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ORIGINAL

Poor timing and failure of source control are risk factors for mortality in critically ill patients with secondary peritonitis

Gennaro De Pascale[1,2], Massimo Antonelli[1,2], Mieke Deschepper[3], Kostoula Arvaniti[4], Koen Blot[5,6], Ben Creagh Brown[7,8], Dylan de Lange[9], Jan De Waele[5,10], Yalim Dikmen[11], George Dimopoulos[12], Christian Eckmann[13], Guy Francois[14], Massimo Girardis[15], Despoina Koulenti[16,17], Sonia Labeau[5,18], Jeffrey Lipman[19,20], Fernando Lipovetsky[21], Emilio Maseda[22], Philippe Montravers[23,24], Adam Mikstacki[25,26], José-Artur Paiva[27], Cecilia Pereyra[28], Jordi Rello[20,29], Jean-Francois Timsit[30,31], Dirk Vogelaers[5,32] and Stijn Blot[5,16*] on behalf of the Abdominal Sepsis Study (AbSeS) group and the Trials Group of the European Society of Intensive Care Medicine

Abstract

Purpose: To describe data on epidemiology, microbiology, clinical characteristics and outcome of adult patients admitted in the intensive care unit (ICU) with secondary peritonitis, with special emphasis on antimicrobial therapy and source control.

Methods: Post hoc analysis of a multicenter observational study (Abdominal Sepsis Study, AbSeS) including 2621 adult ICU patients with intra-abdominal infection in 306 ICUs from 42 countries. Time-till-source control intervention was calculated as from time of diagnosis and classified into 'emergency' (< 2 h), 'urgent' (2–6 h), and 'delayed' (> 6 h). Relationships were assessed by logistic regression analysis and reported as odds ratios (OR) and 95% confidence interval (CI).

Results: The cohort included 1077 cases of microbiologically confirmed secondary peritonitis. Mortality was 29.7%. The rate of appropriate empiric therapy showed no difference between survivors and non-survivors (66.4% vs. 61.3%, $p = 0.1$). A stepwise increase in mortality was observed with increasing Sequential Organ Failure Assessment (SOFA) scores (19.6% for a value ≤ 4–55.4% for a value > 12, $p < 0.001$). The highest odds of death were associated with septic shock (OR 3.08 [1.42–7.00]), late-onset hospital-acquired peritonitis (OR 1.71 [1.16–2.52]) and failed source control evidenced by persistent inflammation at day 7 (OR 5.71 [3.99–8.18]). Compared with 'emergency' source control

*Correspondence: stijn.blot@UGent.be
[5] Department of Internal Medicine and Pediatrics, Ghent University, Campus UZ Gent, Corneel Heymanslaan 10, 9000 Ghent, Belgium
Full author information is available at the end of the article

The AbSeS collaborators are mentioned in the acknowledgment section.

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intervention (< 2 h of diagnosis), 'urgent' source control was the only modifiable covariate associated with lower odds of mortality (OR 0.50 [0.34–0.73]).

Conclusion: 'Urgent' and successful source control was associated with improved odds of survival. Appropriateness of empirical antimicrobial treatment did not significantly affect survival suggesting that source control is more determinative for outcome.

Keywords: Intra-abdominal infection, Secondary peritonitis, Source control, Mortality, Antimicrobial therapy

Introduction

Despite worldwide diffusion and implementation of international guidelines for the management of sepsis and septic shock, morbidity and mortality of severe intra-abdominal infections (IAI) remain high, along with many unavailable answers [1–3]. Peritonitis following anatomical disruption of gastro-intestinal tract is commonly called 'secondary', acquiring the definition of 'complicated' when the infections extends from the primary source to peritoneal cavity [4, 5]. Although secondary peritonitis represents the most frequent clinical picture in patients admitted in the intensive care unit (ICU) with complicated IAI, the right timing of source control, the role of empirical antimicrobial coverage and the clinical impact of antimicrobial resistant microorganisms are still a matter of debate [6, 7]. However, the recent multicenter AbSeS study, including 2621 patients with complicated IAI and sepsis, showed that, regardless the type of IAI, ICU mortality was strongly influenced by the nosocomial setting of acquisition, the presence of anatomical disruption and the occurrence of septic shock [8].

Source control certainly represents a key element in the management of secondary peritonitis, since, also before the antibiotic era, many patients with peritonitis were rescued only by surgical intervention [9, 10]. Depending on peritonitis-related characteristics, surgical source control may be particularly challenging and so far, there is no clear-cut way for evaluating the success of source control. While it seems evident that source control is achieved as soon as possible, executing a major surgical procedure in a clinically unstable patient may be a risk as well.

The importance of source control is not only an issue in bacterial peritonitis, but also in fungal infections. Two large multicenter cohort studies patients with uncontrolled intra-abdominal candidiasis showed a huge mortality rate, ranging between 60 and 90%, irrespective of administration of an adequate antifungal infection [11, 12].

Along with prompt control of the infection source, in critically ill patients with bacterial peritonitis, adequate empirical antibiotics are strongly recommended [13]. In two cohort studies involving more than 400 septic patients with complicated IAI, polymicrobial infections due to antimicrobial resistant bacteria mostly received inappropriate empirical therapy, leading to increased mortality [14, 15]. The optimal scheme and administration time is far from clearly established. In a post hoc analysis of a randomized clinical trial, Montravers and colleagues reported empiric antimicrobial therapy with piperacillin–tazobactam to be associated with more overall post-operative clinical failure, despite the exclusion of cases with empiric antimicrobial therapy not covering all organisms cultured from blood and surgical samples [16].

Take-home message

This multinational study including data from microbiologically documented secondary peritonitis showed that moderately postponed (2–6 h) and successful source control significantly predicted survival in the intensive care unit. Appropriate empirical antimicrobial treatment did not reduce mortality which was strongly increased by acquiring infection in the hospital setting, presence of diffuse peritoneal inflammation, and septic shock.

In light of these considerations, the primary objective of this study was to assess the relationship of timing of source control and appropriateness of empiric antimicrobial therapy with mortality in critically ill patients with secondary peritonitis. The secondary objective of this study is to describe the epidemiological, clinical, and microbiological profile of secondary peritonitis in the intensive care context.

Methods

Data recorded and definitions

We performed a secondary analysis of the data on secondary peritonitis from the 'AbSeS' multinational, observational study [8]. This cohort included critically ill adult patients with IAI from 309 ICUs and 42 countries between January and December 2016. Approval by established national, regional, or local Institutional Review Boards was expedited and granted. The study is registered at ClinicalTrials.gov (number NCT03270345). Protocols and procedures for the patients' inclusion criteria, definitions, methods and collection of data have been previously reported

[8]. Secondary peritonitis is defined according to the International Sepsis Forum Consensus Conference Definitions and only cases with gastro-intestinal tract perforation are considered. Cases were explored according to AbSeS-classification, i.e., setting of infection acquisition, anatomical barrier disruption, and severity of disease expression [17]. Secondary peritonitis could be either localized or diffuse peritonitis (i.e., contamination spread to entire abdominal cavity) [18]. Severity of disease expression is defined as either infection, sepsis, or septic shock [19]. Eligible cultures included intra-operative cultures, trans-abdominal fine-needle aspiration, blood cultures presumably related to the IAI, and cultures from abdominal drains sampled ≤ 24 h post surgery. Thresholds for resistance were those as reported by The European Committee on Antimicrobial Susceptibility Testing (EUCAST) [20]. Antimicrobial resistance was defined as methicillin-resistance for *Staphylococcus aureus*, vancomycin-resistance for enterococci, and for Gram-negative bacteria either production of extended-spectrum beta-lactamase (ESBL), carbapenem-resistance, or fluoroquinolone-resistance (resistance against ciprofloxacin, levofloxacin, or moxifloxacin). To assess relationships between resistance and mortality, we also used the definition of "difficult-to-treat" resistance for Gram-negative bacteria. This combines resistance to all tested carbapenem, beta-lactam, and fluoroquinolone agents, and is associated with worse clinical outcomes in bloodstream infection [21, 22]. Appropriate empiric antimicrobial therapy was defined as the administration of at least one drug with in vitro and clinical activity against the isolated pathogens and initiated within the first 24 h of peritonitis diagnosis. Antimicrobial regimens that did not cover basic Gram-positive, Gram-negative, and anaerobic bacteria were as per definition considered inappropriate. Timing of source control intervention was defined as 'emergency' (i.e., < 2 h of peritonitis diagnosis), 'urgent' (between 2 and 6 h), or 'delayed' (> 6 h) and based on simple explorative data (ESM-1). Success of source control was assessed 7 days post diagnosis or earlier if the patient died within that time window. Source control failure represented either persistent inflammation (clinical evidence of a remaining source of infection) or the necessity of re-intervention following the initial approach (conservative management or source control intervention) [8]. Main outcome is ICU mortality with a minimum of 28 days of observation.

Data management and statistical analysis

Missing, extreme or implausible values were sent back to the study-ICU investigators for review. Where data remained questionable, the senior author (SB) made a final adjudication about study inclusion in agreement with the co-headinvestigator (DV). Essential data needed to keep cases in the AbSeS database included type of IAI, onset of infection, data on anatomical disruption, severity of disease expression, and microbiology or mortality. For the present secondary analysis, the availability of data on microbiology, empiric therapy, and mortality were all required. For all other variables, missing values were not imputed. Simple descriptive statistics were used to characterize the study population, continuous data were summarized by median and interquartile range (IQR), categorical data as *n* (%). To assess relationships with mortality, we used a logistic regression analysis with the logit link function. Variables considered for the logistic regression model included origin of infection acquisition, diffuse peritonitis, severity of disease expression, timing of source control intervention, source control achievement at day 7, antimicrobial resistance, *Candida* involvement, enterococcal involvement, appropriateness of empiric antimicrobial therapy, age, sex, underlying conditions, length of ICU stay, and geographic region. These variables were included irrespective of their relationship with mortality in univariate analysis. 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 covariates that leads to the smallest AIC). As observational studies are susceptible for potential uncontrolled confounding, we calculated the E-value for our logistic regression model using the VanderWeele & Ding approach (ESM-2) [23]. Results of the logistic regression analyses are reported as odds ratio (OR) and 95% confidence intervals (CI). The Kaplan–Meier method was used for unadjusted survival analyses according to timing of source control intervention and source control outcomes at day 7.

Results

General characteristics

The AbSeS cohort contained 1794 patients with secondary peritonitis. Cases were excluded for missing data on microbiology ($n = 671$), antimicrobial therapy ($n = 140$), and mortality ($n = 24$). The final analysis included 1077 patients (Fig. 1).

Characteristics of the study cohort are in Table 1. Most infections were late-onset hospital-acquired. Half of the cases had diffuse peritonitis and nearly all patients presented with sepsis or septic shock. Malignancy, obesity, and diabetes were the most common comorbidities.

Data on source control are reported in Table 2. Most patients underwent infection source control within the first 6 h with 55% within the first 2 h of peritonitis

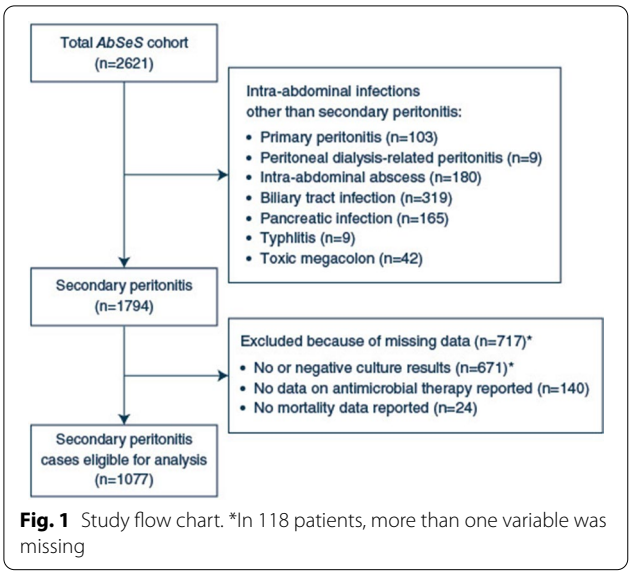

Fig. 1 Study flow chart. *In 118 patients, more than one variable was missing

diagnosis (i.e., the time of diagnosis/clinical suspicion prompting intervention).

Drainage, either surgically or percutaneously, was the initial source control approach in 95% of patients. At Day 7, in 60% of the cases, source control was successful, requiring a second intervention in 109 patients, mainly due to anatomic leakage (Table 2).

Microbiology

Data on microbiology are reported in Table 3. A total of 1643 microorganisms have been isolated from 1077 patients. The majority were Gram-negative bacteria (48.5%), followed by Gram-positive bacteria (32.6%), anaerobic bacteria (9.2%) and yeasts (9.8%). Interestingly, inappropriate empiric antimicrobial therapy was associated with the isolation of *Klebsiella* spp. and non-fermentative rods (*Pseudomonas*, *Stenotrophomonas and Acinetobacter*) enterococci (either *E. faecium* or *E. faecalis*) and *Candida* spp. Finally, inappropriate empirical therapy was more frequently observed in case of antimicrobial resistance involvement.

Mortality

Mortality was 29.7% (Table 1). Non-survivors were older and were more likely to have comorbidities. Regarding IAI characteristics, non-survivors had more frequently a late-onset infection, diffuse peritonitis and septic shock. There were no differences between survivors and non-survivors in rate of multidrug resistance involvement, rate of appropriate empiric therapy, and Simplified Acute Physiology Score (SAPS) II scores. However, mortality increased with increasing Sequential Organ Failure Assessment (SOFA) scores ($p < 0.001$; ESM-3).

In terms of source control, basic patient characteristics regarding timing of source control are reported in ESM-4. Patients undergoing 'emergency' intervention (< 2 h from peritonitis diagnosis) showed a higher mortality compared with 'urgent' source control procedures (2–6 h) (Table 2). Therefore, we compared pre-source control intervention characteristics of patients receiving 'emergency' source control (< 2 h of presentation, $n = 454$) and patients with 'urgent' source control (between 2 and 6 h, n = 340). No difference between the groups was observed in terms of: serum lactate [2.5 mml/L (IQR: 1.6–4.2) vs. 2.6 mmol/L (IQR: 1.6–4.2); $p = 0.972$], pH [7.32 (IQR: 7.25–7.40) vs. 7.34 (IQR: 7.27–7.40); $p = 0.409$], C-reactive protein [142 mg/L (IQR: 26–259) vs. 174 (IQR: 48–269); $p = 0.092$], necessity for mechanical ventilation (73.3% vs. 75.0%; $p = 0.587$), and SAPS 2 scores [50 (IQR: 38–62) vs. 48 (IQR: 39–58); $p = 0.252$]. Shock (29.7% vs. 42.4%; $p < 0.001$) and leucocytosis (29.7% vs. 40.3%; $p = 0.005$) were more common among patients undergoing 'urgent' source control. Therefore, we executed sensitivity analyses on patients with 'emergency' and 'urgent' source control intervention, stratified for presence/absence of septic shock and leucocytosis; this did not alter the observation (ESM-5). Figure 2a illustrates unadjusted survival curves according to timing of source control intervention. Absolute mortality rates for 'emergency' and 'delayed' intervention were 35.9% and 28.6%, respectively, while mortality for patients receiving moderately postponed source control intervention was 23.6%. Successful source control at 7 days was more common among survivors (Table 2). Figure 2b illustrates unadjusted survival curves, according to source control achievement at day 7. Absolute mortality rates for the three groups were 18.7% for successful source control, 25.2% for source control requiring revision, and 55.7% for persistent inflammation: the latter performing the worst, even despite an assumed technically successful source control intervention.

Logistic regression analysis identified late-onset infections, diffuse peritonitis, persisting signs of inflammation, septic shock and underlying conditions (liver failure and malnutrition) as independent risk factors for death (Table 4). For this model, the associated E-value was 1.74 (lower limit 95% CI, 1.62) (ESM-2). Initiation of appropriate empirical antimicrobials was not associated with a significant reduced risk of ICU mortality (OR 0.78, 95% CI, 0.55–1.09). The impact of appropriateness of antimicrobial therapy on mortality was also not different according to source control outcomes (ESM-6). Conversely, the only modifiable condition associated with improved survival was a source control intervention performed between 2 and 6 h from peritonitis diagnosis (OR 0.50, 95% CI 0.34–0.73).

Table 1 Characteristics of critically ill patients with secondary peritonitis according to survival status

Variable	All patients ($n=1077$)	Survivors ($n=757$)	Non-survivors ($n=320$)	p value
Age, years	67 (55–75)	64 (52–73)	73 (64–80)	< 0.001
Sex, male	599 (55.6)	416 (55)	183 (57.4)	0.480
SAPS II score at ICU admission	49 (39–60)	49 (39–60)	48 (36–60)	0.405
Generic characteristics of the intra-abdominal infection				
Setting of infection acquisition				< 0.001
Community-acquired	371 (34.4)	278 (36.7)	93 (29.1)	
Healthcare-associated or early-onset hospital-acquired	259 (24)	196 (25.9)	63 (19.7)	
Late-onset hospital-acquired	447 (41.5)	283 (37.4)	164 (51.2)	
Anatomical barrier disruption				
No disruption	0	0	0	0.004
Disruption with localized peritonitis	529 (49.1)	397 (52.3)	133 (41.6)	
Disruption with diffuse peritonitis	547 (50.8)	360 (47.6)	187 (58.4)	
Severity of disease expression				
Infection without sepsis	74 (6.9)	62 (8.2)	12 (3.8)	< 0.001
Sepsis	687 (63.8)	507 (67)	180 (56.3)	
Septic shock	316 (29.3)	188 (24.8)	128 (40)	
Upper or lower GI-tract perforation[a]				0.095
Upper	233 (21.6)	154 (20.3)	79 (24.7)	
Lower	693 (64.3)	498 (65.8)	195 (60.9)	
Underlying conditions				
Chronic pulmonary disease	137 (12.9)	84 (11.1)	53 (16.6)	0.014
Malignancy	326 (30.3)	208 (27.5)	118 (36.9)	0.002
Neurologic disease	64 (5.9)	32 (4.2)	32 (10)	< 0.001
Liver disease	40 (3.7)	20 (2.6)	20 (6.3)	0.004
Congestive heart failure	25 (2.3)	29 (3.8)	34 (10.6)	< 0.001
Peripheral vascular disease	60 (6.6)	37 (4.9)	23 (7.2)	0.133
Diabetes mellitus	166 (15.4)	98 (12.9)	68 (21.3)	0.001
Immunosuppressed status	120 (11.1)	87 (11.5)	33 (10.3)	0.574
Malnutrition (body mass index < 20)	72 (6.7)	41 (5.4)	31 (9.7)	0.010
Obesity (body mass index ≥ 30)	299 (27.7)	226 (29.9)	73 (22.8)	0.018
Multidrug antimicrobial resistance (with high-level resistance for Gram-negative bacteria)[b]	109 (10.1)	75 (9.9)	34 (10.6)	0.721
Appropriate empiric antimicrobial therapy	699 (64.9)	503 (66.4)	196 (61.3)	0.102
Additional infections complicating the course				
Pneumonia	164 (15.2)	124 (16.4)	40 (12.5)	0.105
Community-acquired	24 (2.2)	13 (1.7)	11 (3.4)	
Healthcare-associated	61 (5.7)	47 (6.2)	14 (4.4)	
Ventilator-associated	79 (7.3)	64 (8.5)	15 (4.7)	
Bloodstream infection	81 (7.5)	55 (7.3)	26 (8.1)	0.625
Pyelonephritis	51 (4.7)	39 (5.2)	12 (3.8)	0.322
Central nervous infection	3 (0.3)	2 (0.3)	1 (0.3)	NA
Surgical site infection	81 (7.5)	56 (7.4)	25 (7.8)	0.813
Osteomyelitis	1 (0.1)	0	1 (0.3)	NA
Other	96 (8.9)	68 (9)	28 (8.8)	0.902

Applying Bonferroni correction, the threshold for statistical significance was $p < 0.00208$, implying a family-wise error rate of 0.049

[a] Not reported, $n=151$

[b] Defined as either methicillin-resistance for *Staphylococcus aureus*, vancomycin-resistance for enterococci, Difficult-To-Treat Gram-negative bacteria (i.e., resistance to all carbapenems, all beta-lactams, and all fluoroquinolones), and fluconazole resistance for *Candida* spp.

Table 2 Source control interventions and achievements

Variable	Survivors (n = 757)	Non-survivors (n = 320)	*p* value
Time-till-source control intervention[a]			< 0.001
'Emergency' (< 2 h)	291 (42.3)	163 (56)	
'Urgent' (2–6 h)	265 (38.5)	75 (25.8)	
'Delayed' (> 6 h)	132 (19.2)	53 (18.2)	
Initial source control approach (combinations possible)[b]			
Drainage	664 (95.8)	282 (94.9)	0.545
Surgical drainage	636	271	
Peritoneal lavage	207	78	
Percutaneous drains	142	60	
Debridement of necrosis	131	50	
Decompressive surgery	49 (7.3)	16 (5.7)	0.395
Restoration of anatomy & function	199 (29.5)	94 (33.7)	0.200
Source control achievement at day 7			< 0.001
Successful	522 (69)	120 (37.5)	
Failure, persistent inflammation	131 (17.3)	165 (51.6)	
Failure, additional intervention required ≤ 7 days	104 (13.7)	35 (10.9)	
Reasons for additional intervention			
Anastomotic leakage	56 (7.4)	18 (5.6)	0.293
Obstruction	8 (1.1)	1 (0.3)	NA
Abdominal compartment syndrome	5 (0.7)	4 (1.3)	NA
Bleeding	4 (0.5)	2 (0.6)	NA
Ischemia	9 (1.2)	3 (0.9)	NA
Abscess formation	6 (0.8)	2 (0.6)	NA
Explorative laparotomy for persistent inflammation	8 (1.1)	3 (0.9)	NA
Other	9 (1.2)	3 (0.9)	NA

NA not applicable

[a] $n = 98$

[b] $n = 87$

Discussion

In this large cohort of critically ill patients with secondary peritonitis, we confirmed that the new *AbSeS*-classification, based on setting of acquisition, presence of anatomical disruption and severity of disease, strongly correlated with ICU mortality. 'Emergency' (< 2 h) and 'delayed' (> 6 h) source control was associated with worse clinical outcomes compared with an 'urgent' (2–6 h) surgical approach, especially when a clinical picture of peritonitis with persistent inflammation was still present at day 7.

Secondary peritonitis represents the most frequent form of IAI affecting ICU patients. It is often complicated by generalized peritoneal inflammation and abscess formation due to extensive anatomical barriers disruption. If source control is not successfully achieved, inducing chronic serositis and colonization with difficult-to-treat microorganisms, it is called 'tertiary' [24, 25]. These definitions, mostly used in clinical trials, may be misleading, due to the overlapping of different clinical and prognostic features regarding anatomical barrier disruption, clinical severity and risk profile for multidrug-resistant pathogens [17, 26]. In the seminal AbSeS manuscript, a new classification focused on the setting of acquisition (community/healthcare/nosocomial), loss of anatomical integrity with either localized or diffuse peritonitis and severity of disease expression (infection, sepsis, septic shock), allowed to identify diseases-specific phenotypes which strongly correlated with ICU mortality [8]. Also, the data from this very large, selected, critically ill population with secondary peritonitis due to different intra-abdominal diseases (i.e., perforation, rather than diverticulitis or pancreatitis), highlight the detrimental importance to correctly classify a specific disease phenotype with the aim at stratifying the need of urgent and aggressive medical and surgical treatments. Patients with late-onset hospital-acquired infections, diffuse peritonitis due to loss of anatomical integrity and in septic shock (similarly with higher SOFA score values) presented the highest risk of mortality and needed prompt ICU

Table 3 Micro-organisms isolated from cultures sampled in critically ill patients with secondary peritonitis

Micro-organism	Inappropriate empiric antimicrobial therapy ($n=378$)	Appropriate empiric antimicrobial therapy ($n=699$)	p value
Gram-negative bacteria	279 (73.8)	517 (74)	0.956
Enterobacterales	230 (60.8)	469 (67.1)	0.040
Citrobacter spp.	2 (0.5)	8 (1.1)	0.508
Citrobacter freundii	4 (1.1)	11 (1.6)	0.594
Escherichia coli	146 (38.6)	49.9 (49.9)	< 0.001
Enterobacter aerogenes	7 (1.9)	18 (2.6)	0.452
Enterobacter cloacae	14 (3.7)	33 (4.7)	0.435
Hafnia alvei	2 (0.5)	3 (0.4)	0.999
Morganella morganii	6 (1.6)	10 (1.4)	0.839
Klebsiella spp.	26 (6.9)	14 (2)	< 0.001
Klebsiella oxytoca	12 (3.2)	20 (2.9)	0.773
Klebsiella pneumoniae	60 (15.9)	71 (10.2)	0.006
Proteus spp.	2 (0.5)	12 (1.7)	0.101
Proteus mirabilis	17 (4.5)	27 (3.9)	0.616
Providencia spp.	0	2 (0.3)	NA
Salmonella enterica	2 (0.5)	2 (0.3)	0.616
Serratia marcescens	4 (1.1)	1 (0.1)	0.054
Enterobacterales, other	6 (1.6)	7 (1)	0.401
Non-fermenting bacteria	94 (24.9)	73 (10.4)	< 0.001
Pseudomonas aeruginosa	50 (13.2)	46 (6.6)	< 0.001
Pseudomonas spp. (other or NI)	9 (2.4)	2 (0.3)	0.002
Stenotrophomonas maltophilia	6 (1.6)	1 (0.1)	0.009
Acinetobacter baumannii	28 (7.4)	13 (1.9)	< 0.001
Acinetobacter spp. (other or NI)	14 (3.7)	14 (2)	0.109
Other Gram-negative bacteria			
Haemophilus influenzae	2 (0.5)	1 (0.1)	0.283
Gram-positive bacteria	216 (57.1)	319 (45.6)	< 0.001
Staphylococci	45 (11.9)	90 (12.9)	0.700
Staphylococcus aureus	13 (3.4)	27 (3.9)	0.866
Coagulase-negative staphylococci	25 (6.6)	49 (7)	0.900
Staphylococcus spp. (other or NI)	10 (2.6)	15 (2.1)	0.603
Enterococci	167 (44.2)	184 (26.3)	< 0.001
Enterococcus faecalis	76 (20.1)	93 (13.3)	0.003
Enterococcus faecium	75 (19.8)	75 (10.7)	< 0.001
Enterococcus spp. (other or NI)	32 (8.5)	26 (3.7)	0.001
Other Gram-positive bacteria			
Streptococcus Group A, B, C, G	18 (4.8)	60 (8.6)	0.021
Streptococcus pneumonia	4 (1.1)	1 (0.1)	0.054
Streptococcus viridans	6 (1.6)	19 (2.7)	0.239
Corynebacterium	1 (0.3)	4 (0.6)	0.478
Anaerobe bacteria[a]	45 (11.9)	106 (15.2)	0.141
Candida spp.	118 (31.2)	43 (6.2)	< 0.001
Specific resistance patterns			
ESBL-producing Gram-negative bacteria	148 (39.2)	86 (12.3)	< 0.001
Fluoroquinolone-resistant Gram-negative bacteria	133 (35.2)	108 (15.5)	< 0.001
Carbapenem-resistant Gram-negative bacteria	81 (21.4)	19 (2.7)	< 0.001
Difficult-to-Treat Gram-negative bacteria[b]	49 (13)	12 (1.7)	< 0.001
Methicillin-resistant *Staphylococcus aureus*	6 (1.6)	9 (1.3)	0.689
Vancomycin-resistant enterococci	35 (9.3)	5 (0.7)	< 0.001
Fluconazole-resistant/dose-dependent *Candida* spp.	10 (2.6)	2 (0.3)	< 0.001

Table 3 (continued)

Table reports *n* patients positive (% of total number of patients with cultures sampled)

ESBL extended-spectrum beta-lactamase

[a] No differences in species level detected (data not shown)

[b] Combines resistance to all beta-lactam antibiotics, all carbapenems, and all fluoroquinolones

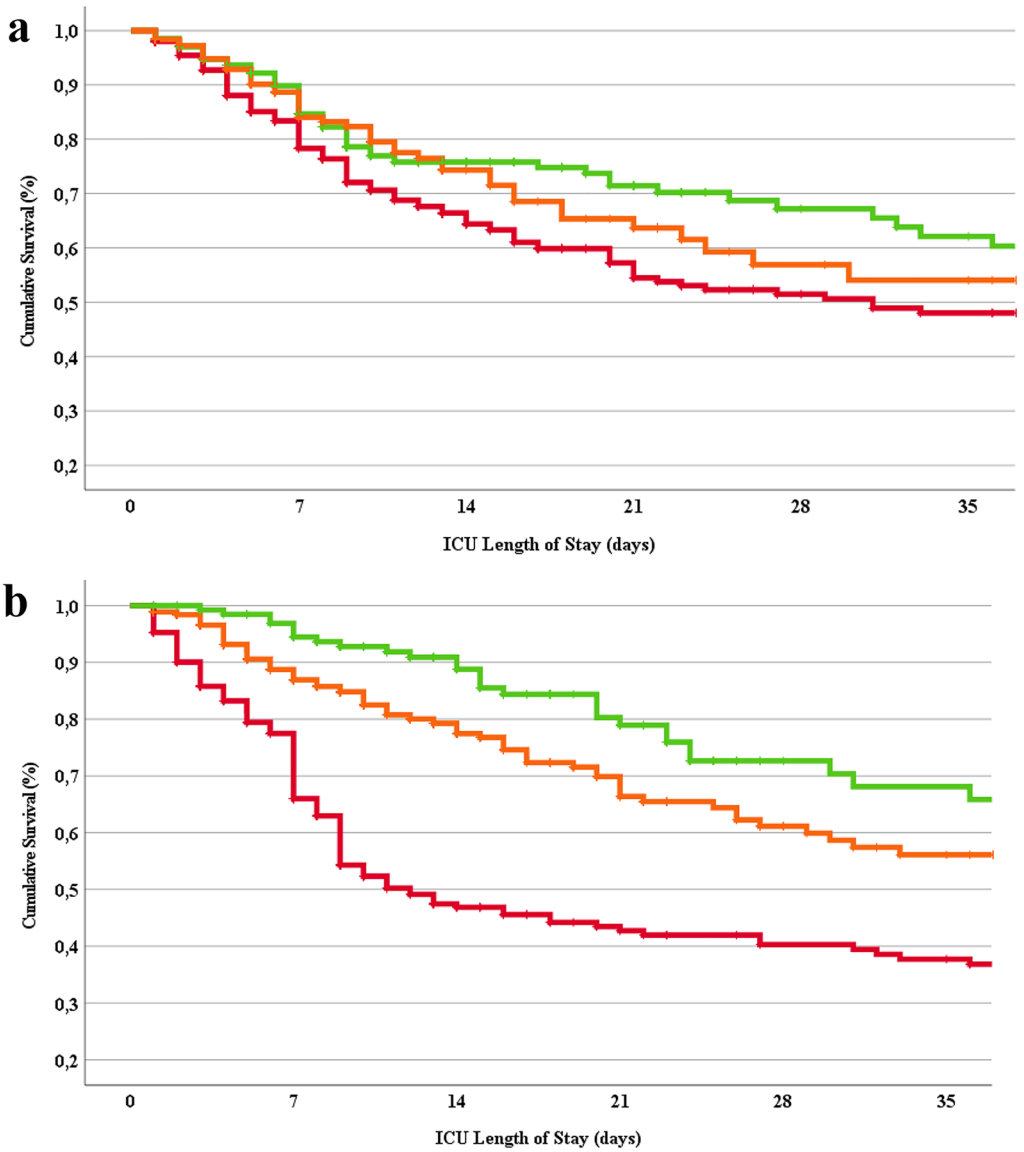

Fig. 2 Survival curves according to timing of source control intervention (**a**) and source control outcomes at day 7 (**b**). **a** Green curve represents cases with 'urgent' source control intervention (between 2 and 6 h); orange curve represents cases with 'delayed' source control intervention (> 6 h); red curve represents cases with 'emergency' source control intervention (< 2 h); log-rank test: $p = 0.005$. **b** Green curve represents cases with successful source control; orange curve represents cases requiring additional source control intervention; red curve represents cases with persistent inflammation; log-rank test: $p < 0.001$

admission, radiological diagnostic assessment and surgical consultation. Indeed, these results reinforce the usefulness of this new classification system for the design of more balanced and unbiased, future randomized trials in this field.

Almost all patients with secondary peritonitis were initially approached with source control, either surgically

Table 4 Adjusted relationships with mortality in critically ill patients with secondary peritonitis

Variable	Odds ratio (95% confidence interval)
Age (per year increase)	1.05 (1.04–1.06)
Setting of infection acquisition	
Community-acquired infection	Reference
Early-onset hospital-acquired infection (≤ 7 days)	0.74 (0.46–1.19)
Late-onset hospital-acquired infection (> 7 days)	1.71 (1.16–2.52)
Anatomical disruption	
Anatomical disruption with localized peritonitis	Reference
Anatomical disruption with diffuse peritonitis	1.34 (0.96–1.87)
Severity of disease expression	
Infection	Reference
Sepsis	1.61 (0.76–3.42)
Septic shock	3.08 (1.42–7.00)
Underlying conditions	
Chronic pulmonary disease	1.40 (0.88–2.23)
Neurologic disease	1.56 (0.83–2.92)
Liver failure	3.77 (1.70–8.38)
Congestive heart failure	1.72 (0.92–3.23)
Diabetes mellitus	1.49 (0.97–2.30)
Malnutrition (body mass index < 20)	2.45 (1.28–4.71)
Obesity (body mass index ≥ 30)	0.70 (0.48–1.02)
Appropriate empiric antimicrobial therapy	0.78 (0.55–1.09)
Time-to-source control intervention	
'Emergency' (< 2 h)	Reference
'Urgent' (2 to 6 h)	0.50 (0.34–0.73)
'Delayed' (> 6 h)	0.90 (0.58–1.41)
Source control achievement at day 7	
Success	Reference
Failure, persistent signs of inflammation	5.71 (3.99–8.18)
Failure, additional intervention required following initial approach	1.54 (0.94–2.54)

An identical regression model was executed after recoding the variable "time-to-source control intervention" with 'urgent' source control being the reference category. This resulted in 'emergency' source control having a relationship with mortality of OR 1.99 (95% CI 1.37–2.91). This allowed the calculation of the *E*-value on the relationship of 'emergency' source control with mortality (ESM-2).

or percutaneously [8]. Although the crucial role of source control interventions in the management of IAIs is beyond any doubt, the correct approach (operative vs. conservative), timing (immediate vs. early vs. delayed after damage control) and type of procedures (surgical vs. percutaneous/endoscopic) are still a matter of debate [27]. On top of that, the source of infection in patients with septic shock may strongly influence final outcome, with lowest mortality rates observed in cholecystitis progressively increasing with perforated viscus and ischemic bowel (38.3% vs. 55.6% vs. 77.9%, respectively) [28]. Azuhata et al., in a well conducted observational study on 154 patients with gastro-intestinal perforation and septic shock, demonstrated that time to surgery in hours significantly impacted 60-day outcome, with a survival rate of 0% when source control was delayed over 6 h, under the condition that patients were supported with early hemodynamic stabilization [29]. In addition, in a very large prospective study, mainly represented by IAIs, those patients undergoing source control, although delayed over 12 h from sepsis onset, showed reduced hospital mortality [30]. Analog to our observation, Bloos et al. reported a significantly higher mortality rate when source control was executed > 6 h (42.9% vs. 26.7%; $p < 0.001$) [31]. Likewise, our data support the adoption of an 'urgent' source control (2–6 h), prioritizing hemodynamic stabilization, in very sick patients undergoing complex surgical procedures. Indeed, patients who received 'emergency' source control, despite a similar degree of clinical severity including the need of mechanical ventilation and vasopressors, showed a higher mortality compared with those ones where the surgical procedure was slightly postponed.

The clinical scenario of source control interventions in patients with IAIs may be very different according to type of infections and patients' clinical status. Among 785 procedures performed in 353 patients, half of the patients required multiple interventions and effective control of the source of infection was ultimately obtained only in 67% of the cases [32]. Also in our cohort, about 60% of the patients obtained at first attempt a successful source control, with 139 subjects needing additional surgical interventions within the first 7 days. Interestingly, the latter group presented an initial survival advantage, probably due to a bias in patients who did not undergo several surgical interventions for the severity of their conditions. Conversely, it is not surprising that patients who presented a clinical picture of un-resolving inflammation showed the highest mortality rate, along with persistent organ failures and uncontrolled source of infection.

Finally, in our large cohort of critically ill patients with secondary peritonitis, infections due to antimicrobial resistant microorganisms (either bacteria or fungi) were at increased risk of inappropriate antimicrobial treatment, which, however, did not influence final clinical outcome. This observation, apparently in contrast with current knowledge on the crucial role of prompt adequate antimicrobials in severe infections [33–36], does only reinforce the need to prioritize the role of clinical stabilization and adequate source control over an intervention focused only on optimal antimicrobial therapy. Nevertheless, in presence of germs resistant to multiple antimicrobials, rescue drugs, although active *in vitro*, may be suboptimal *in vivo* due to pharmacokinetic and

pharmacodynamics (PK/PD) limitations (i.e., colistin, aminoglycosides) [37, 38].

We acknowledge several limitations of this study. First, although prospective, the observational design is prone to multiple confounding factors not allowing to generalize our results. At the same line, we cannot rule out unmeasured confounding. However, E-value calculation indicated that any missing covariate should a have a robust relationship to annihilate the relationship between emergency source control and mortality (ESM-2). Second, there was not a predefined common approach to source control and its definition was discretional, according to different site sub-investigators. Third, we do not have in-depth information on timing and type of hemodynamic support, especially during source control procedures, thus missing potentially relevant elements. Fourth, antimicrobial appropriateness is established on 'in vitro' susceptibility criteria, but PK/PD features and exclusively considers the first 24 h timeframe; aspects, such as appropriate therapy initiated after the first 24 h, synergistic combinations, and de-escalation practices, could not be considered. Finally, by including different types of infection and surgical interventions, we were not able to verify whether the observed results may be valid in specific subgroup populations.

Conclusion

In critically ill patients with secondary peritonitis, hospital-acquired infections, diffuse peritoneal inflammation and septic shock were strong predictors of poor clinical outcome. Failure of source control as characterized by persistent signs of inflammation rather than the need for additional source control intervention, was strongly associated with mortality. Concerning the timing of source control 'emergency' intervention (i.e., within 2 h) was associated with worse outcomes compared with cases receiving source control within the first 6 h despite an apparently similar degree of disease severity. We cautiously assume that initial hemodynamic stabilization before source control intervention may be preferred. On the other hand, we support the idea of aiming for source control as soon as hemodynamic stability has been achieved. Well-designed clinical trials involving most severe patients with similar risk profile of ICU mortality, should assess the effect of early vs. later source control interventions, and the potential relationship with the timing of hemodynamic stabilization and appropriate antimicrobials prescription.

Supplementary Information

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Author details

[1] Department of Anesthesiology, Intensive Care and Emergency Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy. [2] Università Cattolica del Sacro Cuore, Rome, Italy. [3] Data Science Institute, Ghent University Hospital, Ghent, Belgium. [4] Intensive Care Unit, Papageorgiou University Affiliated Hospital, Thessaloniki, Greece. [5] Department of Internal Medicine and Pediatrics, Ghent University, Campus UZ Gent, Corneel Heymanslaan 10, 9000 Ghent, Belgium. [6] Department of Epidemiology and Public Health, Sciensano, Belgium. [7] Surrey Perioperative Anaesthetic Critical Care Collaborative Research Group (SPACeR), Royal Surrey County Hospital, Guildford, UK. [8] Department of Clinical and Experimental Medicine, University of Surrey, Guildford, UK. [9] Department of Intensive Care Medicine, University Medical Center Utrecht, University Utrecht, Utrecht, The Netherlands. [10] Department of Intensive Care Medicine, Ghent University Hospital, Ghent, Belgium. [11] Department of Anesthesiology and Reanimation, Cerrahpasa School of Medicine, Istanbul University-Cerrahpasa, Istanbul, Turkey. [12] 3rd Department of Critical Care, "EVGENIDIO" Hospital, National and Kapodistrian University of Athens, Athens, Greece. [13] Department of General, Visceral and Thoracic Surgery, Klinikum Peine, Medical University Hannover, Hannover, Germany. [14] Division of Scientific Affairs-Research, European Society of Intensive Care Medicine, Brussels, Belgium. [15] Anesthesia and Intensive Care Department, University Hospital of Modena, Modena, Italy. [16] UQ Centre for Clinical Research (UQCCR), Faculty of Medicine, The University of Queensland, Brisbane, Australia. [17] 2ND Critical Care Department, Attikon University Hospital, Athens, Greece. [18] Department of Nursing, Faculty of Education, Health and Social Work, University College Ghent, Ghent, Belgium. [19] Jamieson Trauma Institute and The University of Queensland, Brisbane, Australia. [20] Nimes University Hospital, University of Montpellier, Nimes, France. [21] Critical Care Department, Hospital of the Interamerican Open University (UAI), Buenos Aires, Argentina. [22] Surgical Critical Care, Department of Anesthesia, Hospital Universitario La Paz-IdiPaz, Madrid, Spain. [23] Université de Paris, INSERM, UMR-S 1152-PHERE, Paris, France. [24] Anesthesiology and Critical Care Medicine, Bichat-Claude Bernard University Hospital, HUPNSV, AP-HP, Paris, France. [25] Faculty of Health Sciences, Poznan University of Medical Sciences, Poznan, Poland. [26] Department of Anaesthesiology and Intensive Therapy, Regional Hospital in Poznan, Poznan, Poland. [27] Grupo Infec ao e Sepsis, Intensive Care Department, Faculty of Medicine, Centro Hospitalar Universitario S. Joao, University of Porto, Porto, Portugal. [28] Intensive Care Unit from Hospital Interzonal General de Agudos "Prof Dr Luis Guemes", Buenos Aires, Argentina. [29] Ciberes and Vall d'Hebron Institute of Research, Barcelona, Spain. [30] Université Paris-Cité, IAME, INSERM 1137, 75018 Paris, France. [31] AP-HP, Hôpital Bichat, Medical and Infection Diseases ICU (MI2), 75018 Paris, France. [32] Department of General Internal Medicine and Infectious Diseases, AZ Delta, Roeselare, Belgium.

Acknowledgements

Collaborators AbSeS study. National Coordinators: Algeria: Amin Lamrous (CHU Alger), Argentina: Cecilia Pereyra (Hospital Interzonal Agudos Prof Dr Luis Guemes, Buenos Aires), Fernando Lipovestky (Universidad Abierta Interamericana Hospital, Buenos Aires); Australia: Despoina Koulenti (UQCCR, Faculty of Medicine, The University of Queensland, Brisbane);Belgium: Jan De Waele (Ghent University Hospital, Ghent); Canada: Joao Rezende-Neto (St Michael's Hospital, Toronto); (Colombia: Yenny Cardenas (Hospital Universitario Fundación Santa Fe, Bogotá); Czech Republic: Tomas Vymazal (Motol University Hospital, Prague); Denmark: Hans Fjeldsoee-Nielsen (Fjeldsoee-Nielsen (Nykoebing Falster Hospital, Nykoebing Falster); France: Philippe Montravers (CHU Bichat Claude Bernard, Paris); Germany: Matthias Kott (Universitätsklinikum, Schleswig-Holstein, Kiel); Greece: Arvaniti Kostoula (Papageorgiou General Hospital, Thessaloniki); India: Yash Javeri (Nayati Healthcare, Delhi); Italy: Massimo Girardis (University Hospital of Modena, Modena); Israel: Sharon Einav (Shaare Zedek Medical Centre, Jerusalem); Netherlands: Dylan de Lange (University Medical Center, Utrecht); Peru: Luis Daniel Umezawa Makikado (Clínica Ricardo Palma, Lima); Poland: Adam Mikstacki (Regional Hospital, Poznan); Portugal: José-Artur Paiva (Centro Hospitalar Universitário Sao João, Porto); Romania: Dana Tomescu (Fundeni Clinical Institute, Bucharest); Russian Federation: Alexey Gritsan (Krasnoyarsk State Medical University, Krasnoyarsk Regional Clinical Hospital, Krasnoryarsk); Serbia; Bojan Jovanovic (Clinical Center of Serbia, Belgrade); Singapore: Kumaresh Venkatesan (Khoo Teck Puat Hospital, Singapore); Slovenia: Tomislav Mirkovic (University Medical Centre, Ljubljana); Spain: Emilio Maseda (Hospital Universitario La Paz, Madrid); Turkey: Yalim Dikmen (Istanbul University-Cerrahpasa, Cerrahpasa Medical School, Istanbul); United Kingdom: Benedict

Creagh-Brown (Royal Surrey County Hospital NHS Foundation Trust, Guilford); Investigators: ALGERIA: CHU (Algiers): Amin Lamrous; ARGENTINA: Sanatorio Güemes (Buenos Aires): Monica Emmerich, Mariana Canale; Sanatorio de la Trinidad Mitre (Buenos Aires): Lorena Silvina Dietz, Santiago Ilutovich; Hospital General de Agudos "Dr. Teodoro Alvarez" (Buenos Aires): John Thomas Sanchez Miñope, Ramona Baldomera Silva; Hospital Militar Central (Buenos Aires): Martin Alexis Montenegro, Patricio Martin; Policlinico Central Union Obrera Metalurgica (Buenos Aires): Pablo Saul, Viviana Chediack; Sanatorio San José (Buenos Aires): Giselle Sutton, Rocio Couce; Hospital General de Agudos "Dr. Ignacio Pirovano" (Buenos Aires): Carina Balasini, Susana Gonzalez; Hospital Britanico (Buenos Aires): Florencia Maria Lascar, Emiliano Jorge Descotte; CMPF Churruca-Visca (Buenos Aires): Natalia Soledad Gumiela, Carina Alejandra Pino; Clinica San Camilo (Buenos Aires): Cristian Cesio, Emanuel Valgolio; Hospital Francisco Javier Muñiz (Buenos Aires): Eleonora Cunto, Cecilia Dominguez; Universidad Abierta Interamericana Hospital (Buenos Aires): Fernando Lipovestky; Hospital Alberto Balestrini (Buenos Aires): Nydia Funes Nelson, Esteban Martin Abegao; Hospital Interzonal Agudos Prof Dr Luis Güemes (Buenos Aires): Cecilia Pereyra, Norberto Christian Pozo; Hospital Español (Buenos Aires): Luciana Bianchi, Enrique Correger; Clinica Zabala (Caba): Maria Laura Pastorino, Erica Aurora Miyazaki; Hospital César Milstein (Caba): Norberto Christian Pozo, Nicolas Grubissich; Hospital Regional Victor Sanguinetti (Comodoro): Mariel Garcia, Natalia Bonetto; Hospital Municipal de Urgencias (Cordoba): Noelia Elizabeth Quevedo, Cristina Delia Gomez; Hospital Manuel B Cabrera (Coronel Pringles): Felipe Queti, Luis Gonzalez Estevarena; Hospital Español de Mendoza (Mendoza,Godoy Cruz: Ruben Fernandez, Ignacio Santolaya; H.I.G.A. Prof. Dr. Luis Güemes (Haedo): Norberto Christian Pozo; Hospital Municipa Doctor Carlos Macias (Mar de Ajo): Sergio Hugo Grangeat, Juan Doglia; Hospital Luis C. Lagomaggiore (Mendoza): Graciela Zakalik, Carlos Pellegrini; Hospital Nacional Profesor Alejandro Posadas (Moron): Maria Monserrat Lloria, Mercedes Esteban Chacon; Hospital Provincial de Neuquen (Neuquen): Mariela Fumale; Clinica Modelo S.A (Paraná): Mariela Leguizamon; Sanatorio de la Ciudad (Puerto Madryn): Irene Beatriz Hidalgo, Roberto Julian Tiranti; Sanatorio Nosti (Rafaela): Paola Capponi, Agustin Tita; Hospital Provincial del Centenario (Rosario): Luis Cardonnet, Lisandro Bettini; Sanatorio Parque (Rosario): Agñel Ramos, Luciano Lovesio; Hospital Papa Francisco (Salta): Edith Miriam Miranda, Angelica Beatriz Farfan; Hospital San Juan Bautista (San Fernando del Valle de Catamarca): Carina Tolosa, Lise Segura; Hospital Central San Isidro Dr Melchor A. Posse (San Isidro-Buenos Aires): Adelina Bellocchio, Brian Alvarez; Hospital Guillermo Rawson (San Juan): Adriana Manzur, Rodolfo Lujan; Establecimiento Asistencial Dr Lucio Molas (Santa Rosa): Natalia Fernandez, Nahuel Scarone; Clínica de Especialidades (Villa María): Alan Zazu, Carina Groh; AUSTRALIA: The Bendigo Hospital (Bendigo): Jason Fletcher, Julie Smith; Coffs Harbour Health Campus (Coffs Harbour): Raman Azad, Nitin Chavan; Concord Hospital (Concord): Helen Wong; Mark Kol; Royal Darwin Hospital (Darwin): Lewis Campbell; Royal Brisbane and Women's Hospital (Herston, Brisbane): Despoina Koulenti, Therese Starr; Sir Charles Gairdner Hospital (Nedlands): Brigit Roberts, Bradley Wibrow; Redcliffe Hospital (Redcliffe): Timothy Warhurst; St Vincent's Hospital (Toowommba): Meher Chinthamuneedi, Bernal Buitrago Ferney; BELGIUM: Cliniques du Sud Luxembourg (CSL)-Hôpital Saint-Joseph (Arlon): Marc Simon; Chirec Hospital (Braine-l'Alleud): Daniel De Backer; Cliniques Universitaires St Luc (Brussels): Xavier Wittebole; Brugmann University Hospital (Brussels): David De Bels, Cliniques de l'Europe—St-Michel (Brussels): Vincent Collin; University Hospital Antwerp (Edegem): Karolien Dams, Philippe Jorens; Ghent University Hospital (Ghent): Jan De Waele; Jessa Ziekenhuis (Hasselt): Jasperina Dubois; University Hospitals Leuven (Leuven): Jan Gunst; CHU Ambroise Paré (Mons): Lionel Haentjens; Clinique Saint-Pierre (Ottignies): Nicolas De Schryver, Thierry Dugernier; CANADA: St. Michael's Hospital (Toronto): Joao Rezende-Neto, Sandro Rizoli; CHILE: Hospital Clinico Viña del Mar (Viña del Mar): Paul Santillan CHINA: Jiangsu Province Hospital (Nanjing): Yi Han; Yangpu Hospital of Tongji University (Shanghai): Ewelina Biskup, Changjing Qu; Urumqi General Hospital (Urumqi): Xinyu Li, Wannan Medical College First Affiliated Hospital, Yijishan Hospital (Wuhu): Tao Yu, Lu Weihua; COLOMBIA: Clinica Universitaria Colombia (Bogota): Daniel Molano-Franco, José Rojas, Mederi Hospital (Bogota): Juan Mauricio Pardo Oviedo; Dario Pinilla; Hospital Universitario Fundación Santa Fe (Bogota): Yenny Cardenas, Edgar Celis; Clinica Santa Gracia (Popayan): Mario Arias; CROATIA: Opća bolnica Dubrovnik (Dubrovnik): Anita Vukovic, Maja Vudrag; General Hospital Karlovac (Karlovac): Matija Belavic, Josip Zunic; Clinical Hospital Center Rijeka (Rijeka): Janja Kuharic, Irena Bozanic Kricka; University Hospital Center of Zagreb (Zagreb): Ina Filipovic-Grcic, Boris Tomasevic; University Hospital Center Sestre Milosrdnice (Zagreb): Melanija Obraz, Bruna Bodulica; CZECH REPUBLIC: Nemocnice Břeclav (Břeclav): Martin Dohnal; University Hospital Brno (Brno): Jan Malaska, Milan Kratochvil; Municipal Hospital (Havirov): Igor Satinsky, Peter Schwarz; Hospital Karlovy Vary (Karlovy Vary): Zdenek Kos; University Hospital Olomouc (Olomouc): Ladislav Blahut; University Hospital of Ostrava (Ostrava): Jan Maca; Institute for Clinical and Experimental Medicine (Prague): Marek Protus, Eva Kieslichová; DENMARK: Odense University Hospital (Odense): Louise Gramstrup Nielsen, Birgitte Marianne Krogh; ECUADOR: San Vicente de Paúl Hospital (Ibarra): Francisco Rivadeneira; Hospital Oncologico "Dr. Julio Villacreses Colmont" SOLCA (Portoviejo): Freddy Morales, José Mora; Hospital General Puyo (Puyo): Alexandra Saraguro Orozco; Hospital de Especialidades "Eugenio Espejo" (Quito): Diego Rolando MorochoTutillo, Nelson Remache Vargas; Clinica La Merced (Quito): Estuardo Salgado Yepez; Hospital Militar (Quito): Boris Villamagua; EGYPT: Kasr El AINI Hospital, Cairo University (Cairo): Adel Alsisi, Abdelraouf Fahmy; FRANCE: CHU Amiens (Amiens): Hervé Dupont; CHU Angers (Angers): Sigismond Lasocki; Hôpital Beaujon (Clichy): Catherine Paugam-Burtz, Arnaud Foucrier; Centre Hospitalier Compiegne Noyon (Compiègne): Alexandru Nica, Geneviève Barjon; Centre Hospitalier de Lens (Lens): Jihad Mallat; Hôpital Edouard Herriot (Lyon): Guillaume Marcotte; Hôpital Nord (Marseille): Marc Leone, Gary Duclos; Clinique du Millénaire (Montpellier): Philippe Burtin; CHU Bichat Claude Bernard (Paris): Philippe Montravers, Enora Atchade; Groupe Hospitalier Paris Saint-Joseph (Paris): Yazine Mahjoub, Benoît Misset; Hôpital Bichat (Paris) : Jean-François Timsit, Claire Dupuis; CHU de Rouen, Hôpital Charles Nicolle (Rouen): Benoît Veber; Centre Hospitalier Yves le Foll (Saint-Brieuc): Matthieu Debarre; Hôpitaux Universitaires de Strasbourg, NHC -Nouvel Hôpital Civil (Strasbourg): Oliver Collange; Hôpitaux Universitaires de Strasbourg, Hôpital de Hautepierre (Strasbourg): Julien Pottecher, Stephane Heckets weiler; Hôpital Cochin (Paris): Mélanie Fromentin, Antoine Tesnière; GERMANY: University Hospital Giessen (Giessen): Christian Koch, Michael Sander; Universitätsklinikum Schleswig-Holstein (Kiel): Matthias Kott, Gunnar Elke; University Hospital of Leipzig (Leipzig): Hermann Wrigge, Philipp Simon; GREECE: General Hospital of Agios Nikolaos (Agios Nikolados): Anthoula Chalkiadaki, Charalampos Tzanidakis; Democritus University of Thrace (Alexandroupolis): Ioannis Pneumatikos, Eleni Sertaridou; Evangelismos Hospital (Athens): Zafiria Mastora, Ioannis Pantazopoulos; Hippocrateion General Hospital of Athens (Athens): Metaxia Papanikolaou, Theonymfi Papavasilopoulou; General Hospital Laiko (Athens): John Floros, Virginia Kolonia; University Hospital Attikon (Athens): George Dimopoulos, Chryssa Diakaki; GeneralHospitalAsklepieio Voulas (Athens): Michael Rallis, Alexandra Paridou; General Hospital G. Gennimatas (Athens): Alexandros Kalogeromitros, Vasiliki Romanou; Konstantopouleio Hospital (Athens): Charikleia Nikolaou, Katerina Kounougeri; Agioi Anargiroi General Oncological Hospital of Kifissia (Athens): Evdoxia Tsigou, Vasiliki Psallida; Red Cross Hospital (Athens): Niki Karampela, Konstantinos Mandragos; General Hospital St George (Chania): Eftychia Kontoudaki, Alexandra Pentheroudaki; Thriassio General Hospital of Eleusis (Eleusis): Christos Farazi-Chongouki, Agathi Karakosta; Giannitsa General Hospital (Giannitsa): Isaac Chouris, Vasiliki Radu; University Hospital Heraklion (Heraklion): Polychronis Malliotakis, Sofia Kokkini; Venizelio General Hospital of Heraklion (Heraklion): Eliana Charalambous, Aikaterini Kyritsi; University Hospital of Ioannina (Ioannina): Vasilios Koulouras, Georgios Papathanakos; General Hospital Kavala (Kavala): Eva Nagky, Clairi Lampiri; Lamia General Hospital (Lamia): Fotios Tsimpoukas, Ioannis Sarakatsanos; Agios Andrea's General Hospital of Patras (Patras): Panagiotis Georgakopoulos, Ifigeneia Ravani; Tzaneio General Hospital (Pireaus): Athanasios Prekates, Konstantinos Sakellaridis; General Hospital of Pyrgos (Pyrgos Hleias): Christos Christopoulos, Efstratia Vrettou; General Hospotal of Rethymnon (Rethymnon): Konstantinos Stokkos, Anastasia Pentari; Papageorgiou Hospital (Thessaloniki): Kostoula Arvaniti, Kyriaki Marmanidou; Hippokration Hospial (Thessaloniki): Christina Kydona, Georgios Tsoumaropoulos; G. Papanikolaou General Hospital (Thessaloniki): Militisa Bitzani, Paschalina Kontou; Agios Pavlos Hospital (Thessaloniki): Antonios Voudouris, Elli-Nikki, Flioni; General Hospital of Thessaloniki G.Gennimatas (Thessaloniki): Elli Antypa, Eleftheria Chasou; Theagenio Anticancer Hospital (Thessaloniki): Souzana Anisoglou, Eirini Papageorgiou; General Hospital of Trikala (Trikala): Theoniki Paraforou, Agoritsa Tsioka; Achillopoyleio General Hospital Volos (Volos): Antigoni Karathanou; Xanthi General Hospital (Xanthi): Aristeidis Vakalos; INDIA: CIMS Hospital (Ahmedabad): Bhagyesh Shah, Chirag Thakkar; CHL Hospitals (Indore): Nikhilesh Jain; Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS) (Lucknow): Mohan Gurjar, Arvind Baronia; Ruby Hall Clinic (Pune): Prachee Sathe, Shilpa Kulkarni; Jubilee Mission Medical College & Research Institute (Thrissur): Cherish Paul, John Paul; IRAN: Nemazi

Hospital (Shiraz): Mansoor Masjedi; Anesthesiology and Critical Care Research Center, Shiraz University of Medical Sciences (Shiraz): Reza Nikandish, Farid Zand; Shiraz Trauma Hospital (Shiraz): Golnar Sabetian; Shohada Hospital (Tabriz): Ata Mahmoodpoor; Masih Daneshvari Hospital (NRITLD (Tehran): Seyed Mohammadreza Hashemian; ISRAEL: Hadassah Hebrew University Medical Center (Jerusalem): Miklosh Bala; ITALY: Cardarelli Ospedale (Campobasso): Romeo Flocco, Sergio Torrente; PinetaGrande Private Hospital (Castel Volturno): Vincenzo Pota; Arcispedale Sant'Anna (Ferrara): Savino Spadaro, Carlo Volta; University Hospital of Modena (Modena): Massimo Girardis, Giulia Serafini; Ospedale S.Antonio (Padova): Sabrina Boraso, Ivo Tiberio; Azienda Ospedaliera Universitaria Policlinico Paolo Giaccone (Palermo): Andrea Cortegiani, Giovanni Misseri; Azienda Ospedaliero-Universitaria di Parma (Parma): Maria Barbagallo, Davide Nicolotti; Azienda Ospedaliero-Universitaria Pisana (Pisa): Francesco Forfori, Francesco Corradi; Fondazione Policlinico Universitario A.Gemelli IRCCS (Roma): Massimo Antonelli, Gennaro De Pascale; Regina Elena National Cancer Institute of Rome (Roma): Lorella Pelagalli; Azienda Ospedaliero-Universitaria Citta della Salute e della Scienza di Torino, Presidio Ospedaliero Molinette (Torino): Luca Brazzi, Ferdinando Giorgio Vittone; Policlinico Universitario GB Rossi (Verona): Alessandro Russo, Davide Simion; University-Hospital of Foggia (Foggia): Antonella Cotoia, Gilda Cinnella JAMAICA: University Hospital of the West Indies (Kingston): Patrick Toppin, Roxanne Johnson-Jackson; JAPAN: Kameda General Hospital (Kamogawa): Yoshiro Hayashi, Ryohei Yamamoto; Japanese Red Cross Musashino Hospital (Tokyo): Hideto Yasuda, Yuki Kishihara; Okinawa Prectural Chube Hospital (Uruma, Okinawa): Junji Shiotsuka; MEXICO: UMAE Hospital Especialidades Antonio Fraga Mouret-Centro Medico Nacional La Raza IMSS (Mexico City): Luis Alejandro Sanchez-Hurtado, Brigitte Tejeda-Huezo; Hospital Juárez de Mexico (Mexico City): Luis Gorordo; Instituto Nacional de Cancerologia (Mexico City): Silvio A. Ñamendys-Silva, Francisco J. Garcia-Guillen; Hospital general # 5 IMSS (Nogales, Sonora): Manuel Martinez; Hospital Regional de Alta Especialidad de la Península de Yucatán (Merida, Yacatan): Erick Romero-Meja, Ever Colorado-Dominguez; NETHERLANDS: Deventer Hospital (Deventer): Huub van den Oever, Karel Martijn Kalff; Medisch Spectrum Twente (Enschede): Wytze Vermeijden, Alexander Daniel Cornet; Tjongerschans Hospital (Heerenveen): Oliver Beck, Nedim Cimic; Zuyderland Medisch Centrum (Heerlen): Tom Dormans, Laura Bormans; Erasmus MC University Medical Center (Rotterdam): Jan Bakker, Ditty Van Duijn; Elisabeth-TweeSteden Ziekenhuis (Tilburg): Gerrit Bosman, Piet Vos; University Medical Center (Utrecht): Dylan de Lange, Jozef Kesecioglu; Diakonessenhuis (Utrecht): Lenneke Haas; OMAN: Khoula Hospital (Muscat): Akram Henein; PARAGUAY: Hospital Regional de Luque (Luque): Ariel M Miranda; PERU: Clínica Ricardo Palma (Lima): Luis Daniel Umezawa Makikado, Gonzalo Ernesto Gianella Malca; Victor Lazarte Echegaray Hospital (Trujillo): Abel Arroyo-Sanchez; POLAND: Silesian Hospital Cieszyn (Cieszyn): Agnieszka Misiewska-Kaczur; Wojewodzki Szpital Zesoloby w Koninie (Konin): Frisch Akinyi; First Public Teaching Hospital (Lublin): Miroslaw Czuczwar; Szpital Wojewodzki w Opolu SPZOZ (Opole): Karolina Luczak; SPZZOZ w Ostrowi Mazowieckiej (Ostrow Mazowiecka): Wiktor Sulkowski; Poznan University of Medical Sciences, Regional Hospital in Poznan (Poznan): Barbara Tamowicz, Adam Mikstacki; Centrum Medyczne (Poznan): Beata Swit, Bronisław Baranowski; University Hospital (Poznan): Piotr Smuszkiewicz, Iwona Trojanowska; WSM im. J. Strusia (Poznan): Stanislaw Rzymski; Niepubliczny Zakład Opieki Zdrowotnej Szpital w Puszczykowie im. prof. Stefana Tytusa Dąbrowskiego (Puszczykowo): Mariusz Sawinski, Marta Trosiak; Infant Jesus Teaching Hospital of Warsaw Medical University (Warsaw): Malgorzata Mikaszewska-Sokolewicz; PORTUGAL: Hospital de Braga (Braga): Ricardo Alves, Dina Leal; Centro Hospitalar Algarve (Faro): Andriy Krystopchuk, Pedro Muguel Hilario Mendonca; Centro Hospitalar Universitário Lisboa Central—Hospital Curry Cabral (Lisboa): Rui Antunes Pereira; Centro Hospitalar Universitário Lisboa Norte—Hospital de Santa Maria (Lisboa): Maria Raquel Lopes Marques de Carvalho, Carlos Candeias; Hospital Pedro Hispano (Matosinhos): Elena Molinos, Amélia Ferreira; Centro Hospitalar Sao Joao—Serviço Medicina Intensiva—UCIPU (Porto): Guiomar Castro, José-Artur Paiva; Centro Hospitalar Sao Joao—Serviço Medicina Intensiva—UCIPG (Porto):José-Manuel Pereira; Centro Hospitalar Sao Joao—Infectious Diseases ICU (Porto): Lurdes Santos, Alcina Ferreira; Hospital do Litoral Alentejano (Santiago do Cacém): Dulce Pascoalinho; São Bernardo—Centro Hospitalar Setubal (Setubal): Rosa Ribeiro, Guilherme Domingos; 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