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ORIGINAL

Epidemiology of intra-abdominal infection and sepsis in critically ill patients: "AbSeS", a multinational observational cohort study and ESICM Trials Group Project

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

Abstract

Purpose: To describe the epidemiology of intra-abdominal infection in an international cohort of ICU patients according to a new system that classifies cases according to setting of infection acquisition (community-acquired, early onset hospital-acquired, and late-onset hospital-acquired), anatomical disruption (absent or present with localized or diffuse peritonitis), and severity of disease expression (infection, sepsis, and septic shock).

Methods: We performed a multicenter ($n = 309$), observational, epidemiological study including adult ICU patients diagnosed with intra-abdominal infection. Risk factors for mortality were assessed by logistic regression analysis.

Results: The cohort included 2621 patients. Setting of infection acquisition was community-acquired in 31.6%, early onset hospital-acquired in 25%, and late-onset hospital-acquired in 43.4% of patients. Overall prevalence of antimicrobial resistance was 26.3% and difficult-to-treat resistant Gram-negative bacteria 4.3%, with great variation according to geographic region. No difference in prevalence of antimicrobial resistance was observed according to setting of infection acquisition. Overall mortality was 29.1%. Independent risk factors for mortality included late-onset hospital-acquired infection, diffuse peritonitis, sepsis, septic shock, older age, malnutrition, liver failure, congestive heart failure, antimicrobial resistance (either methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, extended-spectrum beta-lactamase-producing Gram-negative bacteria, or carbapenem-resistant Gram-negative bacteria) and source control failure evidenced by either the need for surgical revision or persistent inflammation.

*Correspondence: stijn.blot@UGent.be
[1] 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

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Conclusion: This multinational, heterogeneous cohort of ICU patients with intra-abdominal infection revealed that setting of infection acquisition, anatomical disruption, and severity of disease expression are disease-specific phenotypic characteristics associated with outcome, irrespective of the type of infection. Antimicrobial resistance is equally common in community-acquired as in hospital-acquired infection.

Keywords: Intra-abdominal infection, Peritonitis, Sepsis, Intensive care, Multidrug resistance, Mortality

Introduction

Severe intra-abdominal infections are a frequent and important issue in intensive care (ICU). According to international literature, the abdomen often ranks first or second among the sources of infection or sepsis [1–3].

Intra-abdominal infections pose several particular clinical challenges. First, there is a large span of disease severity ranging from uncomplicated cases to fulminant septic shock and multi-organ dysfunction. Second, there is the broad spectrum of pathogens including Gram-positive and Gram-negative aerobic bacteria, anaerobes, and fungi [4]. Third, the contribution of microbiological diagnosis is not straightforward as cultures cannot always readily discriminate true pathogens from harmless micro-organisms [5, 6]. Furthermore, source control encompassing all interventions to eradicate the source of infection, control on-going contamination, and to restore anatomic derangements and physiologic function, is key to clinical management and success, but often difficult to achieve [5, 7, 8]. Finally, there is the wide variety of clinical entities within intra-abdominal infections. Besides local abscess formation or solid organ infection (e.g., liver abscesses and infected pancreatic necrosis), a classic approach recognizes three types of peritonitis: i.e., primary peritonitis (peritoneal dialysis-related or spontaneous bacterial peritonitis), secondary peritonitis (following anatomical disruption of the GI tract), or tertiary peritonitis (persistent infection despite adequate source control intervention). In addition, cases of intra-abdominal infection are often classified as uncomplicated or complicated. Complicated describes extension of infection from their source into the peritoneal cavity.

Because of this heterogeneity, the intra-abdominal infections are difficult to study [9]. To bring more clarity in the terminology, an alternative classification for intra-abdominal infections has been proposed [10]. This system classifies intra-abdominal infections according to their setting of acquisition (community-acquired, healthcare-associated or early onset hospital-acquired, or late-onset hospital-acquired), presence of anatomical disruption (either absent or present resulting in localized or diffuse peritonitis), and severity of disease expression (infection, sepsis, or septic shock). This classification defines different phenotypes of the same disease (e.g., diverticulitis) by covering aspects of (i) the extent of intra-abdominal contamination reflecting the complexity of source control, (ii) level of associated organ failure indicating sense of urgency and prognosis, and (iii) likelihood of antimicrobial resistant micro-organisms or otherwise important pathogens which may require broader antimicrobial coverage (enterococci, *Candida* spp.).

Key message

A multinational epidemiological study on intra-abdominal infection in ICU patients revealed that setting of infection acquisition, anatomical barrier disruption, and severity of disease expression are disease-specific phenotypic characteristics associated with mortality.
Antibiotic resistance appeared equally in community-acquired as in hospital-acquired infection.

The objective of the study was to describe the epidemiology of intra-abdominal infection in an international cohort of ICU patients and to validate the predictive value for mortality of an alternative classification system.

Methods

A complete version of the Methods is in Supplement-1. AbSeS was an international, multicenter, prospective observational cohort study conducted between January and December 2016. Consecutive, adult ICU patients diagnosed with intra-abdominal infection, either as primary diagnosis leading to ICU admission or as a complication occurring during the ICU course, were eligible for inclusion. Overall, approval by established national, regional, or local institutional review boards was expedited and granted. The study is registered at ClinicalTrials.gov (number NCT03270345).

Data recorded and definitions

We obtained data describing the hospital and intensive-care facility through a center report form. Anonymous patient data were collected through the case report form. Examples of the center and case report forms are in Supplement-2. Type of intra-abdominal infection was defined according to the International Sepsis Forum Consensus Conference Definitions [11]. Intra-abdominal infections were classified according to setting of infection

acquisition, anatomical barrier disruption, and severity of disease expression [10]. 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 [12]). Healthcare-associated onset is defined by at least one of the following risk factors for multidrug-resistant pathogens: nursing home resident, out-of-hospital parenteral nutrition or vascular access, chronic dialysis, recent hospital admission (<6 months), or recent antimicrobial therapy (<6 months). For convenience sake, 'healthcare-associated and/or early-onset hospital-acquired' cases are designated 'early-onset hospital-acquired'. Intra-abdominal infections were classified as either without anatomical disruption, or with anatomical disruption resulting in localized or diffuse peritonitis (i.e., contamination spread to entire abdominal cavity). Severity of disease expression is defined as either infection, sepsis, or septic shock [13]. Microbiological assessment was left at the discretion of the physician. Eligible cultures included intra-operative cultures, trans-abdominal fine-needle aspiration, blood cultures presumably related to the intra-abdominal infection, 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) [14]. 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 [15, 16]. We deviated from this definition, however, using ESBL production as a proxy for resistance against penicillins, cephalosporins, and monobactams. For reporting microbiological results, the number of patients with cultures sampled is used as denominator. Data on anti-infective management included antimicrobial therapy and source control. Antimicrobial coverage of empiric therapy was evaluated for basic coverage (i.e., coverage of Gram-positive, Gram-negative, and anaerobic bacteria), and the association of an antimicrobial agent or initial choice with potential clinical activity against *Pseudomonas aeruginosa*, methicillin-resistant *S. aureus* (MRSA), enterococci, vancomycin-resistant enterococci (VRE), and *Candida*. In this regard, coverage of enterococci targets *Enterococcus faecalis* [6]. Outcome data included source control assessment 7 days post-diagnosis or earlier if the patient died within that time window. Source control was judged as either successful or having failed. 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). Main outcome is ICU mortality with a minimum of 28 days of observation.

Data management and statistical analyses

Simple descriptive statistics were used to characterize the study population; continuous data were summarized by median and interquartile range, categorical data as *n* (%). Logistic regression analysis was used to assess relationships with mortality. Details on the regression models are in Supplement-1. It can be considered inappropriate to include 'source control achievement at day 7' in the model as this covariate is instrumental to the biological pathway between infection onset and mortality. Therefore, we report a logistic regression model with and without source control achievement.

Results

During the study period, 2850 patients were included; 229 were excluded, because essential data were missing. As such, 2621 patients from 309 ICUs from 42 countries were entered for analysis. Most patients were included in various European regions ($n=1830$; 69.8%), followed by Middle & South America ($n=366$; 14.0%), North Africa & Middle-East ($n=214$; 8.8%), Asia-Pacific ($n=174$; 6.6%), North America ($n=29$; 1.1%), and Sub-Saharan Africa ($n=8$; 0.3%) (Supplement-3).

Characteristics of the study cohort according to setting of infection acquisition are reported in Table 1. Setting of infection acquisition was community-acquired in 828 patients (31.6%), early onset hospital-acquired in 656 patients (25.0%), and late-onset hospital-acquired in 1137 patients (43.4%). Underlying conditions were more frequently observed in cases with healthcare-associated or hospital-acquired infection. Cases with hospital-acquired infection had higher SOFA scores and more often septic shock.

The vast majority of cases involved secondary peritonitis (68.4%), followed by biliary tract infection (12.2%), intra-abdominal abscess (6.9%), and pancreatic infection (6.3%). Primary peritonitis, toxic megacolon, peritoneal dialysis-related peritonitis, and typhlitis were less frequent (<4%). Details on the distribution according to setting of infection acquisition are reported in Table 2.

Microbiology

Microbiological samples were obtained in 1982 patients (75.6%). In 80.4% of these patients, at least one culture was found positive ($n=1594$). Figure 1 reports the type of samples obtained with their respective proportion of culture positivity. Gram-negative bacteria were most frequently isolated (58.6%) with *Enterobacterales* as predominant family (51.7%) and *Escherichia coli* as most common pathogen (36.8%). Gram-positive aerobic bacteria were isolated in 39.4% of patients with enterococci as most prevalent species (25.9%). Furthermore, anaerobic bacteria and fungi were isolated in 11.7% and 13.0% of patients, respectively. Detailed results on isolated micro-organisms are reported in Table 3. Multidrug-resistant micro-organisms were isolated from 522 patients (26.3%). Antimicrobial resistance rates were not different among community-acquired (26.5%), early onset hospital-acquired (29.0%), and late-onset hospital-acquired infection (24.6%) ($p=0.215$). There was also no difference in antimicrobial resistance among patients with infection (27.6%), sepsis (26.9%), and septic shock (25.0%) ($p=0.449$). Antimicrobial resistance is mainly a matter of Gram-negatives, but variations according to geographic region are substantial (Table 4). Regions of particular concern include Eastern- and South-East Europe, North Africa and the Middle-East, and Latin America as > 35% of patients are infected by at least one antimicrobial resistant micro-organism. Antimicrobial resistance rates according to setting of infection acquisition and region are reported in Supplement-5.

Antimicrobial therapy

Data on the first-line empiric antimicrobial therapy was available from 2427 patients (92.6%). A basic schedule covering aerobic Gram-positive, Gram-negative, and anaerobic bacteria was prescribed in 2291 patients (94.4%). An anti-pseudomonal agent was prescribed in 1978 patients (81.8%). Empiric coverage of MRSA and VRE was added in, respectively, 647 patients (26.7%) and 140 patients (5.8%). An antifungal agent was associated in 436 patients (18%). In 365 patients, two agents with anti-anaerobic activity were prescribed (15%). Double anti-anaerobic coverage was more frequently prescribed in hospital-acquired cases (18.2%) compared with community-acquired cases (14.2%). No other differences in antimicrobial coverage according to setting of infection acquisition were observed (Supplement-6).

Source control

Data on the initial approach to control the infection are reported in 2438 patients. A source control intervention was carried out in 2334 patients (95.7%), and included drainage (94.0%), decompressive surgery (7.9%), and restoration of anatomy and function (28.2%). Among patients undergoing source control, persistent inflammation at day 7 was reported in 692 patients (29.6%). An additional intervention was deemed necessary in 382 patients (16.4%). Among patients with an initial conservative approach ($n=104$), 30 patients experienced persistent inflammation (28.8%), and a source control intervention was performed in 5 patients (4.8%). More details on source control interventions and evaluations are summarized in Fig. 2.

Mortality

Overall mortality was 29.1% (752/2588). Univariate relationships with mortality are reported in Supplement-7. Mortality stepwise increased with ascending SOFA scores (Supplement-8). Achievement of source control at day 7 was associated with lower mortality (248/1438, 17.2%) compared with cases with persistent inflammation (367/761, 51.8%) and those requiring surgical revision (110/389, 28.3%) ($p<0.001$). We reported mortality according to setting of infection acquisition, anatomical disruption, and severity of disease expression. Mortality was 23.7% in community-acquired cases, 27.3% in early onset hospital-acquired cases, and 33.9% in late-onset hospital-acquired cases ($p<0.001$). Regarding anatomical disruption, no difference in mortality was observed between patients without anatomical disruption and those with localized peritonitis (respectively, 25.0% and 24.2%, $p=0.135$). Mortality in patients with diffuse peritonitis (36.0%) was higher compared with the former categories ($p<0.001$). Finally, mortality stepwise increased with greater severity of disease expression: 12.8% in infected patients without sepsis, 24.5% in septic patients, and 40.3% in patients with septic shock ($p<0.001$). Table 5 reports mortality rates for all different phenotypes of intra-abdominal infection according to setting of infection acquisition, anatomical disruption, and severity of disease expression. The grid describes a stepwise increase in mortality along with combinations including septic shock, diffuse peritonitis, and late-onset hospital-acquired infection.

Logistic regression analysis identified late-onset hospital-acquired infection, diffuse peritonitis, sepsis and septic shock, older age, malnutrition, diabetes mellitus, liver failure, and congestive heart failure as independent risk factors for death (Table 6). The association of an anti-MRSA agent in the empiric antimicrobial scheme was associated with decreased risk of death. Antimicrobial resistance defined as MRSA, VRE, or difficult-to-treat resistant Gram-negatives did not reached the final models. However, when antimicrobial resistance in Gram-negative bacteria was defined as either ESBL production

Table 1 Patient characteristics of intensive-care unit patients with intra-abdominal infection/sepsis according to setting of infection acquisition

Characteristic	Total cohort ($n=2621$)	Community-acquired ($n=828$)	Early onset hospital-acquired ($n=656$)	Late-onset hospital-acquired ($n=1137$)	p*
Demographics					
Age, years	66 (54–75)	67 (52–77)	66 (54–77)	66 (55–74)	0.213
Sex, male	1488/2615 (56.9)	452 (54.6)	364 (55.5)	672 (59.1)	0.133
Type of ICU admission	2592**	799**	656	1137	
Medical	472 (18.2)	109 (13.7)	131 (20.0)	232 (20.4)	<0.001
Surgical, non-emergency	233 (9.0)	19 (2.4)	39 (5.9)	175 (15.4)	<0.001
Surgical, emergency	1847 (71.3)	660 (82.6)	478 (72.9)	709 (62.4)	<0.001
Trauma	40 (1.5)	11 (1.4)	8 (1.2)	21 (1.8)	0.496
ICU stay, days	9 (4-18)	9 (4–18)	9 (4–17)	10 (5–19)	0.183
Underlying conditions* **					
Chronic pulmonary disease	342 (13.0)	96 (11.6)	90 (13.7)	156 (13.7)	0.324
AIDS	14 (0.5)	6 (0.7)	3 (0.5)	5 (0.4)	0.661
Malignancy	699 (26.7)	116 (14.0)	170 (25.9)	413 (36.3)	<0.001
Neurologic disease	165 (6.3)	42 (5.1)	60 (9.1)	75 (6.6)	0.008
Peptic ulcer disease	176 (6.7)	57 (6.9)	52 (7.9)	67 (5.9)	0.246
Liver disease	127 (4.8)	24 (1.5)	44 (6.7)	59 (5.2)	0.002
Chronic renal failure	282 (10.8)	57 (6.9)	100 (15.2)	125 (11.0)	<0.001
Myocardial infarction	188 (7.2)	48 (5.8)	57 (8.7)	83 (7.3)	0.098
Chronic heart failure (NY Heart Association class IV)	184 (7.0)	36 (4.3)	64 (9.8)	84 (7.4)	<0.001
Peripheral vascular disease	169 (6.4)	34 (4.1)	48 (7.3)	87 (7.7)	0.004
Diabetes mellitus	488 (18.6)	116 (14.0)	141 (21.5)	231 (20.3)	<0.001
Immunosuppression	253 (9.7)	47 (5.7)	83 (12.7)	123 (10.8)	<0.001
Lifestyle risk factors	1363 (52.0)	413 (49.9)	355 (54.1)	595 (52.3)	0.257
Malnutrition (body mass index < 20)	177 (6.8)	46 (5.6)	53 (8.1)	78 (6.9)	0.154
Obesity (body mass index ≥ 30)	735 (28.0)	236 (28.5)	197 (30.0)	302 (26.6)	0.271
Tobacco use (> 20 pack years)	446 (17.0)	127 (7.1)	106 (16.2)	213 (18.7)	0.113
Alcohol abuse (> 10 g alcohol/day)	196 (7.5)	59 (7.1)	49 (7.5)	88 (7.7)	0.261
IV drug abuse	17 (0.6)	8 (1.0)	3 (0.5)	6 (0.5)	–
Severity of acute illness					
SAPS II score at time of ICU admission	49 (39–60)	48 (38–59)	49 (39–61)	49 (38–60)	0.183
SOFA score at diagnosis	6 (3–10)	5 (3–9)	7 (3–10)	6 (3–10)	<0.001
Severity of disease expression					
Infection without sepsis	164 (6.3)	51 (6.2)	42 (6.4)	71 (6.2)	0.981
Sepsis	1590 (60.7)	528 (63.8)	399 (60.8)	663 (58.3)	0.050
Septic shock	867 (33.1)	249 (30.1)	215 (32.8)	403 (35.4)	0.043
Anatomical disruption					
Not present	615 (23.5)	186 (22.5)	166 (25.3)	263 (23.1)	0.413
Yes, with localized peritonitis	981 (37.4)	342 (41.3)	256 (39.0)	383 (33.7)	0.002
Yes, with diffuse peritonitis	1025 (39.1)	300 (36.2)	234 (35.7)	491 (43.2)	0.001

Data are reported as *n* (%) or median (1st–3rd quartile)

SAPS simplified acute physiology score, *SOFA* sequential organ failure assessment

*p value indicates differences between patients with community-acquired infection, healthcare-associated infection or early onset hospital-acquired infection, and late-onset hospital-acquired infection

**Data missing from 29 patients

***More details regarding underlying conditions are reported in Supplement–4

Table 2 Proportion of types of intra-abdominal infection and distribution according to origin of infection acquisition

Type of abdominal sepsis	Total *n* (%)*	Community-acquired *n* (%)**	Early onset hospital-acquired *n* (%)**	Late-onset hospital-acquired *n* (%)**
Primary peritonitis	103 (3.9)	33 (32)	28 (27.2)	42 (40.8)
Secondary and tertiary peritonitis	1794 (68.4)	588 (32.8)	431 (24)	775 (43.2)
PD-related peritonitis	9 (0.3)	0	2 (20)	7 (70)
Intra-abdominal abscess	180 (6.9)	36 (20)	49 (27.2)	95 (52.8)
Biliary tract infection	319 (12.2)	117 (36.7)	95 (29.8)	107 (33.5)
Pancreatic infection	165 (6.3)	45 (27.3)	33 (20)	87 (52.7)
Typhlitis	9 (0.3)	0	3 (33.3)	6 (66.6)
Toxic megacolon	42 (1.6)	9 (21.4)	15 (35.7)	18 (42.9)

PD-related peritoneal dialysis-related

*% Within column; **% within row

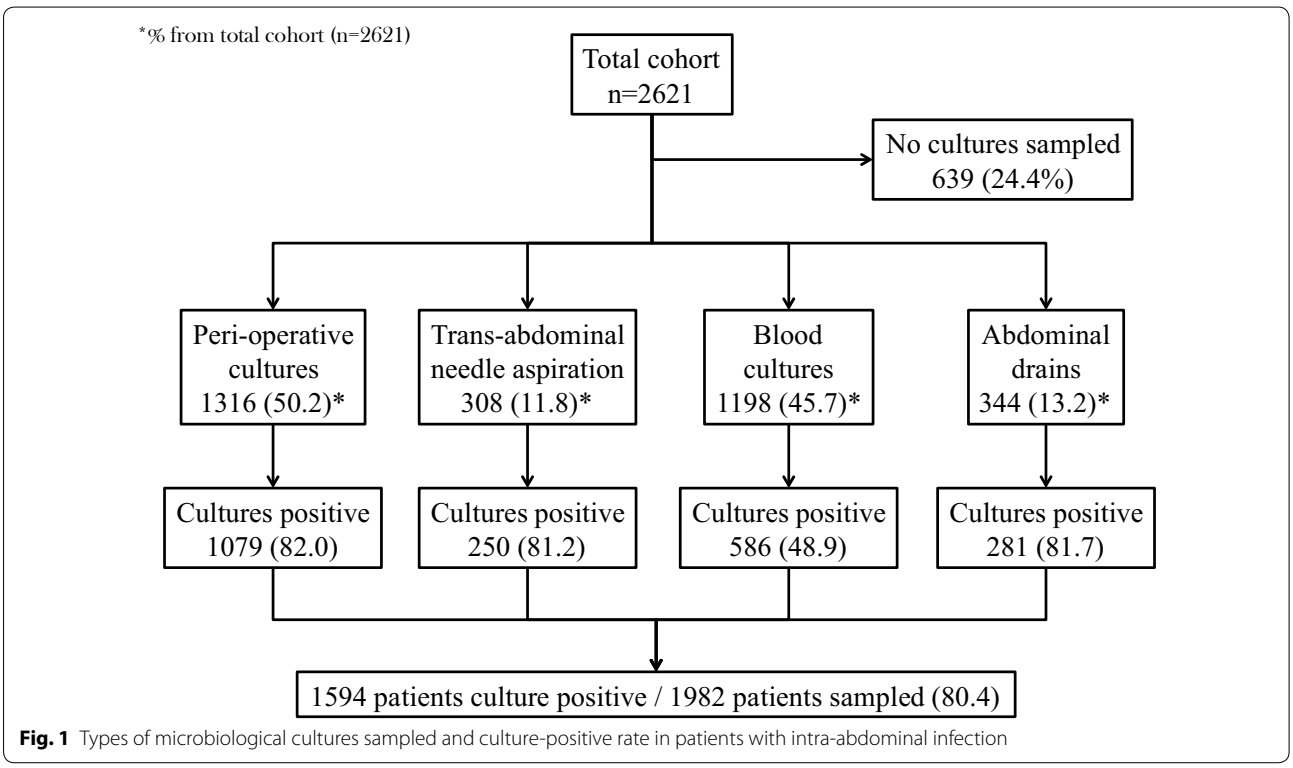


Fig. 1 Types of microbiological cultures sampled and culture-positive rate in patients with intra-abdominal infection

or carbapenem resistance, this covariate became significantly associated with mortality (Supplement-9).

Discussion

This multicenter observational study provided epidemiological insights in critically ill patients with intra-abdominal infection. The multicentre input of sequential cases of intra-abdominal infection offers a global view of the case mix of different presentations of intra-abdominal infection requiring ICU admission or occurring within the framework of an ICU stay. In spite of clinical heterogeneity, the core characteristics of intra-abdominal infection are quite generic including anatomical disruption and polymicrobial infection. Because of the broad variety in intra-abdominal infections, data were described according to a new classification based on setting of acquisition, presence of anatomical disruption, and severity of disease. Irrespective of type of

Table 3 Micro-organisms isolated from cultures sampled in patients with intra-abdominal infection

Micro-organism	Total cohort (*n* = 1982)	Setting of infection acquisition		
		Community-acquired (*n* = 664)	Early onset hospital-acquired (*n* = 482)	Late-onset hospital-acquired (*n* = 836)
Gram-negative bacteria	1161 (58.6)	385 (58)	287 (59.5)	498 (58.5)
Enterobacterales	1024 (51.7)	344 (51.8)	247 (51.2)	433 (51.8)
Citrobacter sp.	21 (1.1)	6 (0.9)	8 (1.7)	7 (0.8)
Citrobacter freundii	18 (0.9)	6 (0.9)	3 (0.6)	9 (0.9)
Escherichia coli	729 (36.8)	252 (38)	172 (35.7)	304 (36.4)
Enterobacter aerogenes	37 (1.9)	15 (2.3)	6 (1.2)	16 (1.9)
Enterobacter cloacae	80 (4)	31 (4.7)	16 (3.3)	34 (4.1)
Hafnia alvei	8 (0.4)	3 (0.5)	2 (0.4)	3 (0.4)
Morganella morganii	25 (1.3)	10 (1.5)	5 (1)	10 (1.2)
Klebsiella sp.	51 (2.6)	22 (3.3)	12 (2.5)	17 (2)
*Klebsiella oxytoca**	44 (2.2)	23 (3.5)	11 (2.3)	10 (1.2)
Klebsiella pneumoniae	170 (8.6)	57 (8.6)	37 (7.7)	76 (9.1)
Proteus sp.	23 (1.2)	9 (1.4)	7 (1.5)	7 (0.8)
Proteus mirabilis	63 (3.2)	28 (4.2)	15 (3.1)	20 (2.4)
Providencia sp.	3 (0.2)	0	1 (0.2)	2 (0.2)
Salmonella enterica	4 (0.2)	2 (0.3)	2 (0.4)	0
Serratia marcescens	12 (0.6)	2 (0.3)	4 (0.8)	6 (0.7)
Enterobacterales, other	24 (1.2)	7 (1.1)	5 (1)	12 (1.4)
Non-fermenting bacteria	233 (11.8)	72 (10.8)	66 (13.7)	95 (11.4)
Pseudomonas aeruginosa	131 (6.6)	41 (6.2)	34 (7.1)	56 (6.7)
Pseudomonas sp. (other or NI)	15 (0.8)	3 (0.5)	4 (0.8)	8 (1)
Stenotrophomonas maltophilia	11 (0.6)	5 (0.8)	2 (0.4)	4 (0.5)
Acinetobacter baumannii	61 (6.2)	18 (2.7)	22 (4.6)	21 (2.5)
Acinetobacter sp. (other or NI)	32 (1.6)	8 (1.2)	12 (2.5)	12 (1.4)
Other Gram-negative bacteria				
Haemophilus influenzae	4 (0.2)	2 (0.3)	0	2 (0.2)
Gram-positive bacteria	781 (39.4)	274 (41.3)	187 (38.8)	320 (38.3)
Staphylococci	195 (9.8)	69 (10.4)	44 (9.1)	82 (9.8)
Staphylococcus aureus	64 (3.2)	23 (3.5)	19 (3.9)	22 (2.6)
Coagulase-negative staphylococci	100 (5)	37 (5.6)	23 (4.8)	40 (4.8)
Staphylococcus sp. (other or NI)	37 (1.9)	11 (1.7)	5 (1)	21 (2.5)
Enterococci	513 (25.9)	173 (26.1)	121 (25.1)	219 (26.2)
Enterococcus faecalis	257 (13)	83 (12.5)	59 (12.2)	115 (13.8)
Enterococcus faecium	216 (10.9)	70 (10.5)	46 (9.5)	100 (12)
Enterococcus sp. (other or NI)	77 (3.9)	33 (5)	18 (3.7)	26 (3.1)
Other Gram-positive bacteria				
Streptococcus Group A, B, C, G	117 (5.9)	44 (6.6)	27 (5.6)	46 (5.5)
Streptococcus pneumoniae	9 (0.5)	4 (0.6)	2 (0.4)	3 (0.4)
Streptococcus viridans	33 (1.7)	13 (2)	7 (1.5)	13 (1.6)
Corynebacterium	8 (0.4)	1 (0.2)	3 (0.6)	4 (0.5)
Anaerobe bacteria	231 (11.7)	83 (12.5)	45 (9.3)	103 (12.3)
Clostridium perfringens	21 (1.1)	7 (1.1)	3 (0.6)	11 (1.3)
Peptostreptococcus sp.	4 (0.2)	1 (0.2)	2 (0.4)	1 (0.1)
Actinomyces sp.	2 (0.1)	1 (0.2)	0	1 (0.1)
Gram-positive anaerobe sp. (other or NI)	53 (2.7)	17 (2.6)	12 (2.5)	24 (2.9)
Clostridium difficile	8 (0.4)	3 (0.5)	1 (0.2)	4 (0.5)
*Bacteroides sp.**	103 (5.2)	46 (6.9)	17 (3.5)	40 (4.8)

Table 3 (continued)

Micro-organism	Total cohort ($n=1982$)	Setting of infection acquisition		
		Community-acquired ($n=664$)	Early onset hospital-acquired ($n=482$)	Late-onset hospital-acquired ($n=836$)
Porphyromonas sp.	2 (0.1)	0	2 (0.4)	0
Prevotella sp.	5 (0.3)	3 (0.5)	0	2 (0.2)
Fusobacterium sp.	9 (0.5)	7 (1.1)	0	2 (0.2)
Gram-negative anaerobe sp. (other or NI)	66 (3.3)	20 (3)	13 (2.7)	33 (3.9)
Fungi	258 (13)	80 (12)	71 (14.7)	107 (12.8)
Aspergillus sp.	3 (0.2)	0	2 (0.4)	1 (0.1)
Candida sp.	257 (13)	81 (12.2)	69 (14.3)	107 (12.8)
Candida albicans	173 (8.7)	56 (8.4)	50 (10.4)	67 (8)
Candida glabrata	35 (1.8)	10 (1.5)	9 (1.9)	16 (1.9)
Candida krusei	3 (0.2)	2 (0.3)	0	1 (0.1)
Candida parapsilosis	9 (0.5)	4 (0.6)	1 (0.2)	4 (0.5)
Candida tropicalis	16 (0.8)	6 (0.9)	2 (0.4)	8 (1)
Candida sp. (other or NI)	20 (1)	2 (0.3)	7 (1.5)	11 (1.3)

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

NI not identified

*$p<0.05$ for differences between setting of infection acquisition

intra-abdominal infection, mortality was higher in late-onset hospital-acquired cases with diffuse peritonitis and septic shock. This classification allows comparison across a spectrum of intra-abdominal infections and might be used for including patients in future clinical trials.

There were no differences in the prevalence of antimicrobial resistance in microbiological cultures sampled in community-acquired vs. early onset vs. late-onset hospital-acquired infection. This may be explained at least in part by the spread of resistance clones/genes into the community, as is the case for ESBL-producing or carbapenem-resistant *Enterobacterales* (formerly known as *Enterobacteriaceae*). This is certainly the case for risk regions such as Eastern and South-East Europe, the Middle-East, and Latin America, and matches with the results of a global point prevalence study on antimicrobial consumption and resistance [17]. This confirms the trend that classic risk factors for antimicrobial resistance involvement are losing predictive value as illustrated in a multicenter study reporting antimicrobial resistance in 39% of infections in patients without an obvious risk profile as evidenced by prior antibiotic exposure and/or hospitalisation [18]. This observation is highly relevant as it might stress the need for last-line antimicrobial therapy in community-acquired infection in selected regions. Considering local ecology together with the individual patient profile, and disease severity remains essential. However, antimicrobial resistance in key-pathogens isolated in intra-abdominal infection does not seem to be associated with increased virulence, as it occurred at similar rates in infection, sepsis, and septic shock. Overall prevalence of enterococci was 26% and thereby substantially higher as previously reported [19–22]. This trend can be attributed to the steadily emergence of enterococci in acute care settings or to the particular composition of a cohort of exclusively critically ill patients [23].

No differences in empiric antibacterial regimens were observed according to setting of infection acquisition. Anti-pseudomonal coverage was provided up-front in not only late-onset cases, a supposed classic risk factor for antimicrobial resistant infection, including *P. aeruginosa* strains, but also in community-acquired or early onset hospital-acquired infections. This is probably triggered by a safety-reflex in physicians, not to miss any potential pathogen, especially *P. aeruginosa* strains. Thus, the risk factor-based antibiotic strategy that appears in all guidelines seems not to be implemented in a large real-life sample of intra-abdominal infection in the ICU, reflecting response to severity.

It is reassuring that the vast majority of intra-abdominal infections in the ICU were approached by an early source control intervention. It has been established that surgery needs to be performed after hemodynamic stabilization, but nevertheless should be performed as early as possible aiming at damage control [24]. The importance of source is evidenced by the increased mortality among patients with persistent inflammation or need for additional surgical intervention.

Table 4 Rates of antimicrobial resistance in intra-abdominal infections according to geographic region

Antibiotic-resistant pathogen	Total cohort (*n* = 1982)	Geographic region							
		Western Europe (*n* = 601)	Southern Europe (*n* = 558)	Eastern and South-East Europe (*n* = 151)	Central Europe (*n* = 99)	North Africa and Middle-East (*n* = 172)	Latin America (*n* = 249)	North America (*n* = 22)	Asia–Pacific (*n* = 123)
Difficult-to-treat resistant Gram-negative bacteria	85 (4.3)	2 (0.3)	38 (6.8)	9 (6)	0	15 (8.7)	16 (6.4)	0	5 (4.1)
Any resistant Gram-negative bacteria*	480 (24.2)	54 (9)	140 (25.1)	59 (39.1)	20 (20.2)	82 (47.7)	90 (36.1)	7 (31.8)	26 (21.1)
ESBL-producing Gram-negative bacteria	326 (16.4)	37 (6.2)	81 (14.5)	37 (24.5)	9 (9.1)	65 (37.8)	69 (27.7)	7 (31.8)	20 (16.3)
Carbapenem-resistant Gram-negative bacteria	145 (7.3)	3 (0.5)	61 (10.9)	23 (15.2)	1 (1)	23 (13.4)	25 (10)	0	9 (7.3)
Fluoroquinolone-resistant Gram-negative bacteria	339 (17.1)	29 (4.8)	108 (19.4)	37 (24.5)	18 (18.2)	57 (33.1)	69 (27.7)	3 (13.6)	17 (13.8)
MRSA	20 (1)	1 (0.2)	5 (0.9)	5 (3.3)	0	5 (2.9)	3 (1.2)	0	1 (0.8)
VRE	56 (2.8)	11 (1.8)	15 (2.7)	5 (3.3)	2 (2)	9 (5.2)	11 (4.4)	1 (4.5)	2 (1.6)
Antimicrobial resistance** (total)	153 (7.7)	14 (2.3)	57 (10.2)	16 (10.6)	2 (2)	29 (16.9)	27 (10.8)	1 (4.5)	7 (5.7)
Antimicrobial resistance*** (total)	522 (26.3)	63 (10.5)	152 (27.2)	65 (43)	21 (21.2)	87 (50.6)	96 (38.6)	8 (36.4)	28 (22.8)

% Represent proportion per column; Resistance rates reflect proportion of patients in which resistant strains are isolated (e.g., *n* MRSA/total *n* patients) and do not represent proportion of resistance within particular pathogens (e.g., *n* MRSA/total *S. aureus* isolates)

Denominator for microbiological data includes only patients in which cultures were sampled (data from South Africa are excluded as they included only seven patients)

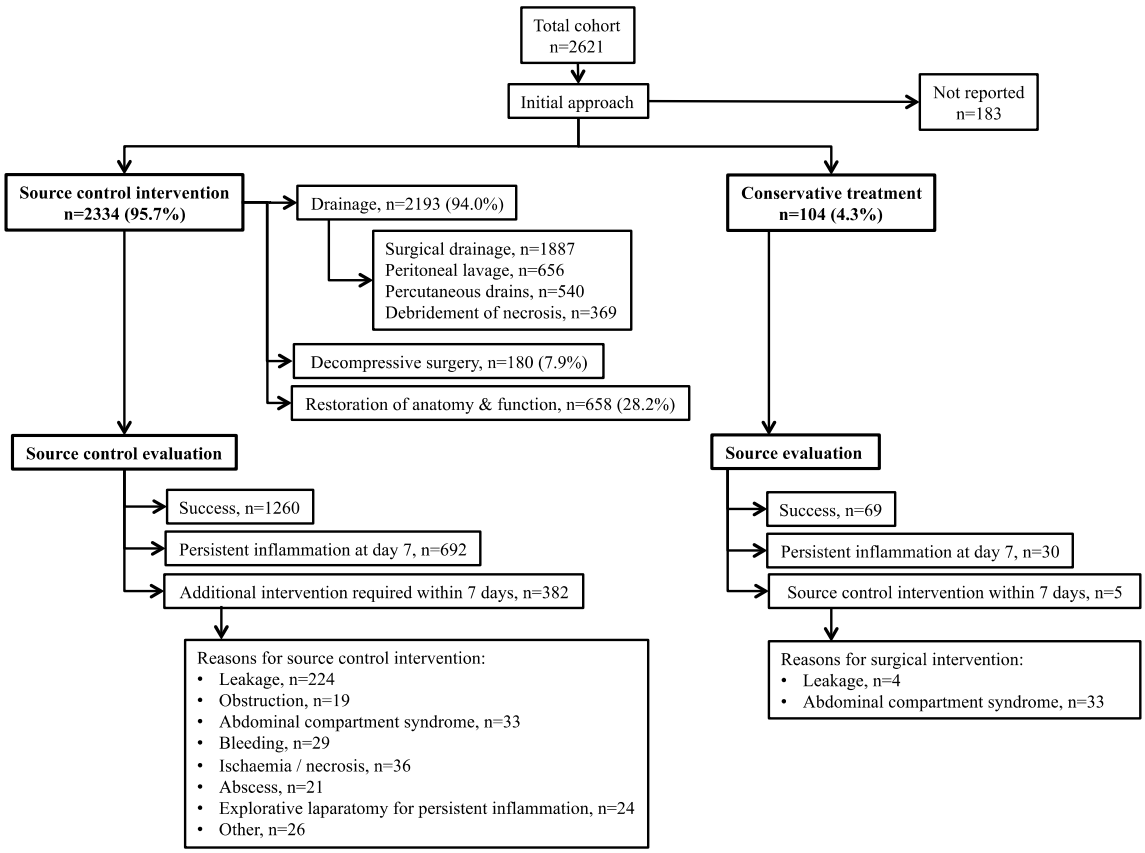
ESBL extended-spectrum beta-lactamase-producing, *MRSA* methicillin-resistant *Staphylococcus aureus, VRE* vancomycin-resistant enterococci

*Gram-negative bacteria that are either ESBL-producing, or carbapenem-resistant, or fluoroquinolone-resistant

**Total rates of multidrug resistance considering difficult-to-treat resistant Gram-negative bacteria, MRSA, and VRE

***Total rates of multidrug resistance considering any type of Gram-negative resistance (either ESBL-producing, or carbapenem-resistant, or fluoroquinolone-resistant bacteria), MRSA, and VRE

Late-onset hospital-acquired infection, diffuse peritonitis, and septic shock were identified as independent risk factors for mortality, and confirm the robustness of the new classification system for risk stratification. Antimicrobial resistance defined as either MRSA, VRE, ESBL-producing, or carbapenem-resistant Gram-negative bacteria was independently associated with increased mortality (Supplement-9). Surprisingly, however, the more strict definition of either MRSA, VRE, or difficult-to-treat resistant Gram-negative bacteria was not associated with increased mortality. Probably, the cohort lacked sufficient power as in only 85 patients, difficult-to-treat Gram-negatives were involved *vs*. 341 ESBL-producing or carbapenem-resistant Gram-negative bacteria. We have no explanation for the favorable association with anti-MRSA agents. This can hardly be due to the anti-MRSA



Legend: Several types of source control interventions could have been executed in a single patient.

Fig. 2 Initial approach to control the source of infection. Several types of source control interventions could have been executed in a single patient

Table 5 Mortality according to alternative classification of intra-abdominal infection

Severity of disease expression	Setting of infection acquisition								
	Community-acquired			Early onset hospital-acquired			Late-onset hospital-acquired		
Septic shock	18/64 28.1%	25/83 30.1%	48/101 47.5%	21/63 33.3%	13/61 21.3%	37/91 40.7%	45/103 43.7%	48/110 43.6%	94/190 49.5%
Sepsis	13/116 11.2%	42/221 19%	37/174 21.3%	27/90 30%	33/170 19.4%	43/128 33.6%	26/147 17.7%	62/237 26.2%	99/275 36%
Infection	1/7 14.3%	3/22 13.6%	4/22 18.2%	0/7 0%	0/21 0%	2/14 14.3%	1/12 8.3%	8/36 22.2%	2/23 8.7%
	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		

activity as such, since MRSA was isolated in only 20 patients. The advantageous association might be due to the anti-enterococcal activity of these agents. Yet, enterococcal coverage as such (not necessarily covering MRSA) was not retained in the final regression model assessing relationships with mortality. Hence, this observation might just be an incidental finding. On the other hand, the absence of an association between empiric antifungal therapy and outcome seems consistent with the finding of other cohort studies and randomized-controlled trials that did not demonstrate the effect of empirical *Candida* coverage and favorable outcome [25, 26].

Table 6 Independent relationships with mortality in critically ill patients with intra-abdominal infection

Variable	Model with source control achievement* OR (95% CI)	Model without source control achievement** OR (95% CI)
Setting of infection acquisition		
Community-acquired infection	Reference	Reference
Early onset hospital-acquired infection (≤ 7 days)	1.15 (0.84–1.58)	1.18 (0.88–1.59)
Late-onset hospital-acquired infection (> 7 days)	1.76 (1.34–2.32)	1.76 (1.36–2.30)
Anatomical disruption		
No anatomical barrier disruption	Reference	Reference
Anatomical disruption with localized peritonitis	1.28 (0.95–1.75)	1.26 (0.95–1.69)
Anatomical disruption with diffuse peritonitis	1.99 (1.49–2.67)	2.04 (1.55–2.70)
Severity of disease expression		
Infection	Reference	Reference
Sepsis	2.44 (1.37–4.66)	2.28 (1.31–4.28)
Septic shock	5.22 (2.91–10)	4.93 (2.80–9.30)
Age (per year increase)	1.03 (1.02–1.04)	1.03 (1.03–1.04)
Underlying conditions		
Malnutrition (body mass index < 20)	2.07 (1.34–3.17)	2.15 (1.43–3.21)
Diabetes mellitus	1.31 (0.99–1.73)	1.32 (1.01–1.72)
Liver failure	2.03 (1.23–3.33)	2.50 (1.55–4.02)
Congestive heart failure	1.86 (1.24–2.81)	1.92 (1.31–2.81)
Empiric antimicrobial coverage		
Anti-MRSA agent	0.77 (0.59–1)	0.77 (0.59–0.98)
Double anaerobe coverage	–	1.28 (0.97–1.71)
Source control achievement at day 7		
Success	Reference	–
Failure, persistent signs of inflammation	4.85 (3.79–6.22)	–
Failure, additional intervention required following initial approach	1.93 (1.41–2.65)	–

The variable "antimicrobial resistance" defined as either MRSA, vancomycin-resistant enterococci (VRE), or difficult-to-treat resistant Gram-negative bacteria did not achieve the final regression model. Supplement-9 reports the results of the logistic regression models with antibiotic resistance defined as either MRSA, VRE, ESBL-producing, or carbapenem-resistant Gram-negative bacteria. In these logistic regression models, antibiotic resistance was associated with increased risk of mortality, while other covariates remained stable

OR odds ratio, *CI* confidence interval, *MRSA* methicillin-resistant *Staphylococcus aureus*

*Area under the receiver-operating curve characteristic: 0.778; **Area under the receiver-operating curve characteristic: 0.689

This study has limitations. This is an observational cohort study disposed to confounding. Some geographic regions are poorly represented obstructing conclusive results. Evaluation of source control achievement remains a subjective appreciation performed by the attending physician; given the study scale, it was not feasible to establish an independent panel for in-depth evaluation of source control as previously reported [27]. At the same line, given the observational study design, there was no predefined approach to source control [7]. In addition, with this paper, we intended to provide a general epidemiological snapshot. Therefore, detailed country-specific or disease-specific analyses fell outside the scope of this report. Finally, we could not report the proportion of ICU patients with intra-abdominal infection/sepsis as the total number of admissions during the inclusion of cases was not recorded.

In conclusion, this multinational cohort of ICU patients with intra-abdominal infection revealed that late-onset healthcare-associated infection, diffuse peritonitis, and sepsis or septic shock are independent risk factors for mortality. Therefore, setting of infection acquisition, anatomical disruption, and severity of disease expression are disease-specific phenotypic characteristics associated with outcome, irrespective of the type of intra-abdominal infection. Antimicrobial resistance is mainly an issue of Gram-negatives and a particular concern in specific geographic areas and associated with worse outcome as was failure of source control.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-019-05819-3) contains supplementary material, which is available to authorized users.

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