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Management and outcome of high-risk peritonitis: a retrospective survey 2005–2009

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SUMMARY

Objectives: To describe the clinical and microbiological aspects of high-risk peritonitis and to analyze their impact on its outcome.
Methods: This was a retrospective review of all culture-positive peritonitis between October 1, 2005 and September 30, 2009. In accordance with recent Infectious Diseases Society of America (IDSA) guidelines, a group of high-risk peritonitis patients was selected based on age, severity of illness, underlying diseases, and acquisition of the infection.
Results: Ninety-three patients with high-risk peritonitis were studied; these patients were divided into subgroups of those with community-associated disease (14%) and those with healthcare-associated disease (86%). The median age of patients was 66 (interquartile range (IQR) 22–95) years. The 30-day mortality rate was 25%. Subgroups differed in age ($p = 0.011$), degree of comorbidity ($p = 0.023$), severity of peritonitis ($p = 0.036$), admission to the intensive care unit (ICU) ($p = 0.002$), length of ICU stay ($p < 0.001$), length of hospital stay ($p < 0.001$), cure at day 30 ($p = 0.001$), and adequate treatment ($p = 0.042$). The microbiological etiology and resistance profiles were similar between the patient groups. Adequate empirical treatment was not related to a better outcome. Severity of disease ($p = 0.005$) and the presence of enterococci ($p = 0.044$) were independently associated with mortality.
Conclusions: The mode of acquisition influences severity and certain parameters of outcome in high-risk peritonitis, but not its microbiological etiology. The outcome seems to depend primarily on severity of peritonitis and much less on the adequacy of treatment.

1. Introduction

Complicated intra-abdominal infections (cIAI) extend beyond the hollow viscus of origin into the peritoneal space and are associated with local or diffuse peritonitis.[1] They are an important cause of morbidity and are frequently associated with a poor prognosis.[2] However, an early clinical diagnosis, followed by adequate surgery and prompt initiation of appropriate antimicrobial therapy can limit the associated mortality.[3] A few enteric species belonging to the normal gut flora are involved in intraperitoneal infections.[4] Healthcare-associated disease has been related to the presence of more resistant flora, such as *Pseudomonas aeruginosa*, *Enterobacter spp*, enterococci, and *Candida spp*.[5] The outcome of cIAI depends on several risk factors, such as advanced age, comorbidity and underlying malignancy, severity of illness, degree of peritoneal involvement, and presence of a healthcare environment. Recent guidelines issued by the Infectious Diseases Society of America (IDSA) and the Surgical Infection Society (SIS) recommend broad-spectrum coverage in the case of high-risk peritonitis, i.e., healthcare-associated disease or severe community-acquired cIAI, because the consequences of treatment failure may be more significant than they are in patients with infections of mild to moderate severity, although this hypothesis has not been rigorously examined in clinical trials.[6]

The aim of our study was to characterize the etiology and outcome of high-risk peritonitis at our institution, in order to validate the recent 2010 IDSA guidelines concerning its management.

2. Methods

This study was conducted at the Brugmann University Hospital, an 854-bed (of which 170 are surgical) university hospital in Brussels, Belgium, with the approval of the institutional review board. Based on data delivered by the Department of Microbiology, the medical records of all adult patients with a positive intra-

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abdominal culture from October 1, 2005 to September 30, 2009 were reviewed, in order to detect the presence of a cIAI. The following data were noted: demographic characteristics, underlying disease, administration of antibiotics during the month preceding the date of onset, clinical presentation, anatomic origin and severity of peritonitis, admission to the intensive care unit (ICU), treatment modalities, and outcome at 30 days after the onset of symptoms. Furthermore, the microbiological etiology of the infection was determined. Since the appropriate recovery of anaerobic organisms was not guaranteed during the study period, we decided to exclude these organisms from the analysis.

2.1. Definitions

A peritoneal fluid culture was considered positive in the presence of growth of at least one pathogen. Only peritoneal fluid drawn by sterile puncture was taken into account.

An intra-abdominal infection was considered complicated if there was localized or generalized peritonitis as a result of perforation of stomach, bowel, or biliary tract; intra-abdominal surgery; or infection of another intra-abdominal organ such as the liver, spleen, pancreas, or the kidneys. Spontaneous bacterial peritonitis and peritonitis related to continuous ambulatory peritoneal dialysis were excluded from the analysis.

High-risk peritonitis was defined as peritonitis requiring broad-spectrum coverage if the 2010 IDSA guidelines were applied. This consists of severe community-associated (CA) and healthcare-associated (HCA) peritonitis. Severe CA peritonitis was defined as peritonitis acquired in the community associated with at least one of the following risk factors: higher severity of illness (APACHE II score $\geq$15), advanced age ($\geq$70 years), and the presence of an immunocompromised state, defined as the presence of an ongoing immunosuppressive treatment, radiotherapy, chemotherapy, or high-dose steroids $>$ 14 days, and/or a history of leukemia, lymphoma, or AIDS. HCA infection was divided into 'community-onset' and 'hospital-onset' HCA infections. Community-onset HCA infection involves patients with community-onset peritonitis and at least one of the following healthcare risk factors: history of surgery, hospitalization, dialysis, or residence in a long-term care facility in the 12 months preceding the culture date, the presence of an invasive device at the time of admission, or a history of methicillin-resistant *Staphylococcus aureus* (MRSA) infection or colonization. Hospital-onset HCA infection involves patients with positive culture results obtained $>$48 h after hospital admission.

The severity of underlying disease was measured using the comorbidity index and score of Charlson et al.[7,8] Severity of peritonitis was assessed by the APACHE II score and the Mannheim peritonitis index.[9,10] Septic shock was defined as sepsis-induced hypotension despite adequate fluid resuscitation, with hypoperfusion or organ dysfunction.

Empirical antimicrobial therapy was defined as treatment given within 24 h after diagnosis and/or surgery. It was considered adequate if active against all the cultured bacteria and/or moulds, administered intravenously at the correct doses, and given for at least 7 days, or replaced by an adequate antimicrobial within this same period.

Outcome was determined at 30 days after the onset of peritonitis. Patients were considered clinically cured if all infection-related symptoms and signs had disappeared, without any evidence of a complication. Infection-related mortality was defined as death during the cIAI episode, without any other obvious cause.

2.2. Microbiology

Peritoneal fluid was collected in sterile pots or syringes and transported to the microbiology laboratory by teletube. In the absence of fluid, a smear of the peritoneal cavity was performed using an appropriate swab (AMIES, Oxoid Transport System, UK). Samples were inoculated onto an aerobic medium (blood and chocolate agar) and incubated at 37 °C (and in 5% CO_2 for chocolate agar plates) for 48 h. Fungi were cultured on Sabouraud–chloramphenicol plates, incubated at room temperature for 15 days. Microorganisms were mainly identified using the Vitek 2 System (bioMérieux, Marcy l'Etoile, France) or by API (bioMérieux) for streptococci. Susceptibility testing was performed according to the types of microorganism recovered, and interpretation was done according to the Clinical and Laboratory Standards Institute (CLSI) 2005 guidelines.

2.3. Analysis

Continuous variables were tested for normal distribution and compared using the Student's *t*-test or the Mann–Whitney test, as appropriate. Categorical data were compared using the Chi-square test or Fisher's exact test. Continuous variables were expressed as mean and standard deviation or as median (interquartile range (IQR)) depending on their distribution. Parameters found to be different by univariate analysis were entered into a stepwise logistic regression model with death as the dependant variable. A double-sided p-value of < 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curves were used to obtain cut-off values of mortality-predicting APACHE II score.

3. Results

Analysis of all positive peritoneal fluid cultures between October 1, 2005 and September 30, 2009 yielded 119 episodes of cIAI. Ninety-three (78%) of these corresponded to the criteria of severe CA or HCA peritonitis. Thirteen (14%) had severe CA peritonitis (group A), because of the presence of: APACHE II score $\geq$15 (n = 4), age $>$70 years (n = 11), and an immunocompromised state (n = 1); three patients had a combination of two risk factors. Forty-three patients (46%) had community-onset HCA disease (group B): history of hospitalization during the last 12 months (n = 31), residence in a nursing home (n = 7), presence of an invasive device (n = 3), and history of MRSA infection or colonization (n = 2). The remaining 37 patients (40%) had hospital-onset HCA peritonitis (group C).

The median age of all 93 patients was 66 years (IQR 22–95). Forty-seven were women and 46 were men. The median Charlson index was 2 (IQR 0–7) and 26% were immunocompromised. The anatomic origin of peritonitis was as follows: colon (40%), small bowel (17%), stomach (13%), biliary tract (8%), appendix (5%), and other (17%). The median Mannheim peritonitis index was 23 (IQR 8–47) and 61 patients (66%) were admitted to the ICU. An APACHE II score was available for 57 of the patients and yielded a median score of 20 (IQR 4–37). The median total hospital stay was 32 days (IQR 1–291) and the median ICU stay was 12 days (IQR 2–151). Empiric antibiotic treatment, of which all contained anaerobic coverage (clavulanic acid, tazobactam, metronidazole, or meropenem) was adequate in 68% of the cases (60/88). Antibiotics had been administered before the onset of cIAI in 25 patients (28%). The isolated pathogen(s) were resistant to the previously given antimicrobial in 60% of these episodes. The median time frame between the onset of infection and surgery was 2 days (IQR 0–60). Twenty-nine percent needed a second revision after initial surgery or drainage because of clinical failure, but at day 30, 42% of the patients were considered cured. The global 30-day mortality rate was 25%, whereas infection-related mortality amounted to 15%. Thirty percent of patients admitted to the ICU died.

One hundred and forty-one microorganisms were cultured. Gram-negative rods were the predominant pathogens (56%),

Table 1
Clinical, treatment, and microbiological characteristics of patients with complicated intra-abdominal infection classified by mode of acquisition

Characteristic	Group A (n = 13)[a]	Group B (n = 43)[b]	Group C (n = 37)[c]
M/F ratio	5/8	20/23	21/16
Age, years, median (IQR)	78 (64–89)	62 (22–95)	67 (23–88)
Charlson comorbidity index, median (IQR)	1 (0–4)	1 (0–7)	3 (0–7)
Mannheim peritonitis index, median (IQR)	26 (9–39)	21 (10–33)	27 (8–47)
Shock, *n* (%)	5 (38)	10 (23)	18 (49)
Admission ICU >24 h, *n* (%)	6 (46)	23 (53)	32 (86)
APACHE II, median (IQR)	26 (10–28)	18 (6–30)	20.5 (4–37)
Length of ICU stay, median (IQR)	18 (2–46)	6 (2–45)	19 (4–188)
Length of hospital stay, median (IQR)	13 (1–61)	21 (2–117)	51 (5–291)
Cure at day 30, *n* (%)	6 (46)	26 (60)	7 (19)
Death at day 30, *n* (%)	3 (23)	8 (19)	12 (32)
Antimicrobial treatment[d]	n = 12	n = 42	n = 34
Narrow-spectrum, *n* (%)	11 (92)	23 (55)	7 (21)
Broad-spectrum, *n* (%)	1 (8)	17 (40)	24 (71)
Fluoroquinolone, *n* (%)	0	3 (7)	3 (9)
Aminoglycoside, *n* (%)	5 (42)	14 (33)	15 (44)
Adequate treatment, *n* (%)	9 (75)	33 (79)	18 (53)
Gram-positive bacteria, *n* (%)	6/18 (33)	16/63 (25)	16/60 (27)
Enterococcus spp, *n* (%)	2 (33)	6 (37)	12 (75)
Other, *n* (%)	4 (67)	10 (63)	4 (25)
Enterobacteriaceae, *n* (%)	10/18 (56)	41/63 (65)	28/60 (47)
Escherichia coli, *n* (%)	6 (60)	25 (61)	16 (57)
Klebsiella spp, *n* (%)	1 (10)	7 (17)	6 (21.5)
Other, *n* (%)	3 (30)	9 (22)	6 (21.5)
Pseudomonas aeruginosa, *n* (%)	1/18 (6)	2/63 (3)	7/60 (12)
Candida spp, *n* (%)	1/18 (6)	4/63 (6)	9/60 (15)
Resistance profile Gram-negative rods[d]			
Narrow-spectrum, *n* (%)	3 (30)	16 (39)	14 (50)
Broad-spectrum, *n* (%)	0	10 (24)	12 (43)
Fluoroquinolone, *n* (%)	0	7 (17)	4 (14)
Aminoglycoside, *n* (%)	0	8 (20)	2 (7)

M, male; F, female; IQR, interquartile range; ICU, intensive care unit; cIAI, complicated intra-abdominal infection.
[a] Group A: severe and/or high-risk community-associated cIAI.
[b] Group B: community-onset healthcare-associated cIAI.
[c] Group C: hospital-onset healthcare-associated cIAI.
[d] Narrow-spectrum: amoxicillin–clavulanic acid or cefuroxime; broad-spectrum: third- or fourth-generation cephalosporin, piperacillin–tazobactam or meropenem.

followed by Gram-positive cocci (27%), *P. aeruginosa* (7%), and moulds (10%). Twenty intra-abdominal cultures were positive for *Enterococcus spp*, of which eight were *Enterococcus faecalis* and five were *Enterococcus faecium*, and 35% showed resistance to ampicillin. *S. aureus* was found in four cases and none of them were methicillin-resistant. *Escherichia coli* was the predominant Gram-negative (59%), followed by *Klebsiella spp* (18%) and other *Enterobacteriaceae* (five *Proteus spp*, four *Citrobacter spp*, three *Enterobacter spp*, three *Morganella spp*, two *Hafnia alvei*, and one *Serratia liquefaciens*). Thirty-six percent of patients having blood cultures had associated bacteremia (Gram negative-rods in seven, Gram-positive cocci in two, a combination of both in two, *P. aeruginosa* in one, and anaerobic pathogens in nine).

Clinical, treatment, and microbiological characteristics of groups A, B, and C are outlined in Table 1. Comparing the three patient groups yielded differences in age ($p = 0.011$), Charlson comorbidity index ($p = 0.023$), Mannheim peritonitis index ($p = 0.036$), admission to the ICU ($p = 0.002$), length of ICU stay ($p < 0.001$), length of hospital stay ($p < 0.001$), cure at day 30 ($p = 0.001$), and adequate treatment ($p = 0.042$). Post-hoc analysis showed that group A differed from groups B and C in age ($p = 0.014$). Group C differed from group B in length of ICU stay ($p < 0.05$) and from groups A and B in length of hospital stay ($p < 0.05$). No significant differences in 30-day mortality or Gram-negative resistance profile were observed between the patient subcategories (Table 1).

Table 2 summarizes the univariate analysis of predictors of death. Patients who died had a higher Charlson index ($p = 0.006$), higher Mannheim peritonitis index ($p = 0.001$), more diffuse peritonitis (odds ratio (OR) 3.24, 95% confidence interval (CI) 1.36–10.74; $p = 0.024$), more often shock (OR 3.61, 95% CI 1.33–9.77; $p = 0.012$), higher APACHE II score ($p = 0.001$), more often had the presence of enterococci (OR 3.45, 95% CI 1.20–9.91; $p = 0.022$), and more often had empiric treatment >24 h after the onset of infection (OR 3.64, 95% CI 1.88–11.11; $p = 0.026$). However, the survival rate was not influenced by age, or by the presence of cancer, acquisition of infection, anatomic origin of peritonitis, being on antimicrobial therapy at the time of admission, inadequate treatment, delayed surgery, need for re-intervention, associated bacteremia, or the presence *P. aeruginosa*.

Stepwise logistic regression of predictors of death (APACHE II, diffuse peritonitis, presence of enterococci, and treatment >24 h after the onset of infection) showed that APACHE II score and the presence of enterococci were independently related to mortality (Table 3). ROC curves predicting mortality yielded a cut-off value of 20.5 for APACHE II (area under the curve (AUC) 0.785, 95% CI 0.656–0.914; $p = 0.001$; sensitivity 81%, specificity 30%).

4. Discussion

Our study characterized 93 episodes of high-risk peritonitis, which, if 2010 IDSA guidelines were applied, would have required broad-spectrum coverage. They were selected among 119 culture-positive cIAI, implying that the majority (78%) were considered at risk of developing complications and/or treatment failure. Indeed, the overall severity of peritonitis was high, demonstrated by the high median APACHE II score and Mannheim peritonitis index (20 and 23, respectively), admission to the ICU (66%), length of hospital stay (32 days), subsequent surgical intervention (29%), and mortality (25%). Community-onset HCA infections showed a less

Table 2
Comparison of clinical, treatment, and microbiological characteristics between non-survivors and survivors

Characteristic	Non-survivors ($n=23$)	Survivors ($n=70$)	p-Value
Age, years, median (IQR)	72 (50–89)	64 (22–95)	NS
Male sex, n (%)	14 (61)	30 (43)	NS
Charlson index, median (IQR)	3 (0–6)	1.5 (0–7)	0.006
Cancer, n (%)	8 (35)	14 (20)	NS
Acquisition, n (%)			NS
Severe and/or high-risk CA	3 (13)	10 (14)	
Community-onset HCA	8 (35)	35 (50)	
Hospital-onset HCA	12 (52)	25 (36)	
Mannheim peritonitis index, median (IQR)	30 (14–39)	21 (8–47)	0.001
Shock, n (%)	13 (57)	20 (29)	0.012
Diffuse peritonitis, n (%)	18 (78)	23 (33)	0.024
APACHE II, median (IQR)	26 (12–37)	19 (4–35)	0.001
Bacteremia, n (%)[a]	8/17 (47)	13/41 (32)	NS
Anatomic origin, n (%)			NS
Colon	12 (52)	25 (36)	
Small bowel	5 (22)	11 (16)	
Stomach	1 (4)	11 (16)	
Length of stay, median (IQR)	32 (1–80)	32 (2–291)	NS
ICU stay >24 h, n (%)	18 (78)	43 (61)	NS
Length of ICU stay, median (IQR)	15 (2–38)	10 (2–151)	NS
Adequate empirical treatment, n (%)	14 (61)	46/65 (71)	NS
Treatment >24 h after onset of infection, n (%)	5 (22)	31/65 (48)	0.026
Delayed surgery (>24 h), n (%)	8 (35)	37/69 (54)	NS
Need for re-intervention, n (%)	6 (26)	21/69 (30)	NS
Enterococci, n (%)	9 (39)	11 (16)	0.022
Pseudomonas aeruginosa, n (%)	5 (22)	5 (7)	NS

CA, community-associated; HCA, healthcare-associated; ICU, intensive care unit; NS, non-significant.
[a] Blood cultures were carried out for 58 patients.

Table 3
Stepwise logistic regression analysis of predictors of mortality

Parameter	Non-survivors ($n=23$)	Survivors ($n=70$)	Adjusted odds ratio	Confidence interval	p-Value
Diffuse peritonitis, n (%)	18 (78)	23 (33)	1.38	0.12–9.05	NS
APACHE II, median (IQR)	26 (12–37)	19 (4–35)	0.87	0.79–0.96	0.005
Treatment delay >24 h, n (%)	5 (23)	30 (51)	0.45	0.095–2.15	NS
Enterococci, n (%)	9 (39)	11 (16)	3.88	1.05–14.28	0.044

NS, non-significant.

severe course when compared to hospital-onset infections, illustrated by significantly lower lengths of hospital and ICU stays and less treatment failure at day 30. These findings suggest that the clinical course of peritonitis and certain parameters of outcome are better in non-hospital-onset than in hospital-onset infections. Hospital-onset peritonitis is known to be characterized by higher complication and mortality rates, caused by more severe underlying disease, a delayed diagnosis, and the impaired immune function in the postoperative period.[5,11] A possible explanation lies in the definition of community-onset HCA infections, issued by Klevens et al.[12] and used in the 2010 IDSA guidelines. This definition is focused on healthcare risk factors for acquiring invasive MRSA infection; this was associated with greater lengths of stay, higher mortality, and increased costs, especially in the case of community-onset HCA infection. It is however less clear whether MRSA risk factors also apply to cIAI and its outcome.

One of the aims of our study was to focus on the microbiological etiology of high-risk peritonitis in order to validate (in a retrospective way) the IDSA recommendation to treat severe CA or community-onset HCA disease with broad-spectrum antibiotics such as meropenem, cefepime, piperacillin–tazobactam, etc. Our data on healthcare-associated disease, even with a community onset, suggest a rather high Gram-negative resistance rate to narrow-spectrum antimicrobials such as amoxicillin–clavulanic acid or cefuroxime (39%), thus suggesting that the healthcare risk factors of Klevens et al. do apply to the microbiological etiology of community-onset HCA infections. Severe CA infections were too small in number for real conclusions about their microbiology to be drawn, but the 30% resistance rate of Gram-negative pathogens to amoxicillin–clavulanic acid or cefuroxime may possibly justify broad-spectrum coverage.

However, our results showed no correlation between adequacy of antibiotic treatment and 30-day mortality, despite a refined definition by adjusting for mode of administration, dosage, and duration of antimicrobial therapy. This absence of relationship between appropriate treatment and outcome might be due to insufficient study power, because several authors have demonstrated a higher rate of complications and/or treatment failure in cases of inadequately treated cIAI, in community- as well as in healthcare-associated disease.[13–15] However, not all of these studies found differences in mortality.[13,16] Possible reasons are the virulence of the microorganisms and their inoculum size, or other factors such as host defense and inadequacy of surgical management explaining failures of antimicrobial therapy even in the presence of drug-susceptible organisms.[4,11,13,16–18] Although adequacy of treatment did not seem to influence outcome, we found that antibiotics given within 24 h after onset of infection was related to better survival rates in the univariate analysis. Evidence suggests that antibiotics are most effective during the early phase of infection because later on, bacterial sequestration in fibrin clots as well as microbial proliferation limit their action.[19]

As in patients with non-high-risk peritonitis, clinical course seemed to depend mostly on severity of peritonitis, measured by the degree of peritoneal involvement, the APACHE II score, and the

Mannheim peritonitis index. An APACHE II score above 20.5 independently predicted mortality. These scores take into account not only the severity of peritonitis but also parameters such as organ failure and underlying illnesses. Our data thus confirm some of the risk factors for treatment failure mentioned in the IDSA guidelines.

Only the presence of *Enterococcus spp* was independently associated with mortality, in contrast with several studies demonstrating a relationship between multidrug-resistant Gram-negative pathogens and mortality.[11,14] Severely ill patients seem to be at risk for enterococcal infections, possibly related to an immunosuppressed state and prolonged antibacterial exposure.[20]

A number of limitations are present in our study. First, as it was a single-center study, microbiological data correspond to our local ecology and therefore cannot be extrapolated to a larger scale. Second, only culture-positive peritonitis was taken into account, thus possibly creating a certain bias by selecting more severe peritonitis related to a larger microbial burden. Third, the total number of CA high-risk peritonitis was too small to be of statistical significance, also suggesting that this type of infection is rare and that there is the risk that it will not be recognized or treated as such. And finally, the absence of any relationship between adequacy of treatment and outcome might be due to insufficient study power.

Despite these limitations, our study shows that the 2010 IDSA guidelines do apply to cIAI in a European tertiary hospital, in particular in selecting peritonitis at risk of developing complications and in predicting their microbiology. However, the clinical course of high-risk peritonitis and certain parameters of outcome seem to depend primarily on its severity. Our results also emphasize the importance of prompt surgery and suggest a modest impact of adequate antimicrobial treatment, even in high-risk patients. However, prospective trials are needed to evaluate the real contribution of antibiotic treatment in this population.

Conflict of interest: No conflict of interest to declare.

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