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## Original Article

## Epidemiology and risk factors for mortality in critically ill patients with pancreatic infection



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# The members of the Abdominal Sepsis Study (AbSeS) group for the Trials Group of the European Society of Intensive Care Medicine have been given in the Appendix section.

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## ABSTRACT

**Background:** The AbSeS-classification defines specific phenotypes of patients with intra-abdominal infection based on the (1) setting of infection onset (community-acquired, early onset, or late-onset hospital-acquired), (2) presence or absence of either localized or diffuse peritonitis, and (3) severity of disease expression (infection, sepsis, or septic shock). This classification system demonstrated reliable risk stratification in intensive care unit (ICU) patients with intra-abdominal infection. This study aimed to describe the epidemiology of ICU patients with pancreatic infection and assess the relationship between the components of the AbSeS-classification and mortality.

**Methods:** This was a secondary analysis of an international observational study (“AbSeS”) investigating ICU patients with intra-abdominal infection. Only patients with pancreatic infection were included in this analysis ( $n=165$ ). Mortality was defined as ICU mortality within 28 days of observation for patients discharged earlier from the ICU. Relationships with mortality were assessed using logistic regression analysis and reported as odds ratio (OR) and 95% confidence interval (CI).

**Results:** The overall mortality was 35.2% ( $n=58$ ). The independent risk factors for mortality included older age (OR=1.03, 95% CI: 1.0 to 1.1  $P=0.023$ ), localized peritonitis (OR=4.4, 95% CI: 1.4 to 13.9  $P=0.011$ ), and persistent signs of inflammation at day 7 (OR=9.5, 95% CI: 3.8 to 23.9,  $P<0.001$ ) or after the implementation of additional source control interventions within the first week (OR=4.0, 95% CI: 1.3 to 12.2,  $P=0.013$ ). Gram-negative bacteria were most frequently isolated ( $n=58$ , 49.2%) without clinically relevant differences in microbial etiology between survivors and non-survivors.

**Conclusions:** In pancreatic infection, a challenging source/damage control and ongoing pancreatic inflammation appear to be the strongest contributors to an unfavorable short-term outcome. In this limited series, essentials of the AbSeS-classification, such as the setting of infection onset, diffuse peritonitis, and severity of disease expression, were not associated with an increased mortality risk.

ClinicalTrials.gov number: NCT03270345

## Introduction

Acute pancreatitis is an acute abdominal condition which is self-limiting and uncomplicated in most cases of edematous pancreatitis. About 15%–30% of the cases develop more severe disease, leading to severe acute necrotic pancreatitis.<sup>[1–4]</sup> Severe acute necrotizing pancreatitis is characterized by high mortality due to a fulminant inflammatory process early in the course of the disease and the development of pancreatic and extra-pancreatic necrosis, infection, and multisystem organ failure (MOF) at a later stage.<sup>[5]</sup> The characterization of these pathways has improved the understanding of the disease, leading to the identification of potential molecular targets, including the mechanisms of calcium signaling and acinar cell injury/death. Additionally, the protective role of the unfolded protein response and the toxic role of unsaturated fatty acids and has possible therapeutic implications. Further research, however, is needed to translate these insights into clinical benefits.<sup>[6]</sup> Despite these achievements, the outcome of severe acute necrotizing pancreatitis has not improved significantly over the past years.<sup>[2]</sup> Among other serious intra-abdominal infections, pancreatic infection complicating severe acute pancreatitis frequently poses a challenge in the intensive care unit (ICU) setting.<sup>[7]</sup>

For this group of patients, multidisciplinary and well-organized management is crucial, including close monitoring, appropriate use of imaging, proper fluid resuscitation, and use of antibiotics, nutritional and organ support. Additionally, the appropriate type and timing of endoscopic procedures, radiological interventions, and surgical interventions are critical.<sup>[8]</sup> Surgical and interventional endoscopic source control are crucial and are both therapeutic and diagnostic. These interventions may include debridement of necrotic tissues (including transgastric necrosectomy), drainage of abscesses, control of the source of infection, restoration of anatomy and function, and, although

infrequently performed, abdominal cleansing and irrigation. Often several surgical interventions are required at different stages of the disease.<sup>[9,10]</sup>

While a dysregulated immune response, together with hemodynamic and coagulation abnormalities, may lead to early onset organ failure (within 24–72 h), a second deterioration phase may be triggered by bacterial or fungal superinfection of the necrotic tissue (i.e., infected pancreatic necrosis), and may, together with exacerbation of the pre-existing inflammation, result in late-onset organ failure (beyond 2 weeks).<sup>[2,11]</sup> Infection may be suspected in patients with a new, otherwise unexplained fever, (peri)pancreatic gas on imaging, bacteremia or candidemia in addition to worsening or persistent leukocytosis and other inflammatory parameters, and overall clinical deterioration.<sup>[8,12]</sup> Bacterial superinfections occur in 10%–50% of patients with pancreatic necrosis.<sup>[13–16]</sup> Compared with sterile necrosis of the pancreas, pancreatic infection has a much worse prognosis, with mortality rates between 30% and 70%.<sup>[8,17–25]</sup>

As in any intra-abdominal infection, the microorganisms involved include a broad spectrum of Gram-positive and Gram-negative bacteria, as well as anaerobic bacteria and in pancreatic infection fungi. Multidrug-resistant (MDR) bacteria are more commonly observed in patients with recent exposure to broad-spectrum antibiotics, underlying medical conditions, and prior hospitalization for more than 5 days.<sup>[10,26]</sup> In addition to patient-related factors, the risk of infection with MDR pathogens differs by the geographical region, local (in-hospital) ecology, and timing of appearance – depending on the disease severity and the intervention methods.<sup>[10,27]</sup>

Given the broad spectrum of presentation, the appropriate classification of intra-abdominal infection and sepsis has long been debated. The international AbSeS study aimed to demonstrate the relationship between a risk classification tool and mortality, independent of the type of intra-abdominal infection.<sup>[7]</sup> The classification is based on three generic features of infection leading to specific clinical phenotypes of intra-abdominal

infection. These features include (1) the setting of infection acquisition defined as either community, healthcare-associated, or early onset hospital-acquired (i.e.,  $\leq 7$  days of hospital admission), or late-onset hospital-acquired infection ( $>7$  days); (2) the absence or presence of anatomical barrier disruption, resulting either in localized or diffuse peritonitis;<sup>[7,28]</sup> and (3) the severity of the disease manifestation, defined according to the Sepsis-3 criteria (i.e., infection, sepsis, or septic shock).<sup>[29]</sup> The components of the *AbSeS*-classification were independently associated with mortality in the entire cohort, including all patients with intra-abdominal infection in the ICU and in the subgroup of patients with secondary peritonitis.<sup>[7,30]</sup>

Although the *AbSeS*-classification allowed adequate risk adjustment of different types of intra-abdominal infections, such as secondary peritonitis, its risk prediction value in other specific types of intra-abdominal infections remains uncertain. We aimed to assess the predictive value of the components of the *AbSeS*-classification in ICU patients with pancreatic infection. Therefore, the aim of this study was to assess risk factors for mortality in a subset of critically ill patients with pancreatic infection using the *AbSeS* risk classification.

## Methods

### Study design

This is a secondary analysis of data from the *AbSeS* study: a multinational observational cohort study of ICU patients with intra-abdominal infection.<sup>[7]</sup> The *AbSeS* cohort included 2621 patients from 309 ICUs in 42 countries. For the present study, only patients with pancreatic infection were considered ( $n=165$ , Figure 1). Approval was granted by established national, regional, or local institutional review boards. The study is registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT03270345). More detailed descriptions of inclusion and exclusion criteria, definitions, methods, and collection of data are described elsewhere.<sup>[7]</sup>

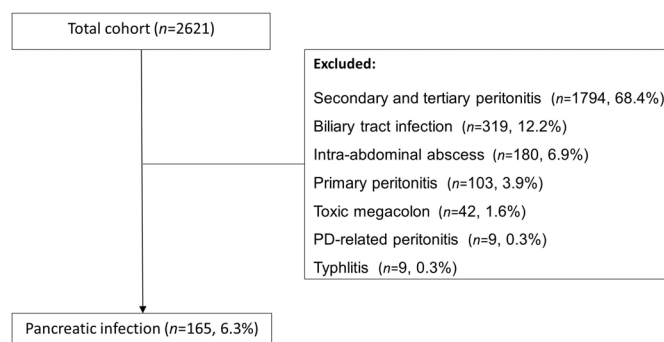
### Variables and definitions

Pancreatic infection was defined according to the International Sepsis Forum Consensus Conference on Definitions of Infection in the Intensive Care Unit.<sup>[31]</sup> Patients were eligible for inclusion if they had (1) microbiologically confirmed pancreatic infection (i.e., positive cultures directly from the pancreas or the surrounding structures by percutaneous aspiration or direct visualization and culture at the time of surgery or from the

bloodstream), (2) probable infected pancreatitis (i.e., the presence of surgical or radiographic evidence of an abnormal collection of an inflammatory focus within the substance of the pancreas or the surrounding structures with a positive Gram stain from the pancreatic collection without evidence from culture), or (3) possible infected pancreatitis (i.e., radiographic or direct surgical inspection with evidence suggestive of pancreatic abscess or other types of infection originating from the pancreas).

The following data were selected from the *AbSeS* database: demographics (sex, age, and body mass index [BMI]), comorbidities (cardiovascular disorders, chronic pulmonary disease, neurologic disease, diabetes, acquired immunodeficiency syndrome [AIDS], liver disease, chronic renal failure, immunosuppression, malnutrition, and obesity), lifestyle risk factors (tobacco, drug, and alcohol abuse), risk factors for MDR pathogens (nursing home resident, out-of-hospital parenteral/nutrition or vascular access, chronic dialysis, recent hospitalization, and antibiotics use in the past 6 months), and components of the *AbSeS*-classification as mentioned above.

The severity of acute illness was assessed using the Simplified Acute Physiology Score (SAPS II score) at the time of ICU admission<sup>[32]</sup> and the Sequential Organ Failure Assessment (SOFA score) at the time of diagnosis.<sup>[33]</sup> The *AbSeS* protocol included a source control evaluation on day 7. Source control failure was defined as either the presence of persistent inflammation or the need for an additional intervention following the initial source control approach. However, source control evaluation is challenging in pancreatic infection. Persistent inflammation may be a sign of ongoing pancreatitis, although the infection is well-controlled. Additionally, recurrent interventions may be a strategy of damage control in acute infected pancreatitis as removal of necrotic material is often not done in a single procedure and can, therefore, not be used as a proxy of source control failure. Consequently, we decided to keep the clinical evaluation on day 7 in the study analysis but did not define it as either successful or failed source control. The clinical evaluation on day 7 was then categorized as “stable,” “unstable as evidenced by persistent signs of inflammation,” or “unstable with need for recurrent interventions.” In this evaluation, having “persistent signs of inflammation” may reflect either source control failure or ongoing pancreatitis. Likewise, the “need for recurrent interventions” may reflect either source control failure or a complicated case with the need for a stepwise damage control strategy. For patients who died before day 7, the source control evaluation was carried out on the last day alive.



**Figure 1.** Included study population of pancreatic infection based on the total *AbSeS* study cohort.

Outcome data included ICU length of stay and ICU mortality within 28 days of observation for patients discharged earlier from the ICU.

To assess microbial etiology and cultures derived from intra-operative sampling, trans-abdominal fine-needle aspiration, abdominal drains ( $\leq 24$  h post-surgery), and blood cultures were considered. The basic empiric antimicrobial coverage (targeting Gram-positive, Gram-negative or anaerobic bacteria, and fungi) was evaluated. EUCAST breakpoints are used as antimicrobial resistance thresholds.<sup>[34]</sup> Antimicrobial resistance was defined as extended-spectrum beta-lactamase production (ESBL), carbapenem-resistance, and fluoroquinolone-resistance in Gram-negative microorganisms<sup>[35]</sup> and methicillin-resistance for *Staphylococcus aureus* (MRSA) or vancomycin-resistance in enterococci (VRE) for Gram-positive bacteria.

### Statistical analyses

Continuous variables were described with median values and 25th to 75th percentiles (interquartile range [IQR]), and frequency and percentage (%) were used to describe categorical variables. The Mann–Whitney *U* test was used for comparisons between continuous variables, and the chi-squared or Fisher's exact tests were used to compare categorical variables.

Logistic regression analysis was performed to assess relationships with mortality. The following variables were considered in the model (irrespective of their relationship in univariate analysis): demographics, comorbidities, day-7 clinical evaluation, and elements of the *AbSeS*-classification (i.e., setting of infection acquisition, anatomical disruption, and the severity of disease expression). Feature selection was performed using the stepwise approach to remove covariates with  $P > 0.15$ . The final model contained, preferably, a maximum of one independent covariate per ten outcome events (dead). Results are reported as odds ratio (OR) and 95% confidence interval (CI). The SOFA score was not considered as it substantially overlaps with the severity of disease expression in the *AbSeS*-classification. Survival analysis of patients according to source control outcome was assessed using the Kaplan–Meier method, and the log-rank test was used to compare the survival curves. Statistical significance was defined as  $P < 0.05$ . Statistical analyses were performed using SPSS Statistics version 28, and all tests were two-tailed.

## Results

### Description of the cohort

The study included 165 patients with pancreatic infection, with a mean age of 58 years. Samples for microbiological analysis were taken in 118 cases, with positive cultures in 89 patients (75.4%), hence considered proven cases of pancreatic infection (53.9%). Other cases were considered possible pancreatic necrosis ( $n=76$ , 46.1%) as no microbiological samples were taken ( $n=47$ , 28.5%) or results of Gram-staining were not reported ( $n=29$ , 17.6%). For patients who had their microbiological samples taken ( $n=118$ ), Gram-negative bacteria were most frequently isolated ( $n=58$ , 49.2%): *Enterobacterales* were isolated in 50 patients (42.4%) and non-fermenting bacteria in 13 patients (11.0%). Gram-positive bacteria were isolated in 34

patients (28.8%), with enterococci being the most prevalent (*E. faecalis*:  $n=13$ , 11.0%; *E. faecium*:  $n=8$ , 6.8%). Anaerobic bacteria were isolated in 18 patients (15.3%) and *Candida* spp. in 16 patients (13.6%). MDR organisms were isolated in seven patients (5.9%).

The overall mortality was 35.2% ( $n=58$ ). Table 1 summarizes patients' characteristics for survivors and non-survivors. Overall, underlying conditions and lifestyle risk factors were more frequent in the non-survivor group. Non-survivors were older, had higher SOFA scores, and experienced more septic shock compared to survivors. Peritonitis (either localized or diffuse) and failure of source control were more common among non-survivors. The non-survivors presented more commonly with late-onset hospital-acquired infection. No difference between the groups was observed regarding the ICU length of stay. No clinically relevant differences in microbial etiology were observed between survivors and non-survivors.

### Source control approaches

Data on source control are reported in Table 2. Source control interventions were performed in 138 patients (83.6%), including drainage ( $n=119$ , 72.1%), decompressive surgery ( $n=10$ , 6.1%), or restoration of anatomy and function ( $n=42$ , 25.5%). Drainage consisted of either open surgical drainage ( $n=96$ ), laparoscopic drainage ( $n=3$ ), peritoneal lavage ( $n=36$ ), percutaneous drains ( $n=25$ ), or debridement of necrosis ( $n=22$ ). In certain cases, a combination of interventions was applied.

### Clinical evaluation on day 7

On day 7, 81 cases (49.1%) were considered “stable,” 56 cases had persistent signs of inflammation (33.9%), and multiple source/damage control interventions were performed in 28 cases (17.0%). Reasons for re-intervention included leakage ( $n=14$ ), obstruction ( $n=3$ ), abdominal compartment syndrome ( $n=2$ ), bleeding ( $n=4$ ), ischemia/necrosis ( $n=4$ ), explorative laparotomy for persistent inflammation ( $n=2$ ), or others ( $n=2$ ).

### Independent relationships with mortality

The objective of the logistic regression analysis was to assess relationships between the *AbSeS*-classification and mortality, alongside other risk factors for death. For that reason, we planned to “force” the *AbSeS*-classification components in the model irrespective of its relationship with the outcome. Due to the limited number of deceased patients ( $n=58$ ), however, the final logistic regression model could not contain more than six independent covariates. The setting of the infection onset had no association with mortality. Therefore, this component of the *AbSeS*-classification was excluded from the model. The final model of the logistic regression analysis identified localized peritonitis, older age, and a clinical evaluation on day 7, indicating persistent inflammation or the need for repeated interventions for source/damage control as independent risk factors for death in critically ill patients with infected pancreatitis (Table 3). Other parameters, such as microbial etiology, comorbidities, and lifestyle risk factors, were not associated with mortality and were excluded ( $P > 0.15$ ).

**Table 1**  
Characteristics of ICU patients with pancreatic infection according to survival status.

Characteristic	Survivors (n=107)	Non-survivors (n=58)	P-value
<b>Demographics</b>			
Age (years)	55 (41–69)	62 (53–74)	0.018
Sex, male	73/106 (68.2)	35/57 (61.4)	0.380
Type of ICU admission			0.556
Medical	56 (53.8)	27 (47.4)	
Surgical, non-emergency	10 (9.6)	8 (14)	
Surgical, emergency	38 (36.5)	22 (38.6)	
ICU stay (days)	15 (5–25)	16 (6–27)	0.717
<b>Underlying conditions</b>			
Chronic pulmonary disease	12 (11.2)	3 (5.2)	0.197
Malignancy	8 (7.5)	4 (6.9)	>0.999
Neurologic disease	2 (1.9)	4 (6.9)	0.186
Peptic ulcer disease	7 (6.5)	4 (6.9)	>0.999
Liver disease	4 (3.7)	5 (8.6)	0.280
Chronic renal failure	5 (4.7)	4 (6.9)	0.721
Myocardial infarction	5 (4.7)	7 (12.1)	0.115
<b>Chronic heart failure</b>			
Congestive heart failure	1 (0.9)	3 (5.2)	
Heart failure	0	3 (5.2)	
Peripheral vascular disease	4 (3.7)	2 (3.4)	>0.999
Diabetes mellitus	22 (20.6)	15 (25.9)	0.436
Immunosuppression	6 (5.6)	4 (6.9)	0.740
<b>Lifestyle risk factors</b>			
Malnutrition (body mass index <20 kg/m <sup>2</sup> )	3 (2.8)	4 (6.9)	0.213
Obesity (body mass index ≥30 kg/m <sup>2</sup> )	34 (31.8)	20 (34.5)	0.723
Tobacco use (>20 pack years)	18 (16.8)	9 (15.5)	0.829
Alcohol abuse (>10 g alcohol/day)	27 (25.2)	11 (19.0)	0.361
<b>Severity of acute illness</b>			
SAPS II score at the time of ICU admission	52 (39–60)	53 (40–65)	0.324
SOFA score at diagnosis	6.1 (4–8)	8.7 (5.8–12)	<0.001
<b>AbSeS-classification</b>			
<b>Severity of disease expression</b>			
Infection without sepsis	6 (5.6)	2 (3.4)	
Sepsis	75 (70.1)	23 (39.7)	
Septic shock	26 (24.3)	33 (56.9)	
<b>Anatomical disruption</b>			
Not present	80 (74.8)	31 (53.4)	0.014
Yes, with localized peritonitis	9 (8.4)	12 (20.7)	
Yes, with diffuse peritonitis	18 (16.8)	15 (25.9)	
<b>Origin of infection onset</b>			
Community-acquired infection	30 (28.0)	15 (25.9)	0.705
Early onset hospital-acquired infection (≤7 days)	23 (21.5)	10 (17.2)	
Late-onset hospital-acquired infection (≥7 days)	54 (50.5)	33 (56.9)	
Empiric antibiotic therapy	73 (76.0)	46 (90.2)	0.038

Continuous variables are presented as median (interquartile range). Categorical variables are presented as n (%).  
ICU: Intensive care unit; NA: Not applicable; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment.

**Table 2**  
Source control characteristics and clinical outcomes at day 7.

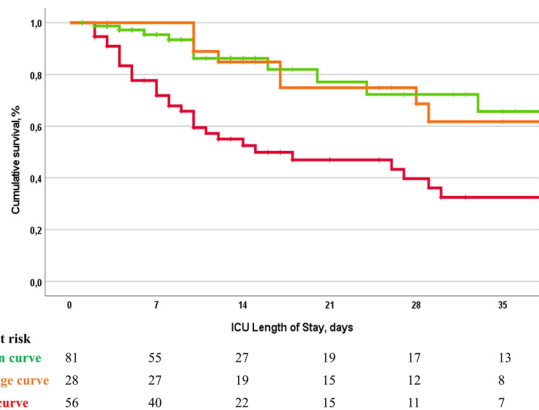
Items	Survivors (n=107)	Non-survivors (n=58)	P-value
<b>Source control approach</b>			
Initial source control applied	86 (80.4)	52 (89.7)	0.124
All drainage	72 (67.3)	47 (81.0)	0.060
Surgical drainage	57 (53.3)	39 (67.2)	0.082
Laparoscopic drainage	0	3 (5.2)	NA
Peritoneal lavage	20 (18.7)	16 (27.6)	0.187
Percutaneous drains	14 (13.1)	11 (19.0)	0.314
Debridement of necrosis	17 (15.9)	5 (8.6)	0.190
Decompressive surgery	9 (8.4)	1 (1.7)	0.101
Restoration of anatomy and function	28 (26.2)	14 (24.1)	0.775
<b>Reasons for additional re-intervention</b>			
Leakage	9 (8.4)	5 (8.6)	>0.999
Obstruction	2 (1.9)	1 (1.7)	>0.999
Abdominal compartment syndrome	1 (0.9)	1 (1.7)	>0.999
Bleeding	1 (0.9)	3 (5.2)	0.125
Ischemia/necrosis	3 (2.8)	1 (1.7)	>0.999
Abscess	0	0	NA
Explorative laparotomy for persistent inflammation	1 (0.9)	1 (1.7)	>0.999
Other	0 (0.0)	2 (3.4)	NA
<b>Clinical evaluation at day 7, outcomes</b>			
Stable	67 (62.6)	14 (24.1)	
Unstable, persistent signs of inflammation	24 (22.4)	32 (55.2)	
Unstable, additional intervention required following initial approach	16 (15.0)	12 (20.7)	<0.001

NA: not applicable.

**Table 3**  
Independent relationships with mortality in critically ill patients with pancreatic infection.

Risk factor	OR	95%CI	P-value
Age (years increase)	1.0	1.0 to 1.1	0.023
Clinical evaluation on day 7 of the pancreatic infection process			
Stable	Reference		
Unstable, persistent signs of inflammation	9.5	3.8 to 23.9	<0.001
Unstable, additional intervention required following the initial approach	4.0	1.3 to 12.2	0.013
Anatomical disruption			
Not present	Reference		
Localized peritonitis	4.4	1.4 to 13.9	0.011
Diffuse peritonitis	1.8	0.7 to 4.6	0.201
Severity of disease expression			
Infection	Reference		
Sepsis	0.5	0.1 to 3.5	0.454
Septic shock	2.4	0.3 to 18.8	0.395

CI: confidence interval; OR: odds ratio.



**Figure 2.** Survival curves according to clinical status at day 7 in critically ill patients with pancreatic infection. The green line represents a stable clinical status (i.e., without overt intra-abdominal inflammation or the need for additional interventions for either source control or damage control). These patients had a median age of 59 years (44–72). In this group, 58 patients had no anatomical barrier disruption (71.6%), 10 had localized peritonitis (12.3%), and 13 had diffuse peritonitis (16.0%). The orange line represents the need for additional intervention following the initial approach. These patients had a median age of 60 years (46–71). In this group, 16 patients had no anatomical barrier disruption (57.1%), 3 had localized peritonitis (10.7%), and 9 had diffuse peritonitis (32.1%). The red line represents a condition with persistent signs of inflammation. These patients had a median age of 59 years (48–75). In this group, 37 patients had no anatomical barrier disruption (66.1%), 8 had localized peritonitis (14.3%), and 11 had diffuse peritonitis (19.6%). The P-value for the Log-rank test for differences between the curves was <0.001.

Because of the significant relationship between the intermittent evaluation on day 7 and the outcome, we further analyzed the survival path stratified by the clinical status one week after diagnosis. These unadjusted survival curves are shown in Figure 2. The cumulative survival curve for a clinical condition with persistent signs of inflammation is significantly lower, with overall higher mortality.

**Discussion**

This secondary analysis of the *AbSeS* study aimed to explore the association between mortality and independent risk factors in ICU patients with pancreatic infection. Our study is the first to report the specific implementation of the *AbSeS*-classification components for grading intra-abdominal infection in ICU pa-

tients with pancreatic infection. Mortality in ICU patients with pancreatic infection was high (35.2%), significantly greater than the overall mortality in the *AbSeS* cohort (i.e., 29.1%).<sup>[7]</sup> The main finding of this study is that older age, localized peritonitis, and unstable clinical condition on day 7 (either due to persistent inflammation or the need for recurrent surgical intervention) are independently associated with mortality. The *AbSeS*-classification components, with previously recognized risk factors, such as late-onset hospital-acquired infection, diffuse peritonitis, and sepsis or septic shock, appeared to have no predictive value in this specific population.

In infected pancreatitis, localized peritonitis was associated with mortality, whereas diffuse peritonitis was not. This observation is counterintuitive, and this may be because diffuse peritonitis is rare in the cohort. Pancreatic infection rarely results in diffuse peritonitis being a retroperitoneal disease. The association with localized peritonitis should also be interpreted with caution as well due to the small numbers involved. A clinical picture of diffuse peritonitis may trigger earlier surgical intervention with a positive prognostic impact: studies have shown that delayed intervention is beneficial.<sup>[8,12,36–40]</sup> In this regard, it is challenging to assess the timing of surgical intervention as the onset of infection on top of a chronic inflammatory process is impossible to determine.

Based on the entire cohort of the *AbSeS* study, Blot et al.<sup>[7]</sup> identified the following variables as independent risk factors for mortality in intra-abdominal infections: higher SOFA scores, diffuse peritonitis, sepsis and septic shock, older age, malnutrition, diabetes mellitus, liver failure, and congestive heart failure. With the exception of older age, these aspects reflect the severity of the acute illness. In contrast, in the present study, the severity of acute illness and chronic underlying conditions did not prove to be significant determinants of mortality. Again, the limited study power must be considered, as it is highly uncommon for clinical aspects such as septic shock not to be associated with an increased risk of mortality. This association has also been reported by Zhu et al.<sup>[41]</sup> in the specific context of patients with severe acute pancreatitis, albeit the outcome window of 24 h may have boosted the relative importance of septic shock as a risk factor for death.

These findings reiterate that adequate source control is the cornerstone in the management of pancreatic infection in ICU patients.<sup>[7,16,24,39]</sup> A minimally invasive step-up approach is

preferable, starting with the least invasive technique and gradually escalating in case of treatment failure.<sup>[23,40,42,43]</sup> The present data indicate that recurrent interventions are associated with poor outcomes. However, this probably reflects complicated cases requiring multiple procedures in the pursuit of damage control. Invasive procedures also carry a risk of superinfection and may worsen the prognosis in patients with sterile necrosis.<sup>[24]</sup> In pancreatic infections, the risk of superinfection is inferior to the beneficial impact of source control – antimicrobials as a single treatment appear to contribute less to infection control, primarily due to the persistence of infection in the necrotic tissues.

Delaying an intervention in stable patients is commonly recommended to allow for the development of a fibrous wall around the necrosis tissue.<sup>[8,12,36–40]</sup> This strategy is associated with fewer complications, such as iatrogenic intraoperative injury, bleeding, postoperative septic and systemic inflammatory response, and reduced mortality.<sup>[36]</sup> Earlier debridement is associated with higher mortality,<sup>[8,12,16,44]</sup> whereas longer delay in intervention may imply overuse of antibiotics, leading to increased incidence of resistant bacteria and the emergence of fungi and other opportunistic microorganisms, all associated with prolonged ICU stay and increased mortality.<sup>[45–47]</sup>

Contrary to our conclusion, other studies conclude that conservative treatment with antibiotics as a single approach can resolve pancreatic infections and prevent the need for surgical intervention<sup>[48–52]</sup> or even reduce the risk of mortality.<sup>[53,54]</sup> Few antibiotics (e.g., carbapenems, quinolones, and metronidazole) are believed to penetrate sufficiently into the necrotic infected focus.<sup>[8,12]</sup> Tian et al.<sup>[55]</sup> suggested restricting the use of broad-spectrum antibiotics and proposed more targeted drug administration based on specimen collection. For most of our patients, a conservative approach based on antimicrobials and organ support alone was probably not possible, given the high prevalence of sepsis or septic shock (Table 1).

Microbiologically, the spectrum of pathogenic microorganisms was generally monomicrobial, with a predominance of Gram-negative bacteria (35.2%), consistent with previous studies.<sup>[7,10,55]</sup> While positive microbiology is as common as in the entire *AbSeS* cohort (71.5% and 75.6%, respectively), the *AbSeS* study reports a strikingly higher number of Gram-negative bacteria (58.6%) from clinical samples. Noor et al.<sup>[56]</sup> claimed that there is a shift from Gram-negative to Gram-positive bacteria caused by the progression of pancreatitis and the longer hospital stay. Interestingly, a low number of patients ( $n=7$ , 4.2%) had MDR bacteria. The overall prevalence of antimicrobial resistance in the *AbSeS* study was higher (26.3%),<sup>[7]</sup> which may be explained by a high incidence of nosocomial infections, especially late-onset hospital-acquired infections in an exclusively ICU cohort.<sup>[55]</sup> Other studies also described the rising emergence of MDR bacteria.<sup>[7,27,57,58]</sup> An explanation for the low MDR rate present in our cohort may be the current policy of withholding the initial empiric broad-spectrum antibiotics, despite ongoing inflammation and organ failure, until the most appropriate antimicrobial therapy is available based on culture results later in the course of the disease, with a secondary deterioration due to documented or probable infection. With this strategy, infection will develop without prior antimicrobial selective pressure toward MDR pathogens.

Infection of necrotic pancreatic tissue increases mortality and the probability of MOF, which is also an important determinant of death.<sup>[18,20,22,25,39,59–61]</sup> The co-existence of both complications has a synergistic effect that doubles the risk of death.<sup>[22,24]</sup> These determinants and the need for ICU admission represent the most severe forms of the disease.<sup>[62]</sup> As our cohort exclusively contains ICU patients with pancreatic infection, they are considered at high risk for extra-pancreatic complications.<sup>[5,55]</sup>

As previously shown, age has a significant impact on mortality in acute pancreatitis.<sup>[63]</sup> Similar to the study by Tian et al.,<sup>[55]</sup> the mean age of patients in the non-survival group was significantly higher than in the survival group. Compared to the overall cohort of the *AbSeS* study, the mean age in the present cohort is significantly lower (66 years and 58 years, respectively), indicating that acute pancreatitis in the ICU is associated with high mortality rates irrespective of age.

First, per protocol, the *AbSeS* database only included patients with infection, making it impossible to assess the impact of infection in a subset of patients with acute pancreatitis. Second, some observations are counterintuitive, indicating that our study might be underpowered. In fact, with only 58 deceased patients, the number of covariates allowed in a logistic regression model to avoid overfitting is quite low. Therefore, larger studies are necessary to elucidate further the impact of the variables in the *AbSeS*-classification on mortality in ICU patients with pancreatic infection. Third, variables potentially influencing the outcome might not have been collected (e.g., the etiology of pancreatitis and location and extent of necrosis).<sup>[64]</sup> Fourth, no specific data were collected regarding the classification of acute pancreatitis, according to the revised Atlanta classification by Banks et al.<sup>[65]</sup> Yet, we assume that the included cases had severe pancreatic infections according to the definitions of the study protocol. Fifth, acute pancreatitis is a complicated disease, as it involves triggering a severe inflammatory process, distinguishing it from other intra-abdominal infections. Therefore, these cases are more difficult to categorize or predict with the *AbSeS*-classification, especially concerning the setting of the infection onset, where the majority are late complications: in contrast to secondary peritonitis, where the infection is part of the disease process from the beginning. Furthermore, the timing of surgical intervention as from infection onset proved impossible as it is unclear when the case of acute pancreatitis became complicated with infection. Finally, as already outlined in the methods section, in infected pancreatitis, source control evaluation on day 7 as per the *AbSeS* protocol proved unusable.

## Conclusions

Older age, localized peritonitis, and a clinical condition reflecting persistent inflammation at 7 days, as well as the need for recurrent interventions within a week in pursuit of source or damage control, were the strongest predictors of mortality in critically ill patients with pancreatic infection. The *AbSeS*-classification system did not predict mortality in this sample of patients.

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Marie Dejonckheere: Writing original draft preparation, statistical analysis, investigation. Massimo Antonelli: conceptual-

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### Ethics Statement

Not applicable.

### Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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