Epidemiology and Age-Related Mortality in Critically Ill Patients With Intra-Abdominal Infection or Sepsis: An International Cohort Study

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Abstract (word count: 250)

BACKGROUND. The objective of this study is to describe the epidemiology and age-related mortality in older critically ill adults with intra-abdominal infections.

METHODS. This is a secondary analysis of a prospective, multinational, observational study (*AbSeS*, ClinicalTrials.gov #NCT03270345) including patients with intra-abdominal infection from 309 ICUs in 42 countries (January-December, 2016). Mortality was considered as ICU mortality with a minimum of 28 days of observation when patients were discharged earlier. Relationships with mortality were assessed by logistic regression analysis.

RESULTS. The cohort included 2337 patients. Four age groups were defined: middle-aged patients as reference category (40-59 years; n=659 [28.2%]), young-old (60-69 years; n=622 [26.6%]), middle-old (70-79 years; n=667 [28.5%]) and very-old patients (≥80 years; n=389 [16.6%]). Secondary peritonitis was the predominant infection (68.7%) and equally prevalent across age groups. Mortality increased with age: 20.9% in middle-aged patients, 30.5% in young-old, 31.2% in middle-old, and 44.7% in very-old patients (p<0.001). Compared to middle-aged patients, young-old age (OR 1.62, 95% CI 1.21-2.17), middle-old age (OR 1.80, 95% CI 1.35-2.41), and very-old age (OR 3.69, 95% CI 2.66-5.12) were independently associated with mortality. Other independent risk factors for mortality included late-onset hospital-acquired intra-abdominal infection, diffuse peritonitis, sepsis/septic shock, source control failure, liver disease, congestive heart failure, diabetes, and malnutrition.

CONCLUSIONS. For ICU patients with intra-abdominal infections, age above 60 years was associated with mortality while patients above 80 years had the worst prognosis**.** Comorbidities and overall disease severity further compromised survival. As all these factors are non-modifiable it remains unclear how to improve outcomes.

Key words: intra-abdominal infection; sepsis; older adults; ICU; mortality

INTRODUCTION

Due to demographic changes older adults constitute a growing proportion among critically ill patients. These patients' clinical status is often burdened with multiple underlying comorbidities making them particularly vulnerable to healthcare-associated complications such as infection. Many critical care studies have focused on older adults. This increased interest is related to the growing proportion of older adults in the general patient population contributing to a rise of hospital and ICU admissions and to the increased mortality of critically ill older adults [1-5]. Age-related features such as physiological alterations in immunity, chronic underlying diseases, malnutrition, frailty and socio-economic status further contribute to the increased infection risk in older adults [6].

Intra-abdominal infections and in particular complicated intra-abdominal infections are difficult to treat. They differ from other severe infections in complexity of identification and diagnosis, diversity of etiology, degree of severity and need for source control [7-13]. Moreover, the increasing prevalence of multidrug resistant (MDR) bacteria challenges the appropriateness of empiric antibiotic therapy thereby increasing the risk for adverse outcomes [14]. Also, critical illness and age contribute to increased morbidity and mortality for patients with intra-abdominal infection [7,8]. Age older than 75 years increases the risk of death in patients with intra-abdominal infections or peritonitis related to viscous perforation [15,16]. Specifically for ICU patients the impact of advanced age on the outcome after intra-abdominal infection and sepsis has not been adequately explored. Furthermore, it is unclear whether older adults are more prone to particular intra-abdominal infections, require more source control interventions, or have a higher risk for MDR involvement. All these issues may change the clinical approach to the older ICU patient with intra-abdominal infection.

The purpose of the present study was to assess the epidemiology and mortality of intra-abdominal infection in young-old, middle-old, and very-old ICU patients, compared with middle-aged patients.

METHODS

The study was reported according to the STROBE statement for observational studies [17]. Ethics approval for participating centres was obtained at hospital, regional or national level. The study is registered at ClinicalTrials.gov (number NCT03270345).

Study design

We conducted a secondary analysis of data from AbSeS, an observational, prospective, international cohort containing adult patients from 309 ICUs and 42 countries between January and December 2016 [8]. Protocols and procedures followed for inclusion/exclusion criteria, definitions, methods and collection of data for AbSeS, are reported elsewhere [8]. Our aim was to describe the epidemiological features of intra-abdominal infection and identify factors related to ICU mortality in older ICU patients.

Patient selection

Following the AbSeS protocol, patients with intra-abdominal infection, either as primary ICU diagnosis or as complication during ICU hospitalization, were included in the study. All patients aged 40 years or older were eligible for analysis in the present study. Patients without outcome data were excluded from analysis. Patients were classified as middle-aged (40-59 years), young-old (60-69 years), middle-old (70-79 years) and very-old (≥80 years).

Variables

For every included patient, the following data were retrieved from the AbSeS database: patients' demographics (sex, age), type of ICU admission (medical, surgical or trauma), comorbidities, Simplified Acute Physiology Score (SAPS) II at the time of ICU admission[18], and SOFA score at the time of diagnosis [19], type of intra-abdominal infection, microbial etiology and antimicrobial resistance profiles, intra-abdominal risk classification and source control evaluation seven days after diagnosis. We also retrieved information regarding ICU length of stay and mortality.

Definitions

The types of intra-abdominal infection were determined based on the International Sepsis Forum Consensus Conference Definitions [20]. Intra-abdominal infections were classified according to the AbSeS risk classification [8,21] which is based on (i) severity of disease expression, (ii) presence or absence of anatomical disruption and consequent localised or diffuse peritonitis, and (iii) setting of infection acquisition. Severity of disease expression is defined as infection, sepsis, or septic shock according to the Sepsis-3 criteria [22]. Intra-abdominal infections were classified as either without anatomical disruption, or with anatomical disruption resulting in either localized or diffuse peritonitis (i.e., contamination spread to entire abdominal cavity). Setting is community-acquired, healthcare-associated and/or early onset hospital-acquired (≤7 days of hospital admission), or late-onset hospital-acquired (>7 days of hospital admission). Healthcare-associated onset is defined by at least one of the following risk factors for MDR pathogens: nursing home resident, out-of-hospital parenteral, nutrition or vascular access, chronic dialysis, recent hospital admission (<6 months), or recent antimicrobial exposure (<6 months). For convenience sake, 'healthcare-associated and/or early-onset hospital-acquired' cases are designated 'early-onset hospital-acquired'. All cultures of intra-operative or trans-abdominal fine-needle aspiration samples, abdominal drains sampled less than 24 hours post-surgery and blood cultures related to the intra-abdominal infection were evaluated by the physicians reporting to AbSeS. Empiric antimicrobial therapy targeting Gram-positive, Gram-negative or anaerobic bacteria and fungi were recorded. Antimicrobial resistance patterns were reported and evaluated according to the EUCAST breakpoints [23]. MDR was defined as extended-spectrum beta-lactamase (ESBL) producing strain, carbapenem-resistance and fluoroquinolone-resistance for Gram-negative bacteria [24], and methicillin-resistance in *Staphylococcus aureus* (MRSA) or vancomycin-resistance in enterococci (VRE) for Gram-positive bacteria. Source control was evaluated at day 7. Failure of source control represented either the necessity of re-intervention following the initial approach (conservative management or source control intervention) or the presence of persistent inflammation reflecting

clinical evidence of a remaining source of infection.

Outcomes

Mortality was the primary outcome. More precisely we assessed the impact of age on mortality after adjustment for other potential risk factors for death. Mortality is defined as ICU mortality with a minimum of 28 days of observation for patients with an earlier discharge. Sample size calculation was not performed due to the study design.

Statistical analysis

Descriptive statistics included percentages as n (%) for categorical variables and median values with 25th to 75th percentiles (interquartile range, IQR) for continuous variables. Patients' baseline characteristics, implicated pathogens, antimicrobial resistance profiles and outcomes were compared among the four age groups. The Chi-square or Fisher exact tests were used for the comparison of categorical variables and analysis of variance (ANOVA) was used for comparison between quintiles. Logistic regression analysis with the logit link function was used to assess independent associations between single variables and mortality and results were reported as odds ratio (OR) with their 95% confidence intervals (CI). We sought a stable model based on both clinical and methodological reasoning and statistical results. All variables potentially related to the outcome sought were considered and those that fulfilled feature selection were included. Feature selection and final fit is done through a stepwise forward and backward approach, depending on the Akaike Information Criterion (AIC) value (dropping and adding variables that lead to the smallest AIC). Irrespective of their relationship with mortality in univariate analysis, the following variables were considered in the logistic regression model: age group, sex, setting of infection acquisition, anatomical disruption, severity of disease expression, SAPS II score, comorbidities (i.e., chronic pulmonary disease, chronic renal failure, neurologic disease, liver disease, myocardial infarction, congestive heart failure, peripheral vascular disease, diabetes, immunosuppression, malnutrition [body mass index <20], obesity

[body mass index >30]), source control achievement, empiric antimicrobial coverage, MDR, and length of ICU stay. We decided not to include SOFA score in the model as it strongly overlapped with the severity of disease classification used to define the phenotype of intra-abdomial infections. For the logistic regression model only cases with no missing values were considered. To rule out length time bias a sensitivity analysis was planned using 28-day mortality instead of the main outcome used throughout the study (i.e., ICU mortality with a minimum of 28 days of observation).

Survival curves for middle-aged, young-old, middle-old, and very-old critically ill patients with intra-abdominal infection were prepared by the Kaplan-Meier method. Cox proportional-hazards regression was used to adjust survival distributions for setting of infection acquisition, anatomical barrier disruption, severity of disease expression, comorbidities, and source control achievement. Patients were censored at 28 days. Adjusted relationships of older age categories with mortality were reported as hazard ratios and 95% CI relative to middle-aged patients (i.e. the reference category). Statistical analyses were performed with R software, version 3.2.2 (R Foundation for Statistical Computing) and SPSS Statistics version 28. All tests were 2-tailed and $p<0.05$ was considered statistically significant.

RESULTS

Characteristics of the patients

The present study included 2337 patients (Figure 1). Among these, 659 (28.2%) were middle-aged, 622 (26.6%) young-old, 667 (28.5%) middle-old and 389 (16.6%) very-old patients. Patient characteristics are presented in Table 1. Neurological disease, chronic renal failure, myocardial infarction, congestive heart failure and peripheral vascular disease were more frequently reported in very-old patients compared to the other groups. Chronic pulmonary disease, diabetes mellitus, liver related diseases, immunodeficiency, malignancy and obesity were more common in middle-aged patients. Very-old patients presented more commonly with community-acquired and early-onset hospital-acquired infection compared to other age groups. Conversely late-onset hospital-acquired infection was more frequent in young-old patients compared to other age groups. No difference was observed between the

age groups regarding SAPS II and SOFA scores, empiric antimicrobial therapy, anatomical barrier disruption or source control achievement, and length of ICU stay.

Supplement 1 shows the distribution of distinct types of intraabdominal infection over the age groups. Secondary peritonitis was the predominated infection without differences in prevalence across the age groups. The prevalence of biliary tract infection increased per age group, whereas intra-abdominal abscesses and pancreatic infections became less prevalent as age increased. No differences in empiric antimicrobial coverage were observed over the age groups (Table 2).

Microbiological findings

Cultures were sampled from 1776 patients (76%), with similar sampling rates in all study groups (p=0.789). No differences in culture results (Supplement 2) or in antimicrobial resistance patterns (Table 3) were observed between the four age groups. However, when all three older age groups were pooled, *Enterococcus faecium* was more frequently isolated from older adults compared with middle-aged patients (11.9% *vs*. 8.1%; p=0.019).

Mortality

The unadjusted mortality rates were higher in very-old (44.7%) compared to middle-old (32.1%), young-old (30.5%) and middle-aged (20.9%) patients (p<0.001). Similar results were observed when adjusted stepwise logistic regression was used (Table 4). Compared to middle-aged patients (reference group) mortality was significantly higher among young-old patients, middle-old patients, and very-old patients. Additional factors related to mortality were late-onset hospital-acquired intra-abdominal infection, diffuse peritonitis, sepsis or septic shock, failure of source control, liver disease, congestive heart failure, diabetes, and malnutrition. Executing the logistic regression by using 28-day mortality did not alter the results (Supplement 3). Figure 2 shows the survival curves for the distinct age groups as adjusted for independent risk factors for mortality. Compared with middle-aged patients, cumulative survival was significantly lower in all three older age categories. However, cumulative survival curves

for young-old and middle-old patients were very alike. Because of the overall high mortality in patients aged 80 years or more (45%), we tried to define specific phenotypes with a particular grim prognosis within this age group. This was done according to the *AbSeS* (abdominal sepsis) risk classification (Table 5). Among octogenarians mortality most often exceeds 50% in patients presenting with sepsis or septic shock and either localized or diffuse peritonitis.

DISCUSSION

This secondary analysis of the *AbSeS* cohort presented the comorbidities, severity of acute disease and infection characteristics of older adult critically ill patients intra-abdominal infections. Mortality was substantially higher among patients aged 60 years or older when compared with their middle-aged counterparts (40-59 years). Patients older than 80 years presented significantly higher mortality compared to younger patients. In very old patients (80 years or more) mortality appeared exceptionally high - up to 70% - among those presenting with either sepsis or septic shock and localized or either diffuse peritonitis. None of the identified risk factors for death are modifiable, and therefore this study cannot provide action targets to potentially improve survival. At the same line, the data presented illustrate the importance of timely organized patient- and family-centered care conferences as suggested by the Surviving Sepsis Campaign guidelines [25-27]. These meetings should promote awareness about sepsis and discuss realistic goals of care.

Similarly to our results, a large observational cohort of severely septic ICU and non-ICU patients in the USA, reported higher mortality among patients >85 years old compared to their general study population (38.4% *vs*. 28.6%)[28]. Dimopoulos et al. observed that age over 85 years among ICU patients with infection was an independent risk factor of mortality [6]. Likewise, Bagshaw et al. concluded that age ≥80 years, regardless of the ICU admission diagnosis, was associated with higher ICU and hospital mortality compared to younger patients [2]. Previous studies suggested that advanced age is a contributing factor for death in patients with secondary peritonitis as well as in critically patients with community-onset intra-abdominal infection [7,16]. Recently, Martin-Loeches at al.

reported that age over 80 years constitutes an independent risk factor for mortality in a large cohort of septic critically ill patients, of whom 35.6% had peritonitis as a primary site of infection [29].

In contrast to our results, Farmer et al. examined the correlation between age and outcome in patients with complicated intra-abdominal infections and found that advanced age (>65 years) as an individual risk factor was not associated with increased mortality risk [30]. While neither our study nor this study was powered for this outcome, our study included almost five times more patients. Also, the 65 years threshold may have led to a loss of age-related resolution. Furthermore, older patients in the Farmer cohort had a higher rate of colon or rectum infections which we did not observe (Supplement 1, upper *vs*. lower gastro-intestinal tract perforation in secondary peritonitis).

For sources of infection other than the abdomen, such as nosocomial bloodstream infection and ventilator-associated pneumonia (VAP), hospital mortality rates were amplified in older ICU patients and notably in the very-old age group [31,32]. Contrariwise, mortality was not different between older adults (>75 years) and younger ICU patients with invasive aspergillosis (73.6% vs. 72.0%, respectively)[33]. The absence of a difference in mortality can be explained by the very high baseline mortality in this particular cohort. Furthermore, in a cohort study of non-critically ill older adults, nosocomial bloodstream infection was not recognized as an independent risk factor for death (HR 1.3, 95% CI 0.6-2.6)[34]. One explanation could be that the impact of severe infectious complications on mortality might be attenuated in the extremes of disease severity. The proportion of infections with *E. coli* and enterococci was very high. The prevalence of infections caused by these pathogens has risen in the past decade, leading to concerns related to potential evolution of resistances [35,36]. With the exception of *E. faecium*, no substantial differences in microbial etiologies were observed between the age groups. In a cohort of older (≥75 years) ICU patients, Dupont et al. reported enterococcal involvement in intra-abdominal infections to be associated with greater morbidity and mortality but the present study could not confirm this association [37]. In the present analysis, MDR was not more common among the older adults and not associated with increased mortality. These findings contrast with the data by Blot et al. in a multicenter European prospective cohort of VAP episodes where the

risk of death was significantly higher in old (65-74 years) and very-old patients (≥75 years) and in patients with high-risk pathogens (i.e., methicillin-resistant *S. aureus, P. aeruginosa, A. baumannii*, or *S. maltophilia*)[32]. As reported earlier [8], one possible explanation is the equivocal sense of cultures sampled from peritonitis. Further investigation is needed to isolate the effect of MDR pathogens on the mortality risk in older ICU patients with intra-abdominal infections from modifiers and covariates.

Besides older age, we identified several factors that were related with increased mortality. These included phenotypic characteristics of the intra-abdominal infection such as setting of infection acquisition, anatomical disruption with diffuse peritonitis, and severity of disease expression. Furthermore, comorbidities and failure of source control were associated with an increased risk of death. In a previous study on older ICU patients with intra-abdominal candidiasis, inadequate source control at day 2 was shown to negatively affect survival [38]. In the present study, the rate of source control intervention was high across all age groups (>95%). It could be presumed that this high rate of source control interventions can – at least in part – be explained by the fact that this study cohort contains exclusively intensive care patients. ICU admission implies a certain preselection of patients with an anticipated chance of survival, encouraging immediate source control intervention if indicated.

The present study has several strengths: the inclusion of a large number of older adult ICU patients, the prospective and multinational design, the inclusion of both community- and hospital-acquired infections, and the investigation of a considerable number of predictors of mortality.

This study has also limitations. Variables potentially influencing the outcome could have been missed as data collection was not targeted specifically for this outcome (i.e., medications, treatment delays, specific frailty score). Also ‘do not reanimate’ resuscitate’ (DNR) data were not available. However, as DNR practices are neither valid universally, nor supported universally by national laws in the participating countries, including these in the data collection would have resulted in an inherent bias. Age classifications were arbitrarily chosen since no strict age definition for critically ill infected patients exists in the literature [6,32,33,38]. As the age >80 years is often considered a substantial risk factor of mortality, we adopted this threshold to define very-old age [29,39,40]. Furthermore, source

control evaluation was left at the discretion of local investigators in charge and not evaluated by an independent panel. Finally, we only were able to report ICU mortality or 28 days mortality. It is not unthinkable that with a larger window of observation mortality figures between the age groups would either further diverge or converge.

CONCLUSIONS

In this international cohort study, we demonstrated an important relationship between the older age and mortality in critically ill older adults with intra-abdominal infection or sepsis. Age above 60 and, and especially above 80 years, was associated with an increased risk of death. Comorbidities, anatomical disruption with diffuse peritonitis, sepsis or septic shock, and failure of source control were additional risk factors significantly related to mortality. As these risk factors for death are non-modifiable, the search for therapeutic targets possibly improving outcomes continues. In the meantime these data clearly stress the importance of care conferences to inform and discuss realistic goals of care with the family.

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Table 1 – Characteristics of critically ill patients with intra-abdominal infection according to age groups

Parameters	Middle-aged (n=659)	Young-old (n=622)	Middle-old (n=667)	Very-old (n=389)	P
Age (years)	52 (47–57)	65 (62–67)	74 (72–77)	84 (82–86)	<0.001
Sex (male)	369 (56.0)	385 (62.2)	385 (57.9)	200 (51.4)	0.007
ICU stay (days)	10 (4–20)	9 (4–18)	8 (4–16)	8 (4–17)	0.129
Underlying conditions					
Chronic pulmonary disease	58 (8.8)	102 (16.4)	119 (17.8)	45 (11.6)	<0.001
Malignancy	162 (24.6)	200 (32.2)	207 (31.0)	105 (27.0)	0.010
Neurologic disease	19 (2.9)	47 (7.6)	50 (7.5)	56 (14.4)	<0.001
Liver disease	42 (6.4)	46 (7.4)	19 (2.8)	6 (1.5)	<0.001
Chronic renal failure	43 (6.5)	64 (10.3)	89 (13.3)	75 (19.3)	<0.001
Myocardial infarction	21 (3.2)	42 (6.8)	73 (10.9)	47 (12.1)	<0.001
Congestive heart failure	16 (2.4)	33 (5.3)	73 (10.9)	55 (14.1)	<0.001
Peripheral vascular disease	20 (3.0)	49 (7.9)	60 (9.0)	39 (10.0)	<0.001
Diabetes mellitus	90 (13.7)	132 (21.2)	172 (25.8)	78 (20.1)	<0.001
Impaired immunity	88 (13.4)	71 (11.4)	55 (8.2)	16 (4.1)	<0.001
Malnutrition	50 (7.6)	38 (6.1)	31 (4.6)	32 (8.2)	0.067
Obesity	197 (29.9)	188 (30.2)	203 (30.4)	73 (18.8)	<0.001
Severity of acute illness					
SAPS II score*	48 (38–59)	50 (40–62)	49 (38–60)	48 (37–60)	0.258
SOFA score**	6 (3–9)	7 (3–10)	6 (3–10)	6 (3–9)	0.242
Intraabdominal infection risk classification					
Setting of infection acquisition					<0.001
Community-acquired	201 (30.5)	160 (25.7)	215 (32.2)	143 (36.8)	
Early-onset hospital-acquired	155 (23.5)	145 (23.3)	163 (24.4)	115 (29.6)	
Late-onset hospital-acquired	303 (46.0)	317 (51.0)	289 (43.3)	131 (33.7)	
Anatomical barrier disruption					0.942
No disruption	163 (24.7)	148 (23.8)	152 (22.8)	86 (22.1)	
Yes, with localized peritonitis	237 (36.0)	232 (37.3)	251 (37.6)	141 (36.2)	
Yes, with diffuse peritonitis	259 (39.3)	242 (38.9)	264 (39.6)	162 (41.6)	
Severity of disease expression					0.043

	Infection	36 (5.5)	48 (7.7)	33 (4.9)	21 (5.4)	
	Sepsis	422 (64.0)	363 (58.4)	382 (57.3)	237 (60.9)	
	Septic shock	201 (30.5)	211 (33.9)	252 (37.8)	131 (33.7)	
Source control intervention		588 (96.1)	554 (95.3)	604 (96.0)	352 (95.9)	0.920
Time to source control intervention***						0.783
<2 hours		230 (39.1)	240 (43.3)	263 (43.5)	148 (42.0)	
2 to 12 hours		246 (41.8)	217 (39.2)	248 (41.1)	144 (40.9)	
12 to 24 hours		52 (8.8)	46 (8.3)	42 (7.0)	34 (9.7)	
24 to 48 hours		24 (4.1)	21 (3.8)	16 (2.6)	10 (2.8)	
>48 hours		36 (6.1)	30 (5.4)	35 (5.8)	16 (4.5)	
Source control evaluation at day 7						0.218
	Success	380 (57.7)	343 (55.1)	363 (54.4)	205 (52.7)	
	Persistent inflammation	173 (26.3)	191 (30.7)	198 (29.7)	132 (33.9)	
	Source control intervention within 7 days required	106 (16.1)	88 (14.1)	106 (15.9)	52 (13.4)	
Mortality at 28 days		113 (17.1)	163 (26.2)	175 (26.2)	157 (40.4)	<0.001
ICU mortality with minimum of 28 days of observation		138 (20.9)	190 (30.5)	214 (32.1)	174 (44.7)	<0.001

Middle-aged: 40-59 years, Middle-old: 70-79 years, Young-old: 60-69 years, Very-old: ≥80 years
Values are presented as percentage (%) or interquartile range (1^{st} - 3^{rd} quartile)
*at the time of intensive care unit admission; **at the time of diagnosing intra-abdominal infection;
***calculated from time of diagnosis or suspicion of intra-abdominal infection;
NA, not applicable; PD, peritoneal dialysis; SAPS: Simplified Acute Physiology Score, SOFA: Sequential Organ Failure Assessment; VRE: vancomycin-resistant enterococci
MRSA: methicillin-resistant *Staphylococcus aureus*

Table 2 - Empiric antimicrobial coverage for intraabdominal infection according to age groups.

Empiric antimicrobial coverage*	**Middle-aged 40-59 yrs (n=659)**	**Young-old 60-69 yrs (n=622)**	**Middle-old 70-79 yrs (n=667)**	**Very-old ≥80 yrs (n=389)**	**P**
Basic schedule covering aerobic Gram-positive, Gram-negative, and anaerobic bacteria	584 (95.0)	541 (94.1)	589 (94.8)	325 (92.1)	0.252
Pseudomonas coverage	508 (82.7)	476 (82.8)	489 (80.7)	282 (80.6)	0.664
Enterococcal coverage (targeting *E. faecalis*)	462 (75.2)	426 (74.1)	450 (72.5)	253 (71.7)	0.571
VRE coverage	32 (5.2)	29 (5.0)	47 (7.6)	20 (5.7)	0.218
MRSA coverage	158 (25.7)	139 (24.2)	173 (27.9)	101 (28.6)	0.363
Candida coverage	105 (17.1)	100 (17.4)	121 (19.5)	56 (15.9)	0.497

**Data on empiric antimicrobial therapy was available in 2164 patients, i.e. 92.6% of the study cohort

Table 3 - Antimicrobial resistance profiles in older critically ill patients with intraabdominal infection according to age groups

		Middle-aged (n=508)	Young-old (n=472)	Middle-old (n=507)	Very-old (n=289)
Resistance in Gram-negative bacteria					
	ESBL	81 (15.9)	78 (16.5)	72 (14.2)	55 (19.0)
	Carbapenem-resistance	39 (7.7)	35 (7.4)	37 (7.3)	15 (5.2)
	Fluoroquinolone resistance	93 (18.3)	83 (17.4)	80 (15.8)	47 (16.3)
	Difficult-to-treat resistant*	28 (5.5)	21 (4.4)	16 (3.2)	11 (3.8)
Resistance in Gram-positive bacteria					
	MRSA	4 (0.8)	4 (0.8)	10 (2.0)	2 (0.7)
	VRE	8 (1.6)	16 (3.2)	16 (3.2)	7 (2.4)
Total antimicrobial resistance**		96 (18.9)	103 (21.8)	108 (21.3)	64 (22.1)

ESBL, extended-spectrum Beta-lactamase-producing Gram-negative bacteria; MRSA, methicillin-resistant Staphylococcus aureus; VRE, vancomycin-resistant enterococci

*Resistant to all beta-lactam antibiotics, carbapenems, and fluoroquinolone agents, **Patients with either ESBL-producing Gram-negative bacteria, carbapenem-resistant Gram-negative bacteria, MRSA or VRE

Middle-aged: 40-59 years, Middle-old: 70-79 years, Young-old: 60-69 years, Very-old: ≥80 years

Table 4 - Independent relationships with mortality in critically ill patients with intra-abdominal infection

Variables		**OR (95% CI)**
Age		
	Middle-aged (40-59 yrs)	Reference
	Young-old (60-69 yrs)	1.62 (1.21-2.17)
	Middle-old (70-79 yrs)	1.80 (1.35-2.42)
	Very-old (≥80 yrs)	3.69 (2.67-5.12)
Setting of infection acquisition		
	Community-acquired infection	Reference
	Early-onset hospital-acquired infection (≤7 days)	1.10 (0.82-1.47)
	Late-onset hospital-acquired infection (>7 days)	1.65 (1.28-2.12)
Anatomical disruption		
	No anatomical barrier disruption	Reference
	Anatomical disruption with localized peritonitis	1.23 (0.93-1.64)
	Anatomical disruption with diffuse peritonitis	1.77 (1.35-2.32)
Severity of disease expression		
	Infection	Reference
	Sepsis	2.17 (1.28-3.87)
	Septic shock	4.03 (2.36-7.24)
Underlying conditions		
	Liver disease	2.07 (1.31-3.26)
	Congestive heart failure	2.01 (1.38-2.94)
	Diabetes mellitus	1.44 (1.12-1.86)
	Malnutrition	2.09 (1.40-3.11)
Empiric antimicrobial therapy with coverage of MRSA		0.74 (0.58-0.94)
Source control achievement at day 7		

	Success	Reference
	Failure, persistent signs of inflammation	5.20 (4.14-6.54)
	Failure, additional intervention required following initial approach	2.02 (1.49-2.71)

Only cases without missing values were considered for the logistic regression model; 181 cases were excluded from the analysis. As such the reported model is based on 2156 patients (overall, no variable in the database had more than 5% missing values).

OR: odds ratio, 95% CI: 95% confidence interval, yrs: years, MRSA: methicillin-resistant *Staphylococcus aureus*

Table 5 – Mortality among very old ICU patients (≥80 years) with intra-abdominal infection according to the *AbSeS* (abdominal sepsis) risk classification.

		Setting of infection acquisition								
		Community-acquired			**Early-onset hospital-acquired**			**Late-onset hospital-acquired**		
Severity of disease	**Septic shock**	5/14 **35.7%**	8/12 **66.7%**	14/20 **70.0%**	2/9 **22.2%**	2/11 **18.2%**	9/17 **52.9%**	0/8 **0%**	9/13 **69.2%**	15/27 **55.6%**
	Sepsis	5/19 **26.3%**	12/36 **33.3%**	21/35 **60.0%**	7/14 **50.0%**	10/32 **31.3%**	13/26 **50.0%**	3/17 **17.6%**	14/29 **48.3%**	19/29 **65.5%**
	Infection	0/2 **0%**	0/1 **0%**	2/4 **50.0%**	0/1 **0%**	0/2 **0%**	1/3 **33.3%**	1/2 **50.0%**	2/5 **40.0%**	0/1 **0%**
		No	Yes, with localized peritonitis	Yes, with diffuse peritonitis	No	Yes, with localized peritonitis	Yes, with diffuse peritonitis	No	Yes, with localized peritonitis	Yes, with diffuse peritonitis
		Anatomical disruption			**Anatomical disruption**			**Anatomical disruption**		

Figure 1 – Patient selection flowchart

Figure 2: Survival curves for middle-aged, young-old, middle-old, and very-old critically ill patients with intra-abdominal infection

Figure 2 - Legend

Grey dashed line represents middle-aged patients; grey solid line represents young-old patients; black dashed line represents middle-old patients; black solid line represents very-old patients. Survival curves are generated by Cox regression and are adjusted for the intra-abdominal risk classification (i.e., setting of infection acquisition, anatomical barrier disruption, and severity of disease expression), comorbidities (i.e., liver disease, congestive heart failure, diabetes, and malnutrition), and source control achievement.

Hazard ratios (HR) and 95% confidence intervals (CI) relative to middle-aged patients (i.e. the reference category) are reported for older age categories: HR 1.39, 95% CI 1.11-1.73 for young-old patients ($p=0.004$); HR 1.53, 95% CI 1.23-1.90 for middle-old patients ($p<0.001$), and HR 2.27, 95% CI 1.80-2.86 for very-old patients ($p<0.001$).