteristics of the patients before relaparotomy are shown in Table 3. Age, sex, origin and severity of the condition of the patients, and site of primary surgical procedure were similar in the two groups. The use of antimicrobial therapy in the 3 months prior to relaparotomy was significantly more frequent and the duration between hospital admission or first surgery and relaparotomy was significantly prolonged when MDRB were recovered. During hospitalization, non-surgical and surgical complications, hospital and ICU length of stay, and mortality were similar in the two groups (Table 4). Overall mortality was 30%. In multivariate analysis, only two variables were found to be independently associated with an increased risk of MDRB: antibiotic treatment in the 3 months prior to hospitalization (OR=5.80, 95% confidence interval (95% CI)=1.99–16.91); and duration between first surgery and relaparotomy ≥5 days (OR=1.10 per additional day, 95% CI=1.02–1.19). Furthermore, no MDRB were isolated in patients with <5 days between the first operation and relaparotomy.
Among the 20 MDRB patients, initial empirical antibiotics were inadequate in 60% (12/20), and were subsequently modified. There was no impact of inadequate antimicrobial treatment on mortality (adequate treatment mortality: 5/8 (63%) versus inadequate treatment mortality: 3/12 (25%); P=0.226). On the other hand, when the bacteria were susceptible (n=95), initial antibiotics were adequate in 90/95 patients (95%). The risk of isolating MDRB increased with the number of POP episodes. Indeed, the evolution of antibiotic resistance showed that when a second or third episode of intra-abdominal infection occurred, 9/20 and 3/4 patients, respectively, had MDRB.

### Discussion

This study, performed in a population of patients at high risk of bacterial resistance, revealed an incidence of MDRB of 17%. Furthermore, the risk of isolating MDRB was independently associated with the use of antimicrobial therapy during the 3 months prior to hospitalization, and the time between first surgery and relaparotomy. Interestingly, no MDRB were recovered if the time between first surgery and relaparotomy was <5 days, and no patient in this situation had received antimicrobial therapy in the previous 3 months.

A few studies have investigated the incidence of bacterial resistance in patients with POP. Most included miscellaneous intra-abdominal infections and both community-acquired and post-operative infections. Accordingly, it is difficult to define bacterial resistance during POP. In a retrospective study performed in 100 POP patients, Montravers et al. detected bacterial strains that were resistant to at least two antimicrobial agents in 37% of their patients. Roehrborn et al. prospectively collected the bacteriological data for 93 patients with POP over a 6 year period. They found an increase in bacterial resistance, especially in patients who received antibiotic treatment before relaparotomy, but did not specifically quantify the level of resistance. More recently, in a prospective study performed in all patients admitted to our hospital with secondary peritonitis, the incidence of MDRB was 31% in a subgroup of 35 patients with POP. In the present study, the incidence of MDRB was lower. Using the same definition of MDRB as in our previous study, it is noteworthy that the incidence of MRSA in our hospital has decreased over the past few years, as reported in other large epidemiological studies in France, in general wards and in the ICU. Consequently, only two cases of MRSA POP were observed in 3 years. The distribution of the other MDRB was the same as in our previous study, with a high incidence of Enterobacter spp., producing cephalosporinase. Such findings have been reported previously in POP, and risk factors for acquiring this species, such as previous use of cephalosporin (second or third generation), presence of central venous catheter or antibiotic therapy on admission to the ICU, were easily identified in our patients.

Previous antibiotic treatment and prolonged length of stay before relaparotomy have been reported to be associated with the appearance of MDRB. In the present study, only the time between first surgery and relaparotomy, and antimicrobial therapy in the previous 3 months before actual hospitalization were independent risk factors for MDRB. Antibiotic administration before first operation and relaparotomy was not significantly more frequent in patients with MDRB. Nevertheless, a large proportion of patients received antibiotic(s) in the two groups (59% in MDRB (−) versus 75% in MDRB (+)). In this context, the effects of antibiotic treatment in the previous 3 months are probably more relevant. Prolonged length of stay between the first operation and relaparotomy was a strong risk factor for MDRB, and it is important to emphasize that no patient who had a length of stay <5 days developed MDRB. This cut-off of 5 days is relevant in clinical practice and must be considered as a benchmark for the choice of empirical antimicrobial therapy. Such stratification has previously been proposed in ventilator-associated pneumonia and secondary peritonitis (community or nosocomial). Concerning intra-abdominal infections, the results of our previous study predicted that such stratification would probably have a greater benefit in POP in critically ill patients. Accordingly, broad-spectrum antibiotic therapy associating a β-lactam (cefepime or imipenem), and amikacin and vancomycin could be proposed as empirical treatment in patients with ≥5 days between the first operation and relaparotomy, or those who have received prior antibiotic treatment. In other cases, patients could receive antimicrobial therapy based on narrow-spectrum antibiotics and without vancomycin, as proposed in community-acquired peritonitis. Finally, it should be emphasized that despite the long delay between first operation and relaparotomy, most bacteria recovered from abdominal fluid were susceptible to all antibiotics, and de-escalation therapy could be applied.

There was no significant difference in mortality between patients with or without MDRB. Although this lack of effect on mortality could be related to a lack of power, controversies remain about the impact of MDRB on mortality in various community and nosocomial infections. Nevertheless, this study is the largest published to date, and was performed prospectively over a 3 year period. The effect of inappropriate antimicrobial therapy on mortality is rarely reported in a large cohort of critically ill patients with POP.
treatment on mortality in patients with POP has also been the subject of debate. Indeed, Montravers et al.\(^1\) found increased mortality whereas Roehrborn et al.\(^2\) did not. Antibiotics, in secondary peritonitis and POP in particular, are only one aspect of treatment, which is largely based on controlling the source of infection. In this context it has been clearly demonstrated that patients in whom source control could not be achieved have a poor prognosis.\(^2\) Interestingly, in the study performed by Montravers et al.,\(^1\) patients in whom source control failed were excluded from the analysis.

Our study has some limitations. Generalization of our results may be limited by the single-centre study design. Nevertheless, it must be pointed out that 32% of the patients admitted to our surgical ICU originated from other institutions. We also only investigated the first episode of POP and this prevents extrapolation of the antimicrobial strategy proposed to other situations that could occur later. Finally, as we did not include intra-abdominal abscess alone, our results cannot be extrapolated in this particular condition.

In conclusion, in a large prospective population of POP patients requiring intensive care, the incidence of MDRB was 17%. The occurrence of MDRB was favoured by antimicrobial therapy in the 3 months before hospital admission, and the time between first operation and relaparotomy. No MDRB were recovered from patients who had a time between first operation and relaparotomy of <5 days. Such findings suggest that empirical treatment with broad-spectrum antibiotics should be used in patients who have received antimicrobial therapy in the previous 3 months, and in those who have a delay between the first operation and relaparotomy of ≥5 days.

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**Transparency declarations**

None to declare.

**References**


