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Original Article

Importance of Source Control in the Subgroup of Intra-Abdominal Infections for Septic Shock Patients: Analysis of 390 Cases

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Abstract. ***Background*: This study aimed to evaluate the epidemiology of septic shock (SS) associated with intraabdominal infections (IAI) as well as associated mortality and efficacy of early source control in a tertiary-care educational hospital.**
***Methods*: Patients who had SS with IAI and consulted by Infectious Diseases consultants between December 2013 and October 2022 during night shifts in our centre were analyzed retrospectively.**
***Results*: A total number of 390 patients were included. Overall, 30-day mortality was 42.5% on day 3, while day 14 and 30 mortality rates were 63.3% and 71.3%, respectively. Source control by surgical or percutaneous operation was performed in 123 of 390 cases (31.5%), and the mortality rate was significantly lower in cases that were performed source control at any time during SS (65/123-52.8% vs 213/267-79.8%, p<0.001). In 44 of 123 cases (35.7%), source control was performed during the first 12 hours, and mortality was significantly lower in this group versus others (24/44-54.5% vs 254/346-73.4%, p=0.009). On the other hand, female gender (p<0.001, odds ratio(OR)= 2.943, 95%CI=1.714-5.054), diabetes mellitus (p= 0.014, OR=2.284, 95%CI=1.179-4.424), carbapenem-resistant Gram-negative etiology (p=0.011, OR=4.386, 95%CI=1.398-13.759), SOFA≥10 (p<0.001, OR=3.036, 95%CI=1.802-5.114), lactate >3 mg/dl (p<0.001, OR=2.764,**

95%CI=1.562-4.891) and lack of source control (p=0.001, OR=2.796, 95%CI=1.523-5.133) were significantly associated with 30-day mortality in logistic regression analysis.
***Conclusion*: Source control has a vital importance in terms of mortality rates for IAI-related septic shock patients. Our study underscores the need for additional research, as the present analysis indicates that early source control does not manifest as a protective factor in logistic regression.**

Keywords: Septic shock; Intra-abdominal infection; Source control.

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Introduction. Sepsis is currently defined as an infection with organ dysfunction. Sepsis and septic shock are important global health problems causing significant mortality and morbidity rates.[1-3] Fast and proper management of septic shock is important in terms of patient survival. Proper management includes early initiation of the antibiotics after the microbial cultures/testing, as well as prompt infectious source control.[4] Infectious source control in intra-abdominal infections comprises the rapid diagnosis of a specific infectious site and its control via a surgical intervention such as drainage of an abscess, necrotic tissue debridement, or removal of an infected device. Several studies have underscored the significance of timely source control interventions. Bloos et al. conducted a comprehensive study demonstrating that delays in surgical source control are significantly associated with increased mortality rates in patients with sepsis. Their findings revealed that every hour of delay in surgical intervention was linked to a 1% rise in 28-day mortality, with notably higher mortality rates observed when surgical source control was delayed beyond 6 hours.[5] Similarly, Azuhata et al. investigated the impact of early initiation of surgical source control in patients with gastrointestinal perforation and septic shock. Their results emphasized the critical importance of prompt surgical intervention, with survival rates declining substantially as the time to initiation of surgery increased, reaching 0% for delays exceeding 6 hours.[6] These studies collectively highlight the imperative of promptly identifying and implementing appropriate source control measures to improve outcomes in patients with sepsis and septic shock. This aligns with recommendations from the 2021 Surviving Sepsis Campaign guideline, which emphasizes the need for expedited source control interventions to rapidly identify or exclude specific anatomical diagnoses of infection requiring emergent source control, implementing any necessary interventions as soon as medically and logistically practical.[7] Herein, we aimed to evaluate the epidemiology of septic shock associated with intra-abdominal infections (IAI) as well as associated mortality and efficacy of early source control (during the first 12 h or afterward) in a tertiary-care educational hospital.

Material and Methods. This study was performed in an 1800+-bedded tertiary-care educational university hospital located in a city with a population of 4.3 million in 2017.[8]

Patients with septic shock (sepsis+hypotension+ adrenergic agent+arterial lactate level of >2mg/dL)[2] and IAI and consulted by Infectious Diseases consultants during night shifts between the December 1st, 2013, and October 15th, 2022, in our center were recorded prospectively and analyzed retrospectively. The patients were evaluated following the first visit on days 3, 14, and 30. Septic shock definition was considered to be sepsis with hypotension requiring vasopressors to maintain a mean arterial blood pressure above 65 mm Hg despite adequate fluid resuscitation.[1] Systemic inflammatory response syndrome (SIRS), Quick Sequential Organ Failure Assessment (qSOFA), and SOFA (sequential organ failure assessment) scores with suspected infection were used for the definition of sepsis.[2,7] SIRS was defined by several clinical variables, including temperature >38°C or <35°C, heart rate >90 beats/min, respiratory rate >20 breaths/min or PCO_2 < 32 mmHg, and WBC > 12000 cells/mm^3 or <4000 cells/mm^3. After that, 2 or more points increase in SOFA score or qSOFA score was used for the definition of sepsis. For qSOFA, the following data were used: 1 point for each systolic arterial blood pressure ≤100 mm Hg, respiratory rate above 21 breaths per minute, or altered mental status.

Case assessment forms included data related to the demographical and clinical findings of septic shock

patients, as well as microbiological culture results, surgical operation schedules, and mortality rates. Clinical assessment and radiological or surgical operation reports determined underlying intra-abdominal infectious foci.

The inclusion criteria were:

- Age ≥ 18-year-old (adult patients were included)
- Meeting the criteria of the septic shock described above as well as a final diagnosis of IAI, which was defined as a complicated IAI infection that extended beyond the hollow viscus of origin into the peritoneal space and was associated with either abscess formation or peritonitis, whereas, uncomplicated infection involved intramural inflammation of the gastrointestinal tract and had a substantial probability of progressing to complicated infection if not adequately treated.[9]

The exclusion criteria were:

- The presence of an infectious source other than IAI
- IAI patients from other hospitals are referred to our center without exact intervention time records, and patients are referred from our center to other centers due to the need for more available beds in intensive care units (ICU).

Microbiological Analysis. Peripheral/catheter blood cultures were inoculated into aerobic and anaerobic culture bottles (BacT/ALERT, BioMérieux, Durham, USA), and an automated microbial detection system (BacT/ALERT 3D, BioMérieux, Durham, USA) was used. Signal-positive blood culture samples, together with other samples like urine, intra-abdominal fluid/pus, etc, were inoculated into 5% blood sheep agar and Eosin Methylene-blue Lactose Sucrose (EMB) agar (BioMerieux, France). MALDI-TOF mass spectrometry (VITEK MS, BioMérieux, France) was used for microbial identification. Antibiotic sensitivity tests were performed using the VITEK2 (BioMérieux, France) system and evaluated according to EUCAST criteria.[10] Carbapenem minimum inhibitory concentration (MIC) levels were determined by gradient tests (E test, BioMérieux, France). An antimicrobial regimen was considered to be appropriate when the isolated pathogens were found to be sensitive to the empirically started antibiotics according to the antibiotic susceptibility test results.

Ethics. The local Institutional Review Board approved the study (21-6.IT/63 on 25/06/2021).

Statistical Analysis. SPSS 25.0 program (Statistical package for the social sciences) was used for the statistical analysis. A comparison of categorical values between the two groups was performed via the Chi-square test. Student t-test was performed for the numerical values of the independent groups.

Binary logistic regression was performed using the enter method. Day 30 mortality rate was the dependent variable, and the variables with a $p<0.05$ in univariate analysis were used as covariates, i.e., source control, source control within the first 12 hours, lactate>3 mg/dL. A p-value of less than 0.05 was considered significant.

Results.

General Characteristics. There were a total of 390 patients (mean age 67.26 ±0.73 years and 44.6% female) fulfilling the study inclusion criteria. A total of 166 (42.6%) cases were aged ≥65-year-old. Mean leucocyte, CRP, procalcitonin, and lactate levels at the time of septic shock diagnosis were 18621 ± 1738/mm^3, 143.05 ± 6.09 mg/L, 34.47 ± 4.81 µg/L, and 11.94 ± 0.95 mg/dL, respectively.

Comorbidities were recorded as 122 patients (31.3%) having malignancy, 103 patients (26.4%) having hypertension, 97 patients (24.9%) having diabetes mellitus, 39 patients (10%) having congestive heart failure, and 27 patients (6.9%) having chronic renal failure.

Table 1 summarizes the underlying IAI foci. The most common intra-abdominal problem was peritonitis without perforation (20%).

Etiological Agents. Microbiological etiology was elucidated in 187 (47.9%) of 143 IAI cases (**Table 1, 2**). The most common pathogen was *E.coli* (73/187, 39%, **Table 2**), and multiple pathogens were isolated from 66 of 187 microbial culture-positive cases. Carbapenem-resistance in Gram-negative pathogens was recorded in 42 of 187 microbiologically-confirmed IAI cases (22.5%), and 22 of the 42 (52.4%) were carbapenem-resistant *K.pneumoniae*. Overall carbapenem-resistance among Gram-negative bacteria was 31.3% (42/134), and overall extended-spectrum beta-lactamase positivity among Gram-negative bacteria was 48.5% (65/134). Yeasts yielded in 15% of the etiologically confirmed cases, and they were the 4th most common etiological agent.

Mortality and Associated Factors. Overall mortality was 42.5% (166/390) on day 3, while day 14 and day 30 mortality rates were 63.3% (247/390) and 71.3% (278/390), respectively. In females, 30-day mortality was significantly higher than in males (138/174 vs 140/216, p=0.002), but there was no significant difference in mortality between cases aged ≥ 65 years vs. others (**Table 3**).

In terms of laboratory findings during the first evaluation of the septic shock case, 30-day mortality among the cases with lactate levels>3 mg/dL was significantly higher (230/298-77% vs 48/92-52%; p<0.001). There was no significant difference in the mean levels of leucocytes (19550 ± 2331/mm^3 vs. 16316

± 1776/mm^3, p=0.401), CRP levels (146.7 ± 7.28 mg/L vs. 133.9 ± 11.14 mg/L, p=0.342), and procalcitonin levels (33.17 ± 5.79 μg/L vs. 37.11 ± 8.77 μg/L, p=0.704) between patients who had 30-day mortality and those who survived.

The mean SOFA score was 10.33 ± 0.16 in 374 patients, while the median qSOFA score was 3 in 244 out of 390 patients. The mean SOFA score among cases with 30-day mortality was 10.93 ± 0.18 versus 8.84 ± 0.28 among survived cases (p<0.001). The mortality rate

Table 1. Underlying intra-abdominal problems of the study cohort.

Subgroups of intra-abdominal septic shock patients	Number (n) and Percentage (%)	Culture positivity rate with subgroups of specimens (n)	Overall, 1 month Mortality Rate (%)
Peritonitis (without perforation)	78 (20%)	46.2% (36/78) • Blood culture - 46 • Urine culture - 24 • Drainage catheter culture - 9 • Peritoneal fluid culture - 8 • Sputum or deep tracheal aspiration -4 • Tissue biopsy culture -1	75.6%
Cholangitis	55 (14%)	36.4% (20/55) • Blood culture - 23 • Urine culture -17 • Drainage catheter culture -3 • Peritoneal fluid culture -3 • Sputum or deep tracheal aspiration culture -2	63.6%
Acute cholecystitis with cholelithiasis	48 (12%)	62.5% (30/48) • Blood culture - 28 • Urine culture - 20 • Drainage catheter culture - 6 • Sputum or deep tracheal aspiration culture -3 Peritoneal fluid culture - 2	77.1%
Ileus possibly associated with ileitis	46 (12%)	46% (21/46) • Blood culture - 28 • Urine culture-12 • Drainage catheter culture - 6 • Deep tracheal aspiration - 3	78.3%
Intestinal Perforation	40 (10%)	33% (13/40) • Blood culture - 24 • Urine culture - 10 • Peritoneal fluid culture - 5 • Drainage catheter culture - 5 • Sputum or deep tracheal aspiration culture - 4	82.5%
Intra-abdominal abscess	35 (9%)	60% (21/35) • Blood culture - 17 • Urine culture -13 • Drainage catheter culture - 6 • Peritoneal fluid culture - 5 • Sputum or deep tracheal aspiration culture - 1	60%
Post-op/intra-abdominal complication	29 (7%)	37.9% (11/29) • Blood culture - 15 • Urine culture - 4 • Peritoneal fluid culture - 2 • Drainage catheter culture - 2 • Sputum or deep tracheal aspiration culture - 3	69%
Mesenteric ischemia	15 (4%)	33.3% (5/15) • Blood culture - 4 • Drainage catheter culture - 2 • Urine culture - 1 • Peritoneal fluid culture - 1	33.3%
Acute pancreatitis	15 (4%)	33.3% (5/15) • Blood culture - 7 • Urine culture - 4 • Drainage catheter culture - 1 • Sputum or deep tracheal aspiration culture - 1	86.7%
Others *	29 (7%)	51.7% (15/29) • Blood culture - 17	65.5%

		• Urine culture - 7 • Drainage catheter culture - 3 • Sputum or deep tracheal aspiration culture - 2 • Peritoneal fluid culture - 1 • Tissue biopsy culture - 1	
Total	**390 (100%)**	**187**, 47.9%**	**71.3%**

Incancerated intestinal herniation, percutaneous endoscopic gastrostomy (PEG) infection, choledochoduodenal fistula, Fournier's gangrene with intraabdominal extension. ****** Multiple pathogens were isolated from 66 of 187 microbial culture positive cases.

Table 2. Pathogens isolated from the study cohort.

Pathogens	Number (n)	Percentage (%)
E.coli	73	39%
Enterococcus spp	42	22%
Klebsiella spp.	38	20%
Yeasts	28	15%
Staphylococcus spp.	18	10%
Acinetobacter spp.	16	9%
Pseudomonas spp.	14	7%
Others*	29	16%
Total	**187**	

**Proteus spp. Enterobacter spp., C.striatum, Morganella spp, Serratia spp., B.cereus, Stenotrophomonas spp.*

among the patients with qSOFA ≥2 was significantly higher than others (p=0.016). The overall univariate analysis for 30-day mortality is in **Table 3**.

Antimicrobial Therapy/Etiology versus Mortality. 30-day mortality in cases with elucidated bacterial etiology vs. others did not change significantly (**Table 3**). Comparing 30-day mortality in cases with Gram-negative etiology versus all others, we observed rates of 98/134 vs. 180/256 (p=0.559). When we compared, 30-day mortality in cases with carbapenem-resistant Gram-negative etiology vs. all others was 86% (36/42 vs. 242/348, p=0.029), and in cases with ESBL-producing Gram-negative bacteria all others was 63.1% (41/65 vs. 237/325; p=0.109). However, 30-day mortality was significantly higher in those with carbapenem-resistant Gram-negative etiology vs. carbapenem-sensitive Gram-negative etiology.

In 36 of the 187 microbiological culture-positive patients, the antimicrobial regimen did not cover the isolated pathogens at the first visit, and 30-day mortality among them vs. others did not differ significantly (23/36-63.9% vs 113/151-74.8%, p=0.185).

Two hundred seven of 287 patients received antifungal-containing treatment, and there was no significant difference in mortality rates among them vs others (207/287-72% vs 71/103-69%, p=0.539). Furthermore, 42 cases had microbiological culture positivity for carbapenem-resistant Gram-negative pathogens, and 14 of them received a colistin-containing regimen with a 30-day mortality of 85.7% (12/14 colistin-receiving cases vs. 24/28 not colistin receiving cases, p=1.000).

When overall 390 cases were considered, 30-day mortality was not significantly different among cohorts in antifungal-containing regimens vs. others (207/287-72% vs 71/103-69%, p=0.539) and in colistin-containing regimens vs. others (39/52-75% vs 239/338-71%, p=0.524). There was no statistically significant difference in mortality among the patients with polymicrobial etiology versus culture-positive cases for single pathogen (50/66-76% vs 86/121-71%, p=0.492).

Impact of Source Control. Source control by surgical or percutaneous operation was performed in 123 of 390 cases (31.5%), and 30-day mortality was significantly lower in cases that were performed source control at any time during the septic shock period vs. others (65/123-%53 vs. 213/267-80%, p<0.001, **Table 3**). Additionally, in 44 out of 123 cases (35.7%), source control was performed within the first 12 hours. The 30-day mortality rate was significantly lower in this group compared to others (those in whom source control was performed after the first 12 hours + source control was not performed anytime during the septic shock period-24/44 or 55% vs 254/346 or 73%, p=0.009, refer to **Table 3**). However, 30-day mortality did not differ in those source controls performed during the first 12 h versus any other time during the septic shock period (24/44-55% vs. 41/79-57%, p=0.854).

In 77 of 123 cases (62.6%), invasive surgical operation/laparotomy was performed, while percutaneous source control was performed in 46 cases (37.4%). Mortality rates among the invasive surgical operation subgroup were statistically higher than the percutaneous source control group (52/77-67.5% vs 13/46-28.3%, p<0.001). The mean SOFA scores did not change significantly (9.80±0.52) in the invasive source controlled group vs. 10.11±0.71 in the percutaneous source controlled group (p=0.752).

30-day mortality was found to be similar among cases with intra-abdominal abscess vs. others (21/35-60% vs. 257/355-72.4%, p=0.122) and among cases with organ or intestinal perforation vs. others (33/40-82.5% vs 244/349-69.9%, p=0.096). Invasive surgical operations were performed more commonly among cases with organ or intestinal perforation in source controlled group (35/37-94.6% vs. 42/86-48.8%, p<0.001), and percutaneous source control was performed more commonly among cases with intra-abdominal abscess (19/22-86.4% vs 27/101-26.7%, p<0.001) in source-controlled group. Univariate analyses of independent

Table 3. Univariate analysis of independent variables on mortality (1 month).

Risk Factors		Mortality, Yes (number (n) and percentage (%))	Mortality, No (n, %)	P value
Age ≥ 65	Present Absent	122 (74%) 156 (70%)	44 (26%) 68 (30%)	0.406
Gender	Male Female	140 (65%) 138 (79%)	76 (35%) 36 (21%)	**0.002***
Hypertension	Present Absent	76 (74%) 202 (70%)	27 (26%) 85 (30%)	0.513
Diabetes mellitus	Present Absent	80 (83%) 198 (68%)	17 (17%) 95 (32%)	**0.005***
Malignancy	Present Absent	90 (74%) 188 (70%)	32 (26%) 80 (30%)	0.464
Chronic Renal Failure	Present Absent	21 (78%) 257 (71%)	6 (22%) 106 (29%)	0.439
Type of Infection	Nosocomial Community acquired	180 (73%) 98 (68%)	66 (27%) 46 (32%)	0.281
qSOFA≥2	Present Absent	256 (73%) 22 (55%)	94 (27%) 18 (45%)	**0.016***
SIRS=4	Present Absent	29 (81%) 249 (70%)	7 (19%) 105 (30%)	0.197
SIRS=3	Present Present	74 (74%) 204 (70%)	26 (26%) 86 (30%)	0.486
SIRS=2	Present Absent	47 (67%) 231 (72%)	23 (33%) 89 (28%)	0.398
Bacterial culture positivity	Present Absent	136 (73%) 142 (70%)	51 (27%) 61 (30%)	0.545
Carbapenem-resistant Gram-negative pathogen	Present Absent	36 (86%) 242 (70%)	6 (14%) 106 (30%)	**0.029***
Antifungal Treatment Containing Regimen	Present Absent	207 (72%) 71 (69%)	80 (28%) 32 (31%)	0.539
Colistin Containing Regimen	Present Absent	39 (75%) 239 (71%)	13 (25%) 99 (29%)	0.524
Source Control	Present Absent	65 (53%) 213 (80%)	58 (47%) 54 (20%)	**0.001***
Source Control Within the first 12 hours	Present Absent	24 (55%) 254 (73%)	20 (45%) 92 (27%)	**0.009***
Source control procedure	Percutaneous Invasive	13 (28%) 52 (68%)	33 (72%) 25 (32%)	**0.001***
Intensive Care Unit Admission	Present Absent	132 (72%) 146 (70%)	51 (28%) 61 (30%)	0.727
SOFA≥10	Present Absent	181 (81%) 89 (57%)	43 (19%) 66 (43%)	**<0.001***
Lactate>3mg/dL	Present Absent	230 (77%) 48 (52%)	68 (23%) 44 (48%)	**0.001***
Antibiotic initiation within the first hour of the vasopressor treatment	Present Absent	20 (69%) 163 (72%)	9 (31%) 62 (28%)	0.694
Transfer to the ward or ICU from the emergency department within the initial 12-hour period after admission	Present Absent	79 (67%) 69 (67%)	39 (33%) 34 (33%)	0.995

**p<0.05.*

variables on 30-day mortality are shown in **Table 3**.

Multivariate Analysis. In logistic regression analysis, female gender (p<0.001, odds ratio (OR) = 2.943, 95%CI = 1.714-5.054), diabetes mellitus (p= 0.014, OR=2.284, 95%CI = 1.179-4.424), carbapenem-resistant Gram-negative etiology (p=0.011, OR=4.386, 95%CI = 1.398-13.759), SOFA≥10 (p<0.001, OR=3.036, 95%CI = 1.802-5.114), lactate >3 mg/dl (p<0.001, OR=2.764, 95%CI =1.562-4.891) and lack of source control (p = 0.001, OR = 2.796, 95% CI = 1.523-5.133) were significantly associated with 30-day mortality (**Table 4**).

Discussion. Herein, we analyzed the outcomes of 390 SS with IAI. The 30-day mortality rate was 71.3%. Source control by surgical or percutaneous operation was performed in 31.5%, and in 35.7% of them, source control was performed during the first 12 hours. On the

Table 4. Results of logistic regression analysis.

Covariate	Odds ratio	95% Confidence interval	P value
Female Gender	**2.943**	**1.714-5.054**	**<0.001**
Diabetes mellitus	**2.284**	**1.179-4.424**	**0.014**
qSOFA≥2	1.585	0.702-3.581	0.268
Carbapenem-resistant Gram-negative etiology	**4.386**	**1.398-13.759**	**0.011**
SOFA≥10	**3.036**	**1.802-5.114**	**<0.001**
Lactate >3 mg/dl	**2.764**	**1.562-4.891**	**<0.001**
Lack of source control within the first 12 hours	1.162	0.509-2.652	0.721
Lack of source control	**2.796**	**1.523-5.133**	**0.001**

other hand, female gender, diabetes mellitus, carbapenem-resistant Gram-negative etiology, SOFA≥10, lactate >3 mg/dl, and lack of source control were significantly associated with 30-day mortality in logistic regression analysis.

Source control in patients with septic shock is vital and recommended by the guidelines. However, the evidence regarding optimal timing for these interventional approaches is relatively limited.[5-7] Thus, this paper is one of the unique studies that emphasizes the impact of source control together with the optimal duration of surgical intervention, especially for the subgroup of septic shock patients with IAI.

In 2003, the Turkish Ministry of Finance, which is responsible for the payback of over 90% of the population's health expenditures, eased a new budget application instruction for regulating the usage of parenteral antibiotics inside and outside of the hospitals. The instruction took effect on March 1st, 2003. According to this instruction, the payback of extended-spectrum antimicrobials (vancomycin, teicoplanin, meropenem, imipenem, antifungals, etc.) has been restricted without prior approval of infectious diseases specialist (IDS). Hence, all septic shock cases that were considered to be starting extended-spectrum antibiotics or consulted to Infectious Diseases Consultants during night shifts were included in the study.[11-13]

Martinez et al.[14] performed a multicenter observational study in Spain with 3663 severe sepsis or septic shock patients. Of these, 1234 cases had the abdominal site of infection source, with 788 (67.2%) patients requiring source control included. They reported that the crude ICU mortality rate was lower for those who underwent source control (21.2% vs 25.1%; p=0.010), but the source control after 12 hours was not found statistically significant in terms of mortality (27.6% vs 26.8%; p=0.789).[14] Kim et al. also performed a multicenter observational study with a total number of 2250 septic shock patients visiting 11 different Emergency Departments. They reported that 28-day mortality was significantly lower in patients who underwent source control (p<0.001). However, no significant association was noted between the duration of source control after 6 hours or 12 hours and mortality.

Additionally, out of the 2,250 patients, 46.6% met the criteria for Sepsis-3 septic shock, and 26.8% underwent source control; nevertheless, source control conducted after 6 or 12 hours showed no significant association with 28-day mortality in Sepsis-3 septic shock, with adjusted hazard ratios of 1.309 (95% CI: 0.612–2.797, p = 0.488) and 1.344 (95% CI: 0.612–2.951, p = 0.462).[15]

The guidelines of the Infectious Diseases Society of America (IDSA) about the diagnosis and management of complicated IAI in adults and children recommends (B-II) an appropriate source control procedure for nearly all patients with IAI.[16] This guideline also recommends (B-II) an urgent approach for hemodynamically stable patients without acute organ failure. Intervention may be delayed for as long as 24 hours with appropriate antimicrobial therapy plus close clinical monitoring. In contrast, it recommends (B-II) that patients with diffuse peritonitis should undergo an emergency surgical procedure as soon as possible.[16] Furthermore, the guideline recommends (B-II) that a percutaneous approach of abscesses and other well-localized fluid collections, if feasible, is preferable to surgical drainage.[16] The percutaneous approach of selected cases may cause fewer physiologic alterations with more acceptable mortality and morbidity rates and may eliminate or reduce the need for open techniques.[17,18] Marshall et al. also reviewed that source control represents a key component of success in the therapy of sepsis, which includes drainage of infected fluids, debridement of infected soft tissues, removal of infected devices or foreign bodies, and definite measures to correct anatomic derangement. Thus, they emphasized that appropriate source control should be part of the systematic checklist in sepsis with Grade E recommendation.[19] Hecker et al. reviewed that an IAI source could be detected in 66% of all surgical patients with sepsis, and the 28-day mortality rate increased from 26.7% to 42.9% in patients with inadequate initial source control.[20] Unlikely the literature, 30-day mortality was found to be as high as 71.3% (53% in the source-controlled group versus 80% in the non-source-controlled group) in our study. In comparison to a multicenter study in our country reporting 6.9% of patients meeting SEPSIS-III criteria for septic shock with a 75.9% mortality rate, our study found a similar 30-day mortality (71.3%) with a focus on Sepsis-3 septic

shock patients, suggesting the potential influence of patient selection on the elevated mortality.[21]

Van de Groep et al. performed a retrospective study with a total number of 353 critically ill patients with IAI, and they concluded that the persistence of organ failure on day 14 was associated with inadequacy of source control while the clinical outcomes were similar between the patients having a surgical versus percutaneous initial approach to source containment.[22] In our study, the mortality was significantly lower in the group source control was performed (65/123 vs 213/267, p<0.001). These data suggest that the source of infection is one of the most important factors in septic shock patients in terms of management and prognosis. Aligned with existing literature, effective source control, encompassing interventions such as surgical procedures or percutaneous drainage, is essential for eradicating the infectious focus and decreasing mortality rates. We believe that source control plays a pivotal role in managing intraabdominal septic shock, highlighting the critical need to promptly address the infection's source for effective management. Despite its significance in the larger picture, source control executed within the initial 12 hours did not emerge as a protective factor against mortality. This nuanced result sheds light on the complexities of timing and effectiveness in source control, highlighting that achieving source control within a specific time frame may not necessarily confer a survival advantage in septic shock patients with intraabdominal infection. Further investigation and analysis are imperative to understand the intricacies of this relationship and to refine our approach to source control in septic shock scenarios.

Jung et al. reported that procalcitonin kinetics failed to predict the outcome in 101 consecutive cases that had perioperative abdominal infection with septic shock.[23] Wang et al. showed that the most accurate index was the SOFA score for predicting the outcome of patients with sepsis caused by abdominal cavity infection when the threshold value was 9.50. They found that sensitivity and specificity were 81.2% and 83.5%, respectively.[24] In our study, we also found that there was no statistically significant difference in the mean values of CRP, procalcitonin, and leucocyte levels among the mortal cases vs. others. On the other hand, SOFA score ≥10 (OR=3.036, 95%CI=1.802-5.114, p<0.001) was significantly associated with 30-day mortality in logistic regression analysis. Conversely, we believe that additional data are necessary to demonstrate the prognostic value of these biomarkers and scoring systems.

The results of the multicentered cohort study by Arvaniti et al.[25] involving 2337 critically ill elderly adults with intra-abdominal infection shed light on crucial risk factors impacting mortality such as late-onset hospital-acquired intra-abdominal infection, diffuse peritonitis, sepsis/septic shock, source control failure, and underlying conditions like liver disease, congestive heart failure, diabetes mellitus, and malnutrition. Our study also revealed distinctive correlations, underscoring that factors like female gender, diabetes mellitus, carbapenem-resistant Gram-negative etiology, SOFA score (≥10), elevated lactate levels (>3 mg/dl), and inadequate source control were notably associated with poorer outcomes. These observations stress the necessity for customized interventions targeting these specific risk elements to enhance patient outcomes in IAI cases.

Our study has several limitations, such as the mortality rates were recorded as all-cause mortality (autopsy could not been performed), repeated source control procedures could not be investigated, and timing of "12 hours" was considered to be a cut-off time for source control. However, to our knowledge, this is one of the unique and the largest studies performed solely in septic shock cases and concluding that surgery performed after 12 h may also contribute to survival and management of these groups of patients and that showed no difference between early source control vs. source control anytime during the septic shock episode. In addition, this is the first study from our country regarding the source control in septic shock patients with IAI.

Conclusions. These data suggest that source control has major and vital importance in terms of mortality rates for IAI-related septic shock patients. This effect was regardless of the timing (< or >12 h) in our study sample. The more favorable outcomes observed during the source control via percutaneous procedures in our cohort need to be confirmed in further studies.

References:

1. Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. Lancet. 2018;392:75-87 https://doi.org/10.1016/S0140-6736(18)30696-2 PMid:29937192
2. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315:801-10 https://doi.org/10.1001/jama.2016.0287 PMid:26903338 PMCid:PMC4968574
3. Akın A, Alp E, Altındiş M, Azak E, Batırel A, Çağ Y, Durmuş G, Kepenek Kurt E, Sağıroğlu P, Türe Z, Candevir Ulu A, Ekmud Sepsis Working Group. Current Diagnosis and Treatment Approach to Sepsis. Mediterr J Infect Microb Antimicrob. 2018;7:17 https://doi.org/10.4274/mjima.2018.17
4. Howell MD, Davis AM. Management of Sepsis and Septic Shock. JAMA. 2017;317:847-8 https://doi.org/10.1001/jama.2017.0131 PMid:28114603
5. Bloos F, Rüddel H, Thomas-Rüddel D, Schwarzkopf D, Pausch C, Harbarth S, Schreiber T, Gründling M, Marshall J, Simon P, Levy MM, Weiss M, Weyland A, Gerlach H, Schürholz T, Engel C, Matthäus-

Krämer C, Scheer C, Bach F, Riessen R, Poidinger B, Dey K, Weiler N, Meier-Hellmann A, Häberle HH, Wöbker G, Kaisers UX, Reinhart K; MEDUSA study group. Effect of a multifaceted educational intervention for anti-infectious measures on sepsis mortality: a cluster randomized trial. Intensive Care Med. 2017;43:1602-12
https://doi.org/10.1007/s00134-017-4782-4
PMid:28466151

6. Azuhata T, Kinoshita K, Kawano D, Komatsu T, Sakurai A, Chiba Y, Tanjho K. Time from admission to initiation of surgery for source control is a critical determinant of survival in patients with gastrointestinal perforation with associated septic shock. Crit Care. 2014;18:R87
https://doi.org/10.1186/cc13854
PMid:24886954 PMCid:PMC4057117
7. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC, Schorr C, Simpson S, Wiersinga WJ, Alshamsi F, Angus DC, Arabi Y, Azevedo L, Beale R, Beilman G, Belley-Cote E, Burry L, Cecconi M, Centofanti J, Coz Yataco A, De Waele J, Dellinger RP, Doi K, Du B, Estenssoro E, Ferrer R, Gomersall C, Hodgson C, Hylander Møller M, Iwashyna T, Jacob S, Kleinpell R, Klompas M, Koh Y, Kumar A, Kwizera A, Lobo S, Masur H, McGloughlin S, Mehta S, Mehta Y, Mer M, Nunnally M, Oczkowski S, Osborn T, Papathanassoglou E, Perner A, Puskarich M, Roberts J, Schweickert W, Seckel M, Sevransky J, Sprung CL, Welte T, Zimmerman J, Levy M. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Crit Care Med. 2021;49:e1063-e1143
https://doi.org/10.1097/CCM.0000000000005337
PMid:34605781
8. Oner AC, Durmaz-Drinkwater B, Grant RJ. Precarity of refugees: the case of Basmane-İzmir, Turkey. Journal of Ethnic and Migration Studies. 2020;47:4651-70
https://doi.org/10.1080/1369183X.2020.1732591
9. Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, O'Neill PJ, Chow AW, Dellinger EP, Eachempati SR, Gorbach S, Hilfiker M, May AK, Nathens AB, Sawyer RG, Bartlett JG. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Surg Infect (Larchmt). 2010;11:79-109
https://doi.org/10.1089/sur.2009.9930
PMid:20163262
10. Brown DF, Wootton M, Howe RA. Antimicrobial susceptibility testing breakpoints and methods from BSAC to EUCAST. J Antimicrob Chemother. 2016;71:3-5
https://doi.org/10.1093/jac/dkv287
PMid:26377864
11. Sipahi OR. Economics of antibiotic resistance. Expert Rev Anti Infect Ther. 2008;6:523-39
https://doi.org/10.1586/14787210.6.4.523
PMid:18662118
12. Arda B, Sipahi OR, Yamazhan T, Tasbakan M, Pullukcu H, Tunger A, Buke C, Ulusoy S. Short-term effect of antibiotic control policy on the usage patterns and cost of antimicrobials, mortality, nosocomial infection rates and antibacterial resistance. J Infect. 2007;55:41-8
https://doi.org/10.1016/j.jinf.2007.02.014
PMid:17512598
13. Önal U, Akyol D, Mert M, Başkol D, Memetali SC, Şanlıdağ G, Kenanoğlu B, Uyan-Önal A, Quliyeva G, Avşar CB, Akdağ D, Demir M, Erdem HA, Kahraman Ü, Bozbıyık O, Özgiray E, Bozkurt D, Akarca FK, Demirağ K, Çankayalı İ, Uyar M, Çilli F, Arda B, Yamazhan T, Pullukçu H, Taşbakan MI, Sipahi H, Ulusoy S, Sipahi OR. Carbapenem-resistant Gram-negative pathogens associated with septic shock: a review of 120 cases. J Chemother. 2022;34:436-45
https://doi.org/10.1080/1120009X.2022.2064703
PMid:35446235
14. Martínez ML, Ferrer R, Torrents E, Guillamat-Prats R, Gomà G, Suárez D, Álvarez-Rocha L, Pozo Laderas JC, Martín-Loeches I, Levy MM, Artigas A; Edusepsis Study Group. Impact of Source Control in Patients With Severe Sepsis and Septic Shock. Crit Care Med. 2017;45:11-9
https://doi.org/10.1097/CCM.0000000000002011
PMid:27611975
15. Kim H, Chung SP, Choi SH, Kang GH, Shin TG, Kim K, Park YS, Han KS, Choi HS, Suh GJ, Kim WY, Lim TH, Ko BS; Korean Shock Society (KoSS) Investigators. Impact of timing to source control in patients with septic shock: A prospective multicenter observational study. J Crit Care. 2019;53:176-82
https://doi.org/10.1016/j.jcrc.2019.06.012
PMid:31247517
16. Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, O'Neill PJ, Chow AW, Dellinger EP, Eachempati SR, Gorbach S, Hilfiker M, May AK, Nathens AB, Sawyer RG, Bartlett JG. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis. 2010;50:133-64
https://doi.org/10.1086/649554
PMid:20034345
17. Akinci D, Akhan O, Ozmen MN, Karabulut N, Ozkan O, Cil BE, Karcaaltincaba M. Percutaneous drainage of 300 intraperitoneal abscesses with long-term follow-up. Cardiovasc Intervent Radiol. 2005;28:744-50
https://doi.org/10.1007/s00270-004-0281-4
PMid:16091990
18. Theisen J, Bartels H, Weiss W, Berger H, Stein HJ, Siewert JR. Current concepts of percutaneous abscess drainage in postoperative retention. J Gastrointest Surg. 2005;9:280-3
https://doi.org/10.1016/j.gassur.2004.04.008
PMid:15694825
19. Marshall JC, Maier RV, Jimenez M, Dellinger EP. Source control in the management of severe sepsis and septic shock: an evidence-based review. Crit Care Med. 2004;32:S513-26
https://doi.org/10.1097/01.CCM.0000143119.41916.5D
PMid:15542959
20. Hecker A, Reichert M, Reuß CJ, Schmoch T, Riedel JG, Schneck E, Padberg W, Weigand MA, Hecker M. Intra-abdominal sepsis: new definitions and current clinical standards. Langenbecks Arch Surg. 2019;404:257-71
https://doi.org/10.1007/s00423-019-01752-7
PMid:30685836
21. Baykara N, Akalın H, Arslantaş MK, Hancı V, Çağlayan Ç, Kahveci F, Demirağ K, Baydemir C, Ünal N; Sepsis Study Group. Epidemiology of sepsis in intensive care units in Turkey: a multicenter, point-prevalence study. Crit Care. 2018;22:93
https://doi.org/10.1186/s13054-018-2013-1
PMid:29656714 PMCid:PMC5901868
22. van de Groep K, Verhoeff TL, Verboom DM, Bos LD, Schultz MJ, Bonten MJM, Cremer OL; MARS consortium. Epidemiology and outcomes of source control procedures in critically ill patients with intra-abdominal infection. J Crit Care. 2019;52:258-64
https://doi.org/10.1016/j.jcrc.2019.02.029
PMid:31054787
23. Jung B, Molinari N, Nasri M, Hajjej Z, Chanques G, Jean-Pierre H, Panaro F, Jaber S. Procalcitonin biomarker kinetics fails to predict treatment response in perioperative abdominal infection with septic shock. Crit Care. 2013;17:R255
https://doi.org/10.1186/cc13082
PMid:24156734 PMCid:PMC4056026
24. Wang Y, Wang D, Fu J, Liu Y. [Predictive value of SOFA, qSOFA score and traditional evaluation index on sepsis prognosis]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2017;29:700-4
25. Arvaniti K, Dimopoulos G, Antonelli M, Blot K, Creagh-Brown B, Deschepper M, de Lange D, De Waele J, Dikmen Y, Eckmann C, Einav S, Francois G, Fjeldsoee-Nielsen H, Girardis M, Jovanovic B, Lindner M, Koulenti D, Labeau S, Lipman J, Lipovestky F, Makikado LDU, Maseda E, Mikstacki A, Montravers P, Paiva JA, Pereyra C, Rello J, Timsit JF, Tomescu D, Vogelaers D, Blot S; Abdominal Sepsis Study (AbSeS) Group on behalf of the Trials Group of the European Society of Intensive Care Medicine. Epidemiology and age-related mortality in critically ill patients with intra-abdominal infection or sepsis: an international cohort study. Int J Antimicrob Agents. 2022;60:106591
https://doi.org/10.1016/j.ijantimicag.2022.106591
PMid:35460850