Journal of Critical Care 50 (2019) 169–176

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Outcomes/Predictions

Risk factors for mortality and cost implications of complicated intra-abdominal infections in critically ill patients

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ARTICLE INFO

Keywords:
Intra-abdominal infections
Adequate empirical therapy
Source control
Hospital costs

ABSTRACT

Purpose: To assess risk factors for 28-day mortality and cost implications in intensive care unit (ICU) patients with complicated intra-abdominal infections (cIAIs).
Methods: Single-center retrospective cohort study of prospectively collected data analysing ICU patients with a microbiologically confirmed complicated intra-abdominal infections.
Results: 137 complicated intra-abdominal infections were included and stratified according to the adequacy of antimicrobial therapy (initial inadequate antimicrobial therapy [IIAT], n = 44; initial adequate antimicrobial therapy [IAAT], n = 93). The empirical use of enterococci/methicillin-resistant *Staphylococcus aureus* active agents and of carbapenems was associated with a higher rate of therapeutic adequacy ($p = 0.016$ and $p = 0.01$, respectively) while empirical double gram-negative and antifungal therapy did not.
IAAT showed significantly lower mortality at 28 and 90 days and increased clinical cure and microbiological eradication ($p < 0.01$). In the logistic and Cox-regression models, IIAT and inadequate source control were the unique predictors of 28-day mortality.
No costs differences were related to the adequacy of empirical therapy and source control. The empirical double gram-negative and antifungal therapy ($p = 0.03$, $p = 0.04$) as well as the isolation of multidrug-resistant (MDR) bacteria and the microbiological failure after targeted therapy were drivers of increased costs ($p = 0.004$, $p = 0.04$).
Conclusions: IIAT and inadequate source control are confirmed predictors of mortality in ICU patients with complicated intra-abdominal infections. Empirical antimicrobial strategies and MDR may drive hospital costs.

1. Introduction

Intra-abdominal infections (IAIs) represent a wide spectrum of pathological conditions, ranging from uncomplicated appendicitis to faecal peritonitis [1]. IAIs are defined as complicated (cIAIs) when infection extends beyond the affected hollow viscus into the peritoneal space, causing either localized or diffuse peritonitis [2-5]. Despite the improvements in patient care, therapeutic failure still occurs and cIAIs remain a leading

Abbreviations: cIAI, (complicated Intra-abdominal Infection); ICU, (intensive care unit); ARDS, (acute respiratory distress syndrome); MDR, (multidrug-resistant); IAAT, (initial adequate antimicrobial therapy); SAPS II, (simplified acute physiology score II); SOFA, (sequential organ failure assessment); ESM, (electronic supplementary material); I-NHS, (Italian National Health Service); DRG, (Diagnosis-Related Group); OR, (odds ratio); ROC, (receiver operating characteristic); CRRT, (continuous renal replacement therapy); MRSA, (methicillin resistant *Staphylococcus aureus*); CA, (community-acquired); SE, (standard error).

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https://doi.org/10.1016/j.jcrc.2018.12.001
0883-9441/

cause of morbidity and mortality as well as of resource utilization in hospitalized and Intensive Care Unit (ICU) patients [6-8]. Indeed, their management turns out to be extremely complex because of their clinical presentation (septic shock, acute respiratory distress syndrome [ARDS]), ageing of the population and the growing prevalence of multidrug-resistant (MDR) microbes [9-11]. A cornerstone in the treatment of complicated intra-abdominal infections is any required source control procedure (surgical and/or radiological interventional), that should be implemented as soon as possible after the diagnosis is made, especially in the presence of septic shock [12]. The other main determinant of outcomes in cIAIs is the initial adequate antimicrobial therapy (IAAT). It should be prescribed early (after blood culture sampling, when clinically allowed) and must target all the microorganisms likely to be involved, including MDR bacteria, on the basis of patient characteristics, clinical presentation and epidemiological risk factors. The Initial inadequate antimicrobial therapy may be then narrowed and targeted on the results of infection site and routine microbiological cultures. Over the last years, literature data clearly demonstrated that the initial antimicrobial choice in patients with cIAIs significantly influences clinical and economic outcomes [6,7,13,14], the latter potentially representing a key point in the clinical decision-making process. Recently, *Dalfino* et al [15] and *Chong* et al [16] showed, in retrospective studies on patients with community-acquired- intra-abdominal infections, that early clinical failure may lead to additional days of antimicrobial therapy and of hospitalization as well as higher costs (with a great part of the extra-costs attributable to antimicrobial therapy). Similarly, in a study that included >6000 hospitalized adults with cIAIs, *Edelsberg et al* [17] demonstrated that IIAT was associated with longer hospitalization, higher hospital charges, and a higher mortality rate. Although the growing need for personalised medicine focused interventions, to our knowledge, a clinical and economic analysis targeted at a selected population of critically ill patients with microbiologically confirmed complicated intra-abdominal infections is still lacking.

Hence, the aim of the present study is to evaluate the impact of both initial inadequate antimicrobial therapy and source control on clinical and economic outcomes in this patients' population.

2. Methods

2.1. Patient population and study design

This study was conducted in the general ICU of a tertiary teaching hospital in Italy admitting approximately 1000 patients per year. We performed a retrospective analysis on data prospectively acquired from electronic ICU charts (Digistat®) and computerized investigation of microbiology laboratory databases. These data included demographic characteristics, medical history, clinical and laboratory findings, the simplified acute physiology score II (SAPS II) (calculated at ICU admission) [18] and sequential organ failure assessment (SOFA) score (calculated at infection occurrence) [19], the occurrence of abnormal laboratory measures, type of treatment and outcome. Because of its observational, non-interventional design, the study was approved by the local ethics committee, which waived informed consent (approval numbers: UCSC43601/16). Eligibility criteria were as follows: complicated intra-abdominal infection with microbiological confirmation; admission between February 2010 and February 2017; length of ICU stay ≥72 h; availability of complete clinical, microbiological and economic data. The primary outcome endpoint was 28-day mortality; secondary outcomes were clinical cure, microbiological eradication, 90-day mortality, total and disaggregated hospital costs.

2.2. Definitions

Infection onset coincided with the collection date of the first microbiological sample culture yielding the study isolate (index culture) and cIAIs were classified according to current guidelines [20], including intra-abdominal abscess related to previous intra-abdominal surgeries, secondary and tertiary bacterial peritonitis, appendicitis/diverticulitis/cholecystitis complicated by perforation and/or faecal contamination, perforation of the large or small intestine with abscess/faecal contamination. Septic shock and ARDS were defined as recommended by current guidelines [12,21]. Clinical and microbiological outcome definitions are listed in the electronic supplementary material (ESM) [22]. Adequate source control included drainage of infected fluid collections, debridement of infected solid tissue, removal of devices/foreign bodies, and definitive measures to correct anatomic derangements resulting in on-going microbial contamination and to restore optimal function within 48 h after diagnosis [11].

2.3. Cost analysis

Italian National Health Service (I-NHS) coverage extends to all members of the population and public hospitals are reimbursed by the NHS for all expenses related to inpatient care, which is reported in the form of Diagnosis- Related Group (DRG) codes. In this study, the cost of cIAIs were derived by the total expenditures incurred by the hospital to provide services or goods for each patient with documented infection. These data were retrieved from the database of the hospital's financial and administrative departments including: personnel, ordinary maintenance, hotel costs, surgical interventions, drugs used, laboratory/instrumental tests and specialists' consultations. The overall cost of antimicrobial treatment derived from the sum of the costs of all antimicrobials received by the patients, according to national official prices per unit. Post-acute care costs and those related to the loss of productivity for the patients themselves were not calculated. All costs were expressed in euros (€).

2.4. Statistical analysis

The Kolmogorov–Smirnov test was used to evaluate the distribution of variables. Data with a non normal distribution were assessed with the Mann–Whitney test, and the median and selected centile (25th–75th) values are given. The data with a normal distribution were assessed with the Student's *t*-test. Categorical variables are given as proportions, and were analysed with the chi-square test or Fisher's exact test, as appropriate. $p < 0.05$ was considered significant. The crude odds ratio (OR) and 95% CI were calculated for each variable. We included all variables in the multivariable logistic regression if they reached $p \leq 0.2$ on univariate analysis. A stepwise selection procedure was used to select variables for inclusion in the final model. The Hosmer–Lemeshow goodness-of-fit test and receiver operating characteristic (ROC) curve analysis were used to assess the goodness of the logistic final model. The Kaplan–Meier method was used for the survival analysis. We considered that 100 patients were needed to perform a multivariate analysis with at least ten variables. Based on local microbiological audit reports, a timeframe of 7 years was considered adequate to address such study population. All statistical analyses were performed using MedCalc software, version 12.2.1 (MedCalc®, MariaKerke, Belgium). Graphing of data was undertaken using Prism version 6.0 for Windows (graphPad Software, San Diego, CA).

2.5. Microbiology analysis

Microbiology analysis details are listed in the ESM [23].

3. Results

3.1. Population characteristics and treatment

During the study period, 206 patients with microbiologically confirmed complicated intra-abdominal infections were admitted to our ICU. Among those potentially eligible patients, 69 were excluded (dead

Table 1
Demographic and clinical characteristics of the 137 patients with IAI included in the study.

Variable	No. (%) of patients		P Value
	IIAT group (n = 44)	IAAT group (n = 93)	
Demographics and comorbidities			
Age, years, [IQR]	68 [56–75]	67 [53–76.3]	0.92
Males	27 (61.4)	60 (64.5)	0.87
CHF	12 (27.3)	18 (19.4)	0.38
COPD	7 (15.9)	20 (21.5)	0.5
CRF	10 (22.7)	20 (21.5)	1
Diabetes	10 (22.7)	16 (17.2)	0.49
CLD	4 (9.1)	6 (6.5)	0.73
Neoplasm	18 (40.9)	34 (36.6.)	0.71
Immunosuppressive status	4 (9.1)	18 (19.4)	0.14
Hospital stay before infection [IQR], days	14.5 [3—32]	9 [3–20.3]	0.2
ICU stay before infection [IQR], days	1.5 [0–5]	0 [0–4]	0.17
Duration of MV before infection [IQR], days	1 [0–3.75]	0 [0–2.25]	0.19
Duration of vasopressors before infection [IQR], days	0 [0–2]	0 [0–2]	0.84
Hospital stay after infection [IQR], days	18.5 [11–37.5]	21 [11.8–41.3]	0.61
ICU stay after infection [IQR], days	12.5 [8–20.5]	15 [6.8–23]	0.8
Duration of MV after infection [IQR], days	9 [3—13]	8 [3–15]	0.74
Duration of vasopressors after infection [IQR], days	6.5 [2.5–10]	5 [3—10]	0.81
Presenting features			
Hospital-acquired infection	30 (68.2)	71 (76.3)	0.41
ICU-acquired infection	14 (31.8)	23 (24.7)	0.41
SAPS II score [IQR]	48 [32.5–58]	46 [36–58]	0.66
SOFA score at infection [IQR]	7 [5–9]	8 [6.8–10]	0.04
Charlson Comorbidity Index[IQR]	5.5 [3–7]	6 [4–7.3]	0.46
Septic shock on occurrence of infection	34 (77.3)	66 (71)	0.4
ARDS on occurrence of infection	10 (22.7)	13 (14)	0.22
CRRT on occurrence of infection	17 (38.6)	30 (32.3)	0.56
PCT on occurrence of infection [interval], ng/mL	1.8 [0.58–54]	3.78 [1.4–25.5]	0.46
1–3 Beta-D-Glucan ≥80 pg/ml on occurrence of infection	15 (34.1)	25 (26.9)	0.42
Type of IAI			
Secondary peritonitis	20 (45.5)	38 (40.9)	0.71
Tertiary peritonitis	3 (6.8)	6 (6.5)	1
Abdominal abscess	7 (15.9)	25 (26.9)	0.2
Pancreatitis	3 (6.8)	8 (8.6)	1
Biliary tract infection	8 (18.2)	11 (11.8)	0.43
Other[a]	3 (6.8)	5 (5.4)	0.71
Polymicrobial infection[b]	33 (75)	58 (62.4)	0.18
Gram-negative bacteria	38 (86.4)	67 (72)	0.08
MDR isolates[c]	25 (56.8)	38 (40.9)	0.07
Secondary bacteraemia	29 (65.9)	42 (45.2)	0.03
Source control			
Inadequate source control	28 (63.6)	36 (38.7)	0.01
Upper abdomen surgery	11 (25)	29 (31.2)	0.55
Lower abdomen surgery	8 (18.2)	35 (37.6)	0.03
Hepatobiliary surgery	12 (27.3)	14 (15.1)	0.1
Other procedures[d]	13 (29.5)	15 (16.1)	0.08
Reoperation	30 (68.2)	63 (67.7)	0.89
Therapeutic aspects			
Combination empirical therapy	30 (68.2)	75 (80.6)	0.17
Empirical gram-positive therapy (*enterococcus* spp. and MRSA)[e]	25 (56.8)	72 (77.4)	0.016
Empirical antifungals	13 (29.5)	37 (39.8)	0.26
Empirical double gram-negative bacteria therapy[f]	10 (22.7)	22 (23.7)	1
Empirical carbapenems	13 (29.5)	51 (54.8)	0.01
Duration of treatment, median days [interval]	15.5 [8.5–20]	14 [9–20]	0.92
De-escalation	16 (36.4)	31 (33.3)	0.85
Clinical and microbiological outcome			
28-day mortality	35 (79.5)	22 (23.7)	<0.01
90-day mortality	37 (84.1)	32 (34.4)	<0.01
Clinical cure	8 (18.2)	65 (69.9)	<0.01
Microbiological eradication[g]	6 (13.6)	38 (40.9)	<0.01

Data are shown as N (%), unless otherwise indicated.
IIAT: initial inadequate antimicrobial therapy; IAAT: initial adequate antimicrobial therapy IQR: interquartile range; SAPS II: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; ICU: intensive care unit; MV: mechanical ventilation; ARDS: acute respiratory distress syndrome; CRRT: continuous renal replacement therapy; PCT: procalcitonin; CHF: chronic heart failure; COPD: chronic obstructive pulmonary disease; CRF: chronic renal failure; CLD: chronic liver disease; IAI: intra-abdominal infection; BSI: bloodstream infection; MDR: multi-drug resistant; Ab, *Acinetobacter baumannii*; Pa, *Pesudomonas aeruginosa*; Kp, *Klebsiella pneumniae*; MRSA, methicillin-resistant *Staphylococcus aureus*.
[a] Gut ischemia in three patients and *Clostridium difficile* colitis in five patients.
[b] IIAT group: 78 total isolated bacteria: 11 monomicrobial infections, 32 infections with two bacteria and one infection with three bacteria. IAAT group: 153 total isolated bacteria, 35 monomicrobial infections, 56 infections with two bacteria and two infections with three bacteria.
[c] MDR species: Carbapenem-R *Kp*, *Ab*, *Pa* (41%), 3rd generation cephalosporin-R *Enterobacteriaceae* (27%), MRSA/ampicillin-R *enterococci* (21%), azole-R fungi (11%).
[d] 25 percutaneous drainages and three endoscopic biliary procedures.
[e] Glycopeptide (n = 56), Tigecycline (n = 21), Linezolid (n = 20).
[f] Anti-pseudomonal beta-lactam plus aminoglycoside/colistin (n = 21) or tigecycline (n = 6) or quinolones (n = 5).
[g] Microbiological outcome was analysed in 105 patients: 41 patients (IIATgroup) and 64 patients (IAAT group).

within 72 h [n = 12]; discharged within 72 h [n = 36], missing data [n = 21]), and 137 were selected for the analysis. The majority of the infections were classified as hospital-acquired (n = 101 out of 137, 73.7%), affecting critically ill patients with septic shock, ARDS and acute kidney injury requiring continuous renal replacement therapy [CRRT] (73%, 16.8% and 34.3%, respectively). Main type of complicated intra-abdominal infections was secondary peritonitis (n = 58, 42.3%) with a relevant rate of abdominal abscesses (n = 32, 23.4%) and biliary tract infections (n = 19, 13.9%). Almost seven out of ten patients harboured a polymicrobial infection (n = 91, 66.4%), where gram-negative bacteria (n = 105, 76.6%) and MDR species (n = 63, 46%) were mostly represented. About half of the patients had positive blood cultures (n = 73, 51.8%). Source control was inadequate in half of the patients (n = 64, 46.7%), including upper and lower abdomen surgery (n = 83, 60.6%) with more than half undergoing at least one reoperation (n = 93, 67.9%). In 105 patients, the empirical antimicrobial treatment included at least two drugs and in 32 of them a double gram-negative therapy was adopted. In one out three of the cases, antimicrobial therapy was de-escalated according to final microbiological results (n = 47, 34.3%) (Table 1). According to antimicrobial susceptibility testing results, 44 patients (32.1%) received an inadequate initial antimicrobial therapy (IIAT group) while 93 (67.9%) received an adequate coverage during the empirical phase of the treatment (IAAT group) (Table 1). There were no significant between-group differences in terms of demographic characteristics and main comorbidities. Similarly, presenting features were similar with the exception of SOFA score at infection occurrence which was lower in the IIAT group compared with the IAAT group (7 [5–9] vs. 8 [6.8–10], p = 0.04). Regarding the type of surgery, patients in the IIAT group more frequently underwent inadequate source control (63.6% vs. 38.7%, p = 0.01) and were more frequently managed with percutaneous or endoscopic procedures (29.5% vs. 16.1, p = 0.08). In the entire cohort 231 pathogens were isolated: 78 in the IIAT group (22 g-positive, 38 g-negative, 14 fungi and four anaerobes) and 153 in the IAAT group (52 g-positive, 67 g-negative, 25 fungi and nine anaerobes). Although the rate of polymicrobial infections did not differ between the groups (75% vs. 62.4%, p = 0.18), patients who received IIAT were more frequently infected with gram-negative (86.4% vs. 72%, p = 0.08) and MDR organisms (56.8% vs. 40.9%, p = 0.07), with a

higher rate of positive blood cultures (65.9% vs. 45.2%, p = 0.03). Interestingly, in the empirical phase, combination therapy was used in the majority of the patients (68.2% in the IIAT group and 80.6% in the IAAT, p = 0.17), and a scheme including gram-positive coverage and carbapenems was associated with a significant higher rate of appropriate therapy (56.8% and 29.5% in the IIAT group, 77.4% and 54.8% in the IAAT group, p = 0.016 and p = 0.01 respectively). On the other hand, the use of a combination therapy including two drugs active against gram-negative bacteria or the use of empirical antifungals did not increase the probability of IAAT (22.7% vs. 23.7%, p = 1 and 29.5% vs. 39.8%, p = 0.26, respectively), (Fig. 1a). Finally, the probability of IIAT was significant higher when MDR bacteria and polymicrobial infections occurred in patients with septic shock (65% vs. 39%, p = 0.02 and 80% vs. 59%, p = 0.046), (Fig. 1b).

3.2. Outcomes and predictors of mortality

Twenty-eight day mortality and 90-day mortality were significantly higher in patients who received IIAT compared with those ones appropriately treated since the beginning (79.5% vs. 23.7%, p < 0.01; 84.1% vs. 34.4%, p < 0.01, respectively). Similarly, clinical cure and microbiological eradication occurred more frequently in those ones who received an adequate empirical coverage (69.9% vs. 18.2%, p < 0.01; 40.9% vs. 13.6%, p < 0.01) (Table 1). On univariate analysis (Table 2) inadequate source control more frequently occurred in deceased patients (68.4% vs. 31.3%, p < 0.01), who showed higher SAPS II and SOFA score, compared with survivors. Similarly, septic shock and ARDS on infection diagnosis and secondary bacteraemia were observed more frequently in patients who died. In multivariable regression analysis, both the initial inadequate antimicrobial therapy and the inadequate source control were independent predictor of 28-day mortality (Table 3). The multivariate Cox-regression model confirmed the association of the IIAT and inadequate source control with 28-day outcomes (OR 4.77, 95% CI 2.78–8.18; OR 3.1, 95% CI 1.76–5.41), and the differences in survival between treatment groups were also found on Kaplan-Meier survival curve analyses (p < 0.01) (Fig. 2).

3.3. Cost analysis

Total mean ± SD and median [IQR] hospital costs for patients with cIAIs were € 38,025 ± 26,348 and 30,939 [21437–27,771], respectively. Compared with national reimburse rules, the median amount of extra expenses attributable to the occurrence of the cIAI was +8898 € [IQR: +25,844 / −1026]. Although ICU LOS related costs were higher in patients who died within the first 28 days and undergoing IIAT or inadequate source control, there were no statistically significant differences in disaggregated costs of hospitalization (ICU and non ICU) and antimicrobials (antibiotics and antifungals) according to 28-day outcome, adequacy of empirical therapy and source control (Table 4). However, the presence of MDR bacteria and the microbiological failure after therapy significantly influenced hospital costs (median [IQR]: € 39,413 [24,417–56,343] vs. 27,606 [19,541–41,574] and € 36,827 [25,727–54,670] vs. 29,340 [19,371–46,007], respectively). Similarly, the adoption of a double gram-negative therapy and the use of empirical antifungals were associated with significantly higher inpatients charges (median [IQR]: € 42,683 [26,136–58,474] vs. 29,460 [20,282–45,497] and € 40,293 [25,933–54,475] vs. 28,569 [20,219–45,322], respectively), without any observed clinical benefit (Fig. 3a and b).

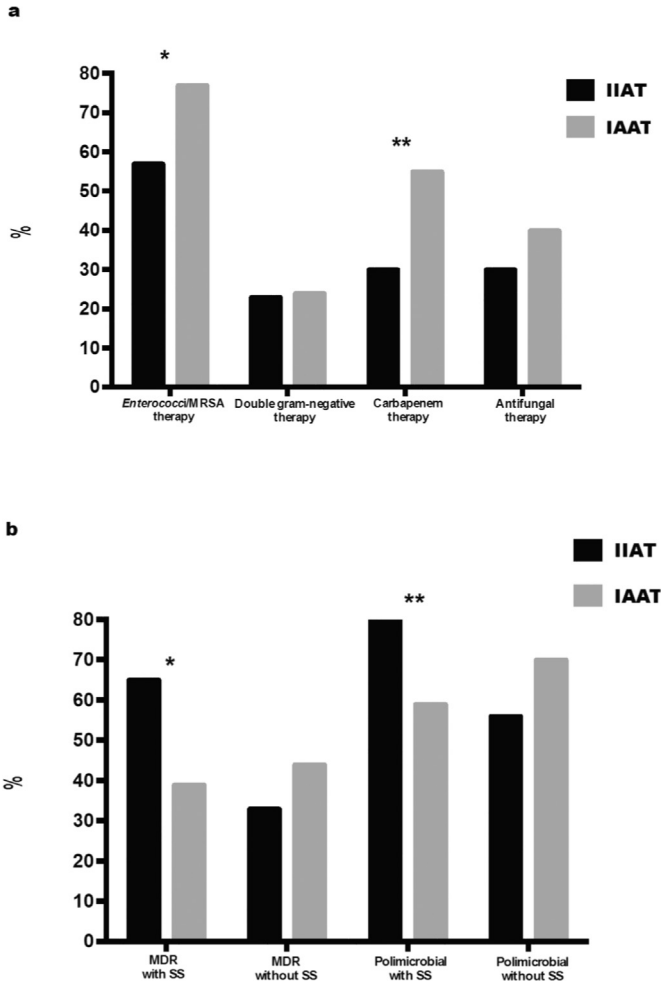

Fig. 1. Empirical therapy adequacy according to antimicrobial types (1a) and resistance (1b). MRSA: methicillin resistant *Staphylococcus aureus*; IIAT: initial inadequate antimicrobial therapy; MDR:multidrug-resistant; SS: septic shock. * p = 0.016 ** p = 0.01. * p = 0.02 ** p = 0.046.

4. Discussion

In this population of critically ill patients with microbiologically confirmed complicated intra-abdominal infections, initial inadequate antimicrobial therapy and inadequate source control increased 28-day mortality. The empirical use of carbapenems as well as of antibiotics active against enterococci/methicillin-resistant *Staphylococcus aureus* (MRSA) increased the rate of treatment appropriateness. On the other hand, the adoption of a strategy including two gram-negative antibiotics or empirical antifungals was associated with increased hospital costs, without observing clinical benefits.

Complicated intra-abdominal infections represent a major issue in the management of critically ill patients, being associated with high mortality and morbidity rate [1,4,9,24,25]. Current literature highlights the importance of early recognition of complicated cases, that requires immediate evaluation and appropriate prompt medical and surgical management [2,20,26]. Adequacy of initial antimicrobial therapy has a pivotal role in the optimization of such patients' outcome, but no >70% of ICU patients with cIAIs have positive microbiological cultures which may drive optimization of targeted treatment [24]. In line with current literature, our patients' clinical and microbiological outcome was strongly influenced by the inadequacy of empirical antimicrobials, with a quite high IIAT rate (44/137, 32.1%) mainly driven by the presence of MDR bacteria and polymicrobial flora (Fig. 1a) [3,7,8,10,13]. Interestingly, in a recent observational study, *Chong* et al. showed that failure in initial antibiotic therapy significantly increased morbidity and length of hospital stay, but that population was almost totally represented by community acquired (CA)-infections with a 9% of IIAT rate [16]. Conversely, in a cohort of 311 nosocomial-cIAIs, one out of five cases underwent antimicrobial escalation according to final microbiological results, with an associated mortality rate of 28% [27]. Compared with current literature, our substantial higher rate of

Table 2
Univariate analysis of factors associated with 28-day mortality.

Variable	No. (%) of patients		Univariate analysis	
	Alive (n = 80)	Deceased (n = 57)	P Value	OR (95% CI)
Demographics and comorbidities				
Age, years, [IQR]	67 [52.5–76.5]	67 [57–75]	0.56	1.01 [0.98–1.03]
Males	53 (66.3)	34 (59.6)	0.43	0.75 [0.37–1.52]
CHF	16 (20)	14 (24.6)	0.55	1.28 [0.57–2.9]
COPD	16 (20)	11 (19.3)	0.92	0.96 [0.41–2.25]
CRF	15 (18.8)	15 (26.3)	0.29	1.55 [0.68–3.49]
Diabetes	13 (16.3)	13 (22.8)	0.34	1.52 [0.65–3.59]
CLD	5 (6.3)	5 (8.8)	0.58	1.44 [0.39–5.24]
Neoplasm	26 (32.5)	26 (45.6)	0.12	1.74 [0.87–3.51]
Immunosuppressive status	12 (15)	10 (17.5)	0.69	1.21 [0.48–3.02]
ICU stay before infection [IQR], days	0 [0–4]	1 [0–5]	0.36	0.98 [0.94–1.02]
Duration of MV before infection [IQR], days	0 [0–2]	0.5 [0–3]	0.28	0.98 [0.93–1.03]
Duration of vasopressors before infection [IQR], days	0 [0–2]	0 [0–2]	0.15	0.92 [0.83–1.03]
Presenting features				
Hospital-acquired infection	58 (72.5)	42 (73.7)	0.7	1.17 [0.53–2.53]
ICU-acquired infection	21 (26.3)	16 (28.1)	0.81	1.09 [0.51–2.35]
SAPS II score [IQR]	42 [31–55.5]	51 [39.8–58.3]	0.03	1.02 [1.01–1.04]
SOFA score at infection [IQR]	8 [6.5–10]	8 [5–10]	0.06	0.91 [0.83–1.01]
Charlson Comorbidity Index [IQR]	5,5 [3.5–7]	6 [4–8]	0.25	1.07 [0.95–1.21]
Septic shock on occurrence of infection	54 (67.5)	46 (80.7)	0.05	2.21 [0.97–5.07]
ARDS on occurrence of infection	10 (12.5)	13 (22.8)	0.1	2.12 [0.85–5.24]
CRRT on occurrence of infection	24 (30)	23 (40.4)	0.21	1.58 [0.77–3.22]
PCT on occurrence of infection [interval], ng/mL	4,1 [1.7–27.7]	2.3 [0.6–18.5]	0.24	0.99 [0.98–1.01]
Beta-D-Glucan ≥80 pg/ml on occurrence of infection	23 (28.8)	17 (29.8)	0.89	1.05 [0.5–2.22]
Type of infection and therapy				
Secondary peritonitis	34 (42.5)	24 (42.1)	0.96	0.98 [0.5–1.96]
Tertiary peritonitis	6 (7.5)	3 (5.3)	0.6	0.69 [0.16–2.86]
Abdominal abscess	20 (25)	12 (21.1)	0.59	0.8 [0.35–1.8]
Pancreatitis	8 (10)	3 (5.3)	0.3	0.5 [0.13–1.97]
Biliary tract infection	10 (12.5)	9 (15.8)	0.59	1.31 [0.5–3.47]
Others	2 (2.5)	6 (1.1)	0.07	4.59 [0.89–23.62]
Polymicrobial infection	51 (63.8)	40 (70.2)	0.43	1.34 [0.65–2.77]
MDR isolates	36 (45)	27 (47.4)	0.84	1.08 [0.54–2.13]
Secondary bacteraemia	36 (45)	35 (61.4)	0.06	1.94 [0.97–3.9]
Source control				
Inadequate source control	25 (31.3)	39 (68.4)	< 0.01	4.77 [2.3–9.9]
Upper abdomen surgery	22 (27.5)	18 (31.6)	0.61	1.21 [0.58–2.56]
Lower abdomen surgery	29 (36.3)	14 (24.6)	0.14	0.57 [0.27–1.22]
Hepatobiliary surgery	11 (13.8)	15 (26.3)	0.07	2.24 [0.94–5.33]
Other procedures	18 (22.5)	10 (17.5)	0.48	0.73 [0.31–1.73]
Reoperation	57 (71.3)	36 (63.2)	0.32	0.69 [0.34–1.43]
Therapeutic aspects				
Combination empirical therapy	61 (76.3)	44 (77.2)	0.55	1.3 [0.55–3.08]
IIAT	9 (11.3)	35 (61.4)	< 0.01	12.55 [5.23–30.1]
Empirical anti Gram-positive bacteria coverage (*enteroccus* spp. and MRSA)	56 (70)	41 (71.9)	0.81	1.1 [0.52–2.34]
Empirical anti fungal coverage	30 (37.5)	20 (35.1)	0.77	0.9 [0.44–1.83]
Empirical anti Gram-negative double coverage	22 (27.5)	10 (17.5)	0.17	0.56 [0.24–1.3]
Empirical therapy with carbapenems	39 (48.8)	25 (43.9)	0.57	0.82 [0.42–1.63]
Duration of treatment, median days [interval]	15 [8.5–20]	14 [9–20]	0.82	0.99 [0.95–1.04]
De-escalation	24 (30)	23 (40.4)	0.21	1.58 [0.77–3.22]

Data are shown as N (%), unless otherwise indicated.
IIAT: initial inadequate antimicrobial therapy; IQR: interquartile range; SAPS II: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; ICU: intensive care unit; MV: mechanical ventilation; ARDS: acute respiratory distress syndrome; CRRT: continuous renal replacement therapy; PCT: procalcitonin; CHF: chronic heart failure; COPD: chronic obstructive pulmonary disease; CRF: chronic renal failure; CLD: chronic liver disease; IAI: intra-abdominal infection; BSI: bloodstream infection; MDR: multi-drug resistant; MRSA: methicillin resistant *Staphylococcus aureus*.

inappropriate empirical therapy may be explained by the peculiarity of the study population which was mainly represented by the sickest patients with multi-organ failure. On top of that, the majority of these cases were secondary/tertiary peritonitis, sharing many risk factors for the isolation of MDR bacteria. All these peculiarities may contribute to explain the high mortality rate observed in our study. Nonetheless, the majority of published studies are focused on less severe forms of complicated intra-abdominal infections, such as CA-infections, excluding higher-risk patients requiring ICU admission, where a definitive and adequate medical and surgical approach may not be feasible in most cases. Additionally, our setting was predominantly characterized by both polymicrobial and antimicrobial resistant infections where, especially in presence of septic shock, initial inadequate treatment was significantly higher, leading to increased overall mortality. Indeed, it is not surprising that either the empirical use of agents active against enterococci and MRSA (i.e. glycopeptides, linezolid, tigecycline) or of carbapenems was associated with a lower rate of initial inadequate antimicrobial therapy, explaining the observed high rate of empirical combination therapy (n = 105, 76.6%). In such a peculiar setting it is not simple to accomplish the goals of antimicrobial stewardship programs and the adoption of narrower spectrum empirical antibiotics may be associated with a dangerous increase in antimicrobial inappropriateness. Conversely, de-escalation still retains its clinical and epidemiological outstanding relevance, as far as less broad spectrum antibiotics may

Table 3
Multivariable logistic regression analysis of factors associated with 28-day mortality.

Variable	P	OR (95% CI)
Initial inadequate antimicrobial therapy	<0.01	11.4 (4.02–32.3)
Inadequate source control	0.004	4.1 (1.56–10.64)

We included all variables in the multivariable logistic regression if they reached p ≤ 0.2 on univariate analysis (neoplasm, p = 0.12; duration of vasopressors before infection, p = 0.15; SAPS II score SOFA score at infection, p = 0.03; septic shock at infection occurrence, p = 0.05; ARDS at infection occurrence, p = 0.1; other type of infection, p = 0.07; secondary bacteraemia, p = 0.06; inadequate source control, p < 0.01; lower abdominal surgery, p = 0.14; hepatobiliary surgery, p = 0.07; IIAT, p < 0.01; empirical anti-Gram negative double coverage, p = 0.17). A stepwise selection procedure was used to select variables for inclusion in the final model ROC curve analysis was used to assess the goodness of the final logistic regression model (AUC ± SE = 0.87 ± 0.03 with 95% CI 0.8–0.92; chi-square statistics p < 0.001).
AUC: area under the curve; OR: odds ratio; ROC: receiver operating characteristic; SE: standard error.

be used and source control has been successful. All these observations are in line with current guidelines and expert opinions which highlight the importance to empirically cover MDR bacteria in presence of recognized risk factors [12], adding a supplemental gram-negative agent in selected settings where carbapenem resistance rate may be a clinical issue [28]. Similarly, the adoption of a biomarker-driven antifungal therapy is widely recognized as a successful approach to reduce ecological pressure without increasing the rate of inappropriate empirical antifungal therapy which, otherwise, is a strong predictor of hospital mortality [11,29,30].

Source control represents the mainstay of cIAIs management, especially in critically ill setting [31,32]. In our cohort, we observed a high rate of inadequate source control, reaching 63.6% and 38.7% in IIAT and IAAT respectively, being a strong independent predictor of 28-day mortality. These results are in line with current literature addressing

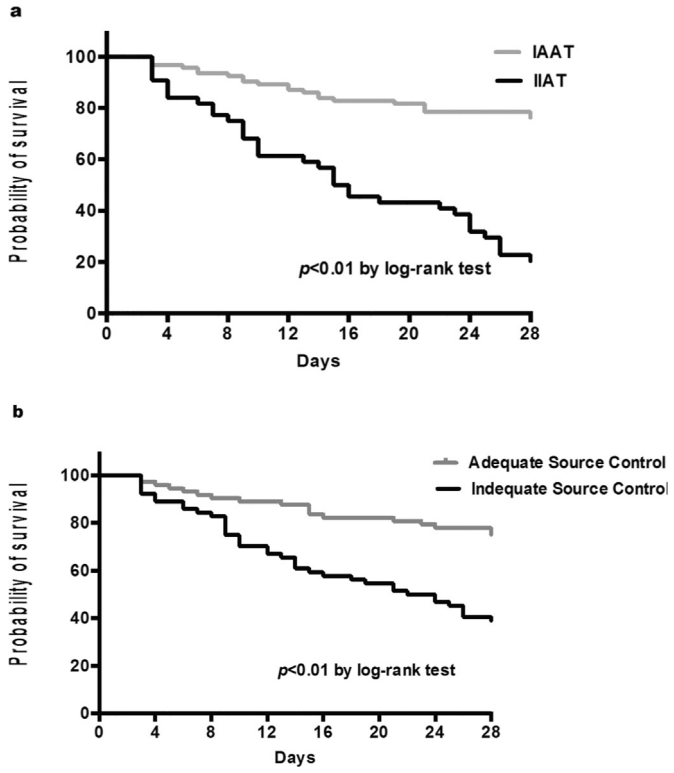

Fig. 2. Kaplan-Meier curves showing the impact of IIAT (a, *black line*) and Inadequate source control (b, *black line*) on 28-day mortality. IIAT: initial inadequate antimicrobial therapy; IAAT: initial adequate antimicrobial therapy.

Table 4
Cost of hospitalization for 137 patients with IAIs, stratified by outcome, empirical therapy and source control.

Costs (€)	Alive (28-day)	Deceased (28-day)	P Value
ICU LOS	17,360 [11,935-26,040]	21,700 [9493-29,566]	0.55
Non ICU LOS	11,616 [4356-18,029]	9196 [4840-15,972]	0.9
Antibiotics	1306 [694–2622]	1518 [733–2774]	0.92
Antifungals	2473 [1296-4305]	2394 [419–4394]	0.8
Costs (€)	IAAT	IIAT	P Value
ICU LOS	17,360 [9765–26,040]	22,785 [10,850-30,922]	0.23
Non ICU LOS	10,164 [4840-16,456]	9680 [4235-17,545]	0.89
Antibiotics	1282 [696–2554]	1615 [788–3771]	0.59
Antifungals	2394 [1332-4188]	2535 [398–4616]	0.98
Costs (€)	Adequate source control	Inadequate source control	P Value
ICU LOS	16,275 [9222-25,497]	21,700 [11,121-29,023]	0.17
Non ICU LOS	10,648[4598-18,150]	9196 [4477-16,335]	0.64
Antibiotics	1229 [670–2498]	1437 [849–3354]	0.4
Antifungals	2887 [1368-5130]	2283 [609–3157]	0.12

Data are shown as median [25th and 75th quartile].
ICU: Intensive Care Unit; LOS: Length of stay; IAAT: initial adequate antimicrobial therapy; IIAT: initial inadequate antimicrobial therapy.

the importance to manage surgically/percutaneously the source of infection in order to limit bacterial contamination, control anatomical derangements and restore normal physiology. The paramount relevance of such concepts has been recently confirmed by current Surviving Sepsis Guidelines which recommend to implement the adequate

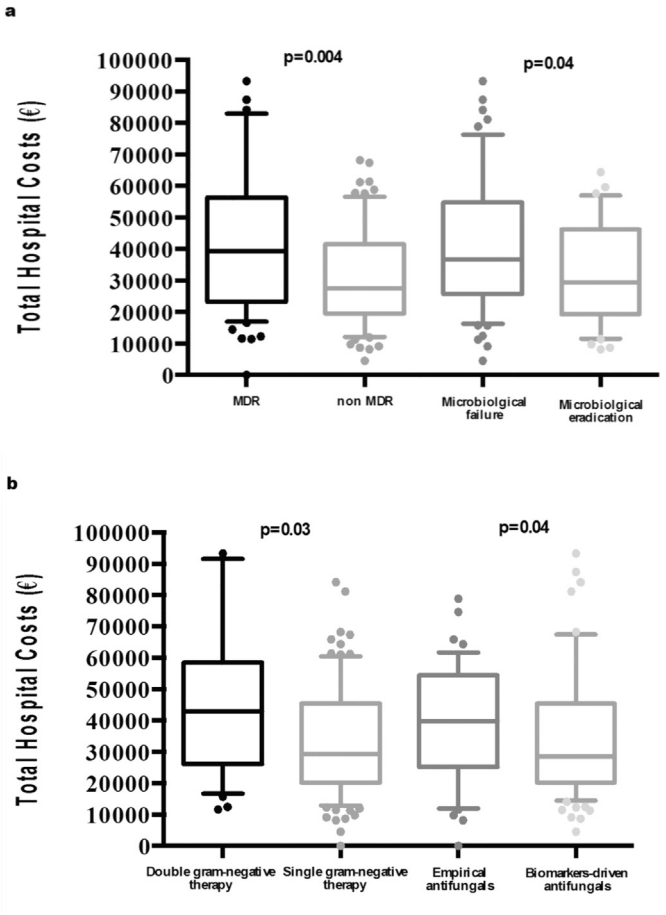

Fig. 3. Total hospitalization costs in subgroups defined by multidrug resistance, microbiological eradication (a) and type of antimicrobial empirical therapy (b). MDR: multidrug-resistance.

control of the infection source as soon as sepsis diagnosis has been ascertained [12]. Indeed, in a recent multicenter observational study on 3663 patients with sepsis and septic shock, those ones (32%) undergoing source control (i.e. complicated abdominal, urinary and soft tissue infections) showed a lower mortality rate despite greater severity and worse compliance with resuscitation bundle [33]. On top of that, also timing to source control represent a critical, often under-recognized, issue, and a delay of >6 h in the surgical approach of a cIAIs has been observed to be independently associated with increased mortality [34]. The relevant rate of inadequate source control in our population may be explained by the high severity of enrolled patients, mainly with persisting and diffuse peritonitis requiring multiple reoperations [35]. In these categories damage control surgery principles including open abdomen management with negative pressure therapy, although efficiently reducing the infectious 'inoculum' without increasing the risk of intra-abdominal hypertension and compartment syndrome, require further interventions to accomplish a definitive and complete surgical control of the intra-abdominal infection [36]. In addition, a recent observational study confirmed that, along with SAPS II values and the need for antifungals, initial urgent surgical intervention represents an independent risk factor for mortality [37]. In light of that, it is not surprising that the lack of a prompt source control has contributed to our lower de-escalation rate (34.3%) and longer antimicrobial courses (15 days), compared with current literature and international recommendations [38,39]. We did not observe significant hospital costs differences according to the adequacy of either initial antimicrobial therapy or source control, but both microbiological failure and multidrug resistance were associated with increased economical burden. This result is in contrast to previous observations where clinical failure and inadequate antibiotics were strong determinants of increased costs, mainly driven by longer hospitalizations, duration of treatment and higher numbers of interventional procedures [6,15-17,40]. In our cohort the lack of economical impact of initial inadequate antimicrobial therapy and source control could be explained by the detrimental clinical effect of both conditions which were associated with higher mortality and shorter length of ICU and hospital stay. However it is noteworthy that, although not significantly, ICU-related expenses were higher in those patients who died and underwent inadequate source control or antimicrobial therapy. Such differences were probably blunted by other out-of-ICU economical drivers that we couldn't take into account in our analysis. On the other hand expenditures related to antimicrobials costs, which accounted for less 20% of the total costs, did not differ between the groups, but the use of double gram-negative therapy and empirical antifungals determined higher costs without increasing therapeutic appropriateness. All these observations may have a relevant clinical meaning and could be taken into account in the difficult decision-making regarding critically ill patients with cIAIs, with the aim at delivering personalised medicine interventions. Our investigation has several limitations. First, the retrospective and monocentric design of the study, along with a fairly small study population, reduces the generalizability of the observed results and a prospective multinational validation is warranted to confirm them. Second, including very sick patients with difficult to treat cIAIs, the clinical and economical evaluations are not applicable in the setting of less severe cases with uncomplicated infections. Third, due to the timeframe of the study, recently approved drugs (ceftolozane-tazobactam and ceftazidime-avibactam) for cIAIs treatment were not evaluated in their potential role as carbapenem sparing strategies. Finally, by including different types of infection and surgical interventions, we were not able to verify whether the observed clinical and economical results may be valid in specific subgroup populations. Nevertheless, our paper is one of the few available studies aimed to address the clinical and economic impact of appropriate antimicrobial therapy and adequate source control in a population of critically ill, high-risk, ICU patients with microbiologically confirmed complicated intra-abdominal infections.

5. Conclusions

Our findings highlight the importance of adequate antimicrobial therapy and source control as potentially modifiable determinants of poor clinical and microbiological outcome in ICU patients with complicated intra-abdominal infections. Different antimicrobial strategies and multidrug-resistance profiles are drivers of both inappropriate empirical therapy and increased hospital costs. Nonetheless the mortality and morbidity of such complicated infections in the critically ill setting remains extremely high. Future studies should focus on possible strategies to optimize healthcare and economical resources in this peculiar patients' population.

Ethics approval and consent to participate

The study was approved by the local ethic committee, (approval numbers: UCSC43601/16). Due to its observational, non-interventional design, informed consent was waived.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing interest

The authors declare that they have no competing interests

Funding

None.

Authors' contribution

GDP and SC had full access to all the data in the study and take responsibility for the integrity and the accuracy of the data analysis. GDP, MA, SC and MM conceived the study, and participated in its design and coordination and helped to draft the manuscript. SC and GDP were in charge of the statistical analysis, participated in analysis and interpretation of data, helped to draft the manuscript, and critically revised the manuscript for important intellectual content. SC, MSV, SLC, TT, GB, LM, IU and MO collected the data for the study and participated in statistical analysis. AC, LM, GB, IU, MO, TS and MT participated in the conception, design and development of the database, helped in analysis and interpretation of data, helped in drafting of the manuscript and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript

Acknowledgement

We are indebted to Valentina Di Gravio, RN, for her scientific support. The study was partially supported by MSD Italia.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2018.12.001.

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