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Epidemiology and outcomes of source control procedures in critically ill patients with intra-abdominal infection

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ABSTRACT

Purpose: To describe the characteristics and procedural outcomes of source control interventions among Intensive Care Unit (ICU) patients with severe intra-abdominal-infection (IAI).
Material and methods: We identified consecutive patients with suspected IAI in whom a source control intervention had been performed in two tertiary ICUs in the Netherlands, and performed retrospective in-depth case reviews to evaluate procedure type, diagnostic yield, and adequacy of source control after 14 days.
Results: A total of 785 procedures were observed among 353 patients, with initial interventions involving 266 (75%) surgical *versus* 87 (25%) percutaneous approaches. Surgical index procedures typically involved IAI of (presumed) gastrointestinal origin (72%), whereas percutaneous index procedures were mostly performed for infections of the biliary tract/pancreas (50%) or peritoneal cavity (33%). Overall, 178 (50%) patients required multiple interventions (median 3 (IQR 2–4)). In a subgroup of 236 patients having their first procedure upon ICU admission, effective source control was ultimately achieved for 159 (67%) subjects. Persistence of organ failure was associated with inadequacy of source control at day 14, whereas trends in inflammatory markers were non-predictive.
Conclusions: Approximately half of ICU patients with IAI require more than one intervention, yet successful source control is eventually achieved in a majority of cases.

1. Introduction

Severe intra-abdominal infection (IAI) represents the second most common cause of sepsis in critically ill patients, affecting approximately 5% of patients presenting to an intensive care unit (ICU) [1-3]. An additional 1–2% acquire new abdominal infections while being treated in the ICU [2-4]. Hospital mortality associated with IAI varies between settings and disease entities, but is generally high at 23–38% [1,5,6]. Furthermore, treatment of abdominal sepsis is often long and complex, as reflected by a 20% point-prevalence in a worldwide cross-sectional ICU survey [5].

Achieving prompt control over the anatomic source of infection is a cornerstone of abdominal sepsis management. Guidelines of the Surviving Sepsis Campaign state that source control procedures must be performed as soon as possible, targeting a delay of not >6–12 h from diagnosis [7]. Indeed, in patients with septic shock due to gastrointestinal perforation, each hour of delay to intervention was associated with reduced survival [8]. Nevertheless, evidence regarding optimal timing of interventions in septic patients remains weak [9-12]. In addition, an association between the apparent (initial) success rate of interventions and survival has also been demonstrated [9,13]. However, definitions of procedural adequacy have mainly focused on technical success and did not incorporate early postoperative clinical response.

Source control procedures may involve drainage, debridement, device removal, abdominal and/or bowel decompression, and restoration of anatomy and function (e.g., resection, bowel diversion, or closure of perforations) [14,15]. Although the pathophysiological benefits of reducing microbial load are obvious [16], usage of specific procedures and their impact on patient outcome has been less well investigated than other aspects of sepsis management [17]. The present study aimed to describe the characteristics of various types of interventions in a large consecutive series of critically ill patients with presumed abdominal sepsis, as well as their timing, diagnostic yield, and apparent (immediate) success rate. Furthermore, we performed a systematic

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evaluation of adequacy of source control 14 days after the intervention. These data may aid physicians in making better informed decisions during the treatment of ICU patients with abdominal sepsis.

2. Materials and methods

2.1. Study design

This study was nested within the Molecular Diagnosis and Risk Stratification of Sepsis (MARS) cohort, for which consecutive patients were prospectively enrolled in the mixed ICUs of two university medical centers in the Netherlands (AMC Amsterdam 2011–2013 and UMC Utrecht 2011–2015). During the MARS-study, (suspected) infectious events, antimicrobial treatment, and organ failure criteria were prospectively recorded on a daily basis for all patients. Subsequently, we performed retrospective in-depth case reviews of all sepsis patients having ≥1 open-surgical, laparoscopic, endoscopic, or percutaneous intervention aimed at containing an intra-abdominal source of infection (including secondary infected pancreatitis) at the day before or during ICU admission. In order to describe the full spectrum of critically ill patients with presumed IAI, we did not exclude subjects in whom intervention yielded negative findings. However, patients were excluded from analysis if their first source control intervention (index procedure) had not been performed in a study hospital, or if they did not fulfil Sepsis-3 organ failure criteria during at least one day in the ICU (i.e., Sequential Organ Failure Assessment (SOFA)-score increase ≥2 after correction for chronic comorbidities) [18]. Fig. S1 (Appendix I) shows further details regarding patient inclusion and associated data sources.

In the patients with at least one intra-abdominal source control procedure during ICU admission we evaluated all procedures that were performed during the period starting from two weeks before presentation until ICU discharge. In both hospitals on-demand strategies were in place, implying that elective re-interventions involving only inspection, drainage, or peritoneal lavage were not performed [19]. The institutional review boards of both study centers approved an opt-out procedure for the parent study (protocol number 10-056C). An additional waiver of informed consent was obtained for chart review (17-018C).

2.2. Data collection

Data regarding demographics, comorbidities, vital signs, laboratory results, SOFA-scores, infectious events, and antimicrobial therapies were prospectively recorded during the MARS-study [20]. However, specific information regarding technical features and diagnostic findings during source control procedures, as well as additional clinical data observed prior to ICU admission, were collected *via* retrospective chart review. For this, a single physician-investigator (TLV or KvdG) making use of a standardized case registration form, examined operative reports, radiology records, and chart notes of all involved clinical disciplines. Equivocal cases were discussed in consensus meetings with both investigators and a senior intensivist (OC).

2.3. Assessment of source control adequacy

In the subgroup of patients who had their first intervention while under prospective surveillance (i.e., within a 24-h time window of presentation to ICU), we evaluated both immediate procedural adequacy (based on technical criteria) and adequacy after 14 days (based on clinical and radiological criteria). Detailed definitions of these concepts are provided in Table 1 and evaluated criteria are described in the Supplementary Methods (Appendix II). We opted *a priori* for a 14-day follow up period based on the fact that 95% of (first) repeat procedures occurred within this timeframe. Furthermore, we considered later adjudication more likely to be confounded by ICU complications that were not directly related to (failure of) source control. In addition to [1] immediate procedural adequacy and [2] adequacy on day 14, we also performed a final assessment of source control in all patients two weeks after their last procedure in the ICU. Finally, we assessed in this subgroup of patients antimicrobial drug use, concurrent infections, and disease severity markers following the index procedure in association with adequacy of source control on day 14. Of note, we specifically restricted this analysis to patients with their index procedure upon ICU admission in order to reduce heterogeneity caused by variations in disease stage upon presentation.

Table 1
Study definitions of evaluated outcomes.

Immediate procedural adequacy (yes/no):
Source control was considered technically adequate, if the operative report and clinical chart mentioned a successful eradication or containment of the infectious source.

Adequacy of source control on day 14:
- *Adequate:* Review of both the clinical chart and all available imaging studies yielded no evidence for a remaining source of infection (of any clinical significance) on day 14, and no additional procedures had been performed.
- *Delayed adequate:* One or more additional interventions had been performed following the index procedure, yet no evidence for a remaining source of infection (of any clinical significance) remained on day 14.
- *Inadequate:* Patient died before day 14, or a residual or new anatomical source of infection was suspected on day 14 based on clinical chart review, which needed to be radiologically confirmed if imaging studies had been performed.

Adequacy on final assessment (yes/no):
The final assessment of source control was performed on day 14 after the last procedure during ICU stay and classified as adequate when review of both the clinical chart and all available imaging studies yielded no evidence for a remaining source of infection (of any clinical significance).

2.4. Statistical analysis

Patient and disease characteristics were compared between groups using Chi-square tests, Fisher exact tests, or Wilcoxon rank sum tests as appropriate. Missing values in time series data of disease severity markers were replaced with estimates derived from multiple imputation using the MICE-package in R (see Supplementary Methods, Appendix II). Subsequently, median values and interquartile ranges (IQRs) for these parameters were estimated based on the mean values observed across imputed datasets. Analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC) or R version 3.4.1 (R foundation for Statistical Computing, Vienna, Austria). Figures were made using GraphPad Prism version 7.02 (GraphPad Software, La Jolla, CA).

3. Results

During the enrollment period, 968 critically ill patients had been treated for (presumed) IAI; 385 (40%) of these subjects underwent at least a single intervention to control an abdominal source of infection in the day before or during ICU admission and were thus eligible for study inclusion. After applying exclusion criteria, 353 (92%) patients remained. Among these, 175 (50%) subjects underwent only a single (index) procedure, whereas the remaining 178 (50%) individuals accounted for 432 repeat procedures (median 3 (IQR 2–4) procedures per patient in total). Median length of ICU stay was ten days (IQR 4–20) overall, including the time contributed by 69 (20%) patients having ≥1 ICU readmission (s). Death in hospital occurred in 147 (42%) subjects.

3.1. Timing of the index procedure

Most patients were admitted to the ICU immediately prior to (n = 101, 29%) or after (n = 135, 38%) their first source control procedure, whereas 53 (15%) and 64 (18%) remaining subjects underwent their index procedure either >24 h before or after first presentation to the ICU, respectively. In 167 (71%) of 236 acute presentations, the time of sepsis onset (i.e., ≥2 points increase of SOFA-score) could be precisely

determined based on chart review. Median delay between sepsis onset and first intervention was 7 h (IQR 3–14 h, range 0–96 h). For 90 (54%) patients this was more than the six hours recommended by the Surviving Sepsis Campaign. Among reasons that could be identified, time required to establish a diagnosis was most prevalent (88%). Other sources for delay included a need for clinical optimization before intervention (34%), deliberate decision to await the infectious source to mature (7%), and logistical restrictions (6%).

3.2. Sources of infection

For 266 (75%) of 353 patients the first source control procedure concerned a laparotomy or laparoscopy, whereas percutaneous techniques were used in the remaining 87 (25%) subjects (Table 2). A surgical initial approach was more frequently selected in IAI patients in whom previous abdominal surgery had been performed and/or in whom the source of infection was of gastrointestinal origin. Specifically, evidence of intestinal perforation or anastomotic leakage was observed in 96 (36%) and visceral ischemia in 40 (15%) cases, whereas 20 (8%) patients had signs of both. Among patients with a percutaneous index procedure, sources of infection mainly included the biliary tract 22 (25%), pancreas 20 (23%), and cases of peritonitis/intra-abdominal abscesses without identifiable cause 26 (30%). However, clinical outcomes did not differ between patients having a surgical *versus* percutaneous initial approach to source containment. Of note, evidence of infection was not apparent in 24 (7%) of 353 subjects during the first procedure, of which seven had confirmed infection upon later re-intervention.

3.3. Characteristics of (repeat) interventions

Among the 178 patients undergoing multiple interventions, the median interval was 3 (IQR 1–6) days between index and first repeat, and 9 (IQR 3–19) days until final procedure. Patients in whom percutaneous interventions had been performed more often required repeat procedure(s) than surgical patients (Fig. 1, Table 2). Furthermore, in 33 (25%) of these conversion to a surgical approach occurred within two weeks. Table 3 shows procedural characteristics for the 353 index procedures and 432 performed repeat procedures. Peritonitis due to visceral perforation and/or ischemia was a common finding during index procedures, whereas abscesses were more frequently observed during repeat procedures. This suggests temporal evolution of underlying infectious etiology. Consequently, index procedures typically involved restoration of anatomy and function (e.g., resection, bowel diversion, or closure of perforations) in combination with intra-peritoneal lavage, whereas repeat procedures more often aimed at drainage of infected collections. Full closure after laparotomy was less frequently achieved during repeat compared to index procedures (48% *versus* 81%, $p < 0.001$), yet subsequent use of advance wound management was similar (34% *versus* 44%, $p = 0.24$).

3.4. Diagnostic yield of interventions

Among the 699 interventions that could be evaluated in sufficient detail, macroscopic signs of infection were reported on 427 (61%) occasions. These included presence of turbid ascites or peritoneal fibrin depositions 230 (33%), visceral perforation 197 (28%), intra-abdominal abscesses 175 (25%), and intestinal ischemia as precursor of infection 95 (14%). Microbiological specimens were obtained during 386 (55%) procedures overall, and this practice was more frequent during index than repeat interventions (Table 3). A single pathogen was identified in specimens of 64 (17%) procedures, whereas polymicrobial results were reported in 249 (65%). Among the most frequently isolated pathogens were *Enterococcus faecium* (29%), *Escherichia coli* (23%), *Enterococcus faecalis* (17%), and *Candida albicans* (15%). Cultures remained

Table 2
Characteristics of 353 critically ill patients with presumed abdominal sepsis by type of index procedure.

Variable	Total ($n = 353$)		Type of Index Procedure				*p*-value
			Surgical		Percutaneous		
			$n = 266$ (75%)		$n = 87$ (25%)		
Demographics and comorbidities							
Age (years)	65	(56–72)	65	(58–72)	64	(55–71)	0.33
Sex (male)	212	(61)	156	(59)	56	(64)	0.34
Body mass index (kg/m^2)	26	[23–30]	26	[23–30]	26	[22–28]	0.17
Solid malignancy	118	(33)	100	(38)	18	[21]	0.004
Immune deficiency	74	[21]	59	[22]	15	[17]	0.33
Chronic corticosteroid use	45	[13]	34	[13]	11	[13]	0.97
Infection characteristics							
Community-acquired onset	127	(36)	95	(36)	32	(37)	0.86
Prior abdominal surgery (within 14 days)	157	(44)	128	(48)	29	(33)	0.02
Gastro-intestinal initial source of infection[a]	202	(57)	191	(72)	11	[13]	<0.001
IAI non-confirmed or refuted[b]	76	[22]	61	[23]	15	[17]	0.26
APACHE-IV score	84	(71–103)	83	(71–103)	85	(70–106)	0.65
Antimicrobial therapy before index procedure (days)	0	(0–1)	0	(0–1)	0	(0–2)	0.004
ICU-stay before index procedure (days)	0	(0–1)	0	(0–0)	0	(0–2)	0.21
Clinical outcome							
Patients with >1 procedure	178	(50)	124	(47)	54	(62)	0.01
- Total number of required procedures	3	[2–4]	3	[2–4]	3	[2–4]	0.30
- Days from index until last procedure	9	[3–19]	10	[3–17]	9	[4–21]	0.56
LOS in ICU (days)	10	[4–20]	11	[4–21]	11	[4–21]	0.85
LOS in hospital after index procedure (days)	27	(13–56)	27	(12–56)	28	(14–56)	0.75
Mortality 14 days after final procedure	110	(31)	82	(31)	28	(32)	0.81
- Probably related to abdominal sepsis	84	[24]	58	[22]	26	[30]	0.02
Mortality in hospital	147	(42)	110	(41)	37	(43)	0.85
Mortality 1 year after index procedure	195	(55)	151	(57)	44	(51)	0.31
- Days to death from index procedure	22	(5–81)	22	(4–84)	23	(8–68)	0.98

APACHE: Acute Physiology And Chronic Health Evaluation. *IAI*: intra-abdominal infection. *ICU*: Intensive Care Unit. *LOS*: length of stay. Data are presented as frequencies (column percentages) and medians (Q1-Q3).

[a] For patients with a surgical index procedure this concerned in 93 (49%), 85 (45%), and 13 (7%) patients the small-, large bowel, and upper gastrointestinal tract, respectively.

[b] Based on post-hoc assessment of likelihood of infection by trained researchers based as previously described [20].

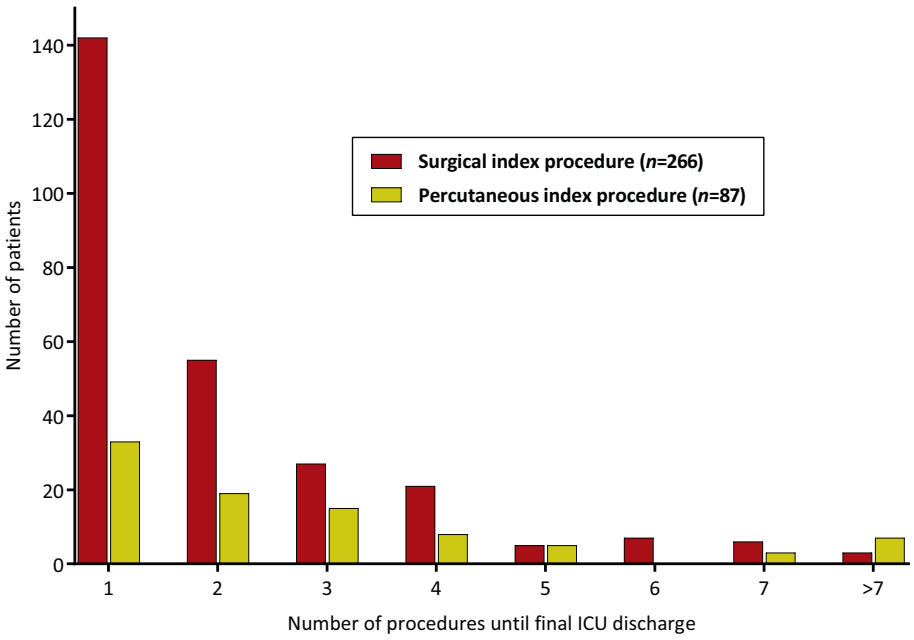

Fig. 1. Number of source control procedures stratified by type of index procedure ($n = 353$).

Table 3
Characteristics of 785 source control interventions in 353 critically ill patients with presumed abdominal sepsis.

Variable	Index procedures		Repeat procedures		*p*-value
	$n = 353$		$n = 432$		
Anatomical source of infection:					<0.001
- Esophagus or stomach	14	[4]	16	[4]	
- Small intestine	98	[28]	92	[21]	
- Large intestine	90	[26]	41	[9]	
- Biliary tract (including liver)	49	[14]	75	[17]	
- Pancreas	24	[7]	36	[8]	
- Spleen	3	[1]	1	(0)	
- Peritonitis/abscess without evident source	51	[14]	139	(32)	
- Negative procedure, no source identified	24	[7]	32	[7]	
Primary technique:					<0.001
- Surgical: laparotomy	242	(69)	221	(51)	
- Surgical: laparoscopy	24	[7]	9	[2]	
- Percutaneous: ultrasound-guided	50	[14]	108	[25]	
- Percutaneous: CT-guided	14	[4]	55	[13]	
- Percutaneous: endoscopic	20	[6]	32	[7]	
- Percutaneous: without imaging	3	[1]	7	[2]	
Principle of source control (multiple may apply):					
Restoration of anatomy and function[a]	186	(53)	141	(33)	<0.001
Drainage	92	[26]	195	(45)	<0.001
Debridement	80	[23]	80	[19]	0.15
Decompression of abdomen or intestine	27	[8]	13	[3]	0.003
Intraperitoneal lavage	138	(39)	117	[27]	<0.001
Source identified but no intervention	5	[1]	6	[1]	0.97
Diagnostic findings (multiple may apply):[b]					
Macroscopic signs of peritonitis	113	(38)	118	[30]	0.03
Intra-peritoneal abscess	62	[21]	114	[29]	0.01
Intestinal perforation/anastomosis leakage	112	(37)	86	[22]	<0.001
Intestinal ischemia	58	[19]	37	[9]	<0.001
Other infected or necrotic organ/tissue	26	[9]	30	[8]	0.58
Microbiological specimen(s) obtained	191	(64)	195	(49)	<0.001

CT: computed tomography. *ICU:* Intensive Care Unit. Data are presented as frequency (column percentage).
[a] Including, among others, resection, bowel diversion and closure of perforations.
[b] For 52 index- and 33 repeat procedures not registered in sufficient detail, since procedures were not performed just before or during an ICU admission.

all-negative following the remaining 73 (16%) procedures. Microbiological findings of these cultures obtained during the interventions (including negative results) guided optimization of therapy (including starting, changing, or stopping of antimicrobial drugs within five days of the procedure date) in 106 (28%) cases.

3.5. Procedural outcomes

Adequacy of source control was assessed for the 236 patients who had their first intervention within 24 h of presenting to the ICU, according to the definitions listed in Table 1. Results of this adjudication process are shown in Table 4. The index procedure resulted in adequate source control in 93 (39%) patients by day 14. In another 65 (28%) patients, source control was classified as delayed adequate since additional interventions had been required in the meantime, and for the residual 78 (33%) subjects it was considered still (or again) inadequate by day 14. The latter group included 54 patients who died. For comparison: immediately following the index procedure, drainage and control of the infectious source was deemed technically successful in 227 (96%) cases, and only one procedure had been terminated early due to dismal intraoperative findings. Of note, patients with surgical and percutaneous index procedures had similar rates of adequacy (Table S1, Appendix III). At final follow-up (i.e., 14 days after the last intervention performed during ICU admission), 159 (67%) were considered to have adequate source control. Nine (4%) patients were still considered to have inadequate control of the infectious source, whereas 68 (29%) had died.

3.6. Patient outcomes

Patients achieving (delayed) adequate source control were younger and had lower APACHE-IV scores than patients categorized as having inadequate containment on day 14, but the time delay from sepsis onset until first intervention did not differ between groups (Table S1, Appendix III). Although minor baseline differences in CRP, WBC and fever were apparent, temporal trends in these inflammatory markers were similar (Fig. 2). In contrast, persistence of shock, continued intolerance for enteral feeding, and high SOFA-scores during the first week after the index procedure seemed predictive of failure to effectively control the source of infection.

Table 4
Infectious outcomes in the 236 patients who had their first source control procedure upon ICU admission.

Variable	Source control by day 14						
	Adequate		Delayed adequate		Inadequate[a]		*p*-value
	n = 93 (39%)		*n* = 65 (28%)		*n* = 78 (33%)		
Immediate procedural adequacy	93	(100)	60	(92)	75	(96)	0.14
Adequacy on final assessment[b]	91	(98)	55	(85)	13	[17]	<0.001
Prior cultures available for guidance	13	[14]	6	[9]	8	[10]	0.60
Antimicrobial use on day 1:							
Beta-lactam[c]	93	(100)	64	(98)	73	(94)	0.02
Metronidazole	76	(82)	54	(83)	72	(92)	0.12
Vancomycin	12	[13]	1	[11]	12	[15]	0.77
Aminoglycoside	15	[16]	1	[24]	18	[23]	0.01
Antifungal	8	[9]	7	[11]	15	[19]	0.10
Other	8	[9]	2	[3]	4	[5]	0.37
Antimicrobial use from restricted formulary in first week:							
Carbapanems	16	[17]	18	[28]	14	[18]	0.22
Piperacilline-tazobactam	6	[6]	4	[6]	2	[3]	0.49
Quinolone	12	[13]	6	[9]	3	[4]	0.12
Vancomycin	20	[22]	21	(32)	21	[27]	0.31
Antifungal[d]	7	[8]	7	[11]	11	[14]	0.38
Concurrent infections in first week[e]	14	[15]	13	[20]	17	[22]	0.50
- Pneumonia	5	[5]	3	[5]	6	[8]	
- Empyema or mediastinitis	2	[2]	4	[6]	4	[5]	
- Catheter related bloodstream	–		2	[3]	1	[1]	
- Urinary tract	4	[4]	1	[2]	2	[3]	
- Wound or soft tissue infections	1	[1]	2	[3]	2	[3]	
- Other	2	[2]	1	[2]	2	[3]	
Discharged alive from ICU before day 7	65	(70)	24	(37)	7	[9]	<0.001
Death in ICU	3	[3]	4	[6]	50	(64)	<0.001

Data are presented as frequency (column percentage) and median (Q1-Q3).
[a] Inadequate source control group included 54 (69%) patients who died before day 14.
[b] Based on evaluating adequacy on day 14 after the final procedure observed during ICU stay.
[c] Beta-lactams concerned for 75% third generation cephalosporins.
[d] Restricted antifungals concerned echinocandins, amphotericin-B, posaconazol and voriconazol.
[e] Concerned only infections observed in the ICU with a probable or definite likelihood of infection based on post-hoc assessment of likelihood of infection as previously described [20].

Cephalosporins and metronidazole were most frequently used for initial treatment of IAI across all subgroups (overall, 196 (83%) of patients received this combination; Table 4). This largely concerned empirical therapy, as guidance by previous culture results (i.e., obtained before ICU admission) was available for only 27 (11%) of evaluated subjects. Although restricted formulary antimicrobial drug use was also comparable between groups, aminoglycosides were more frequently prescribed in patients who were (later) classified as having delayed or inadequate source control. Of note, new-onset (concomitant) infections were observed in 44 (19%) patients during the first week in ICU, with pneumonia being most prevalent.

4. Discussion

In a large cohort of critically ill patients with IAI we observed that approximately half of patients required more than a single intervention to contain their source of infection, despite the fact that the initial procedure was considered technically successful in virtually all cases. Ultimately, adequate source control was achieved for 67% on day 14 after the final intervention.

Prompt and adequate source control is an independent determinant of survival following abdominal sepsis. For example, in patients with septic shock due to gastrointestinal perforation each hour of delay was associated with reduced survival [8], whereas other studies have reported inconsistent results [9-12]. Importantly, our data indicated that delays to intervention were mostly a consequence of underlying diagnostic uncertainty, hampering straightforward interpretation of observed outcome relations. Similarly, previous studies have merely used technical and procedural success criteria to define adequacy of source control [9,13,21-23], yet our study demonstrates that persistent or recurrent infection may develop in 61% of cases. Of interest, infectious outcome did not differ between patients with a surgical and a percutaneous index procedure.

In order to provide ICU clinicians with a practical tool to support decisions regarding the need to obtain additional imaging studies and/or initiate (re)interventions, future studies should focus on outcomes such as resolutions of infection and clinical improvement rather than on all-cause mortality. However, to the best of our knowledge, only a single study in IAI patients has previously focused on the resolution of infection (rather than mortality) as its primary outcome of interest [24]. In line with our own findings, this study also observed a predictive association between persistence of organ failure after initial intervention and ultimate failure of source control. Future prediction rules should also incorporate both procedural findings and infection characteristics, as well as time trends of biomarkers related to organ failure [25]. Unfortunately, simple inflammatory markers such as C-reactive protein and white blood cell count seemed non-predictive in our study, which was in line with a previous evaluation of procalcitonin in IAI patients [26]. Novel markers better reflecting the host response to infection should thus be evaluated for this purpose [27]. Furthermore, IAI is a very heterogenous disease entity and typically associated with protracted recovery. Consequently, (very) large study populations implementing repetitive measurement of predictor variables will be required.

Clinical guidelines advise to obtain microbiological specimens during each procedure in critically ill patients with IAI [28,29]. Although the collection of samples for culturing was suboptimal in our study (i.e., 55% among evaluated procedures), our data clearly underline their diagnostic importance. In fact, optimization of antimicrobial therapy occurred after 28% of procedures during which specimens were collected. Obviously, these may have been more frequently collected in cases with large diagnostic uncertainty and specimens not collected during the procedures were not evaluated. Nevertheless, it is important for clinicians to be aware of the great potential relevance of microbiological specimens obtained during source control procedures.

An important strength of our study relates to the fact that we evaluated source control interventions of all types. Most previous studies have focused on surgical procedures exclusively, whereas our data indicate that 25% of first interventions and 37% overall, involve an (image guided) percutaneous technique. However, the fact that our study was limited to two tertiary centers in the Netherlands may reduce generalizability of these findings. For instance, our study population included a relatively high proportion of patients admitted to the hospital for high risk oncologic surgery. This may be reflected by the 42% hospital mortality rate observed by us, which is higher than the 23–31% death rates reported in other cohorts of ICU patients with IAI [6,11,12].

There are also other limitations to our study. First, the evaluation of source control was pragmatic yet somewhat subjective, since it was primarily performed by a single physician-investigator. However, ambivalent cases were discussed among at least three investigators (kedge, TV, OC) to reduce variability. Second, we did not measure (nor control for) some important aspects of sepsis treatment, in particular adequacy and exact timing of antimicrobial treatment and organ support. For this reason, we refrained from assessing causal associations between (adequacy of) intervention and patient outcome. Similarly, we also could not ascertain whether risk factors for failure of source control identified by our study are statistically independent. Finally, the descriptive analyses of temporal changes in disease severity in the first week after intervention

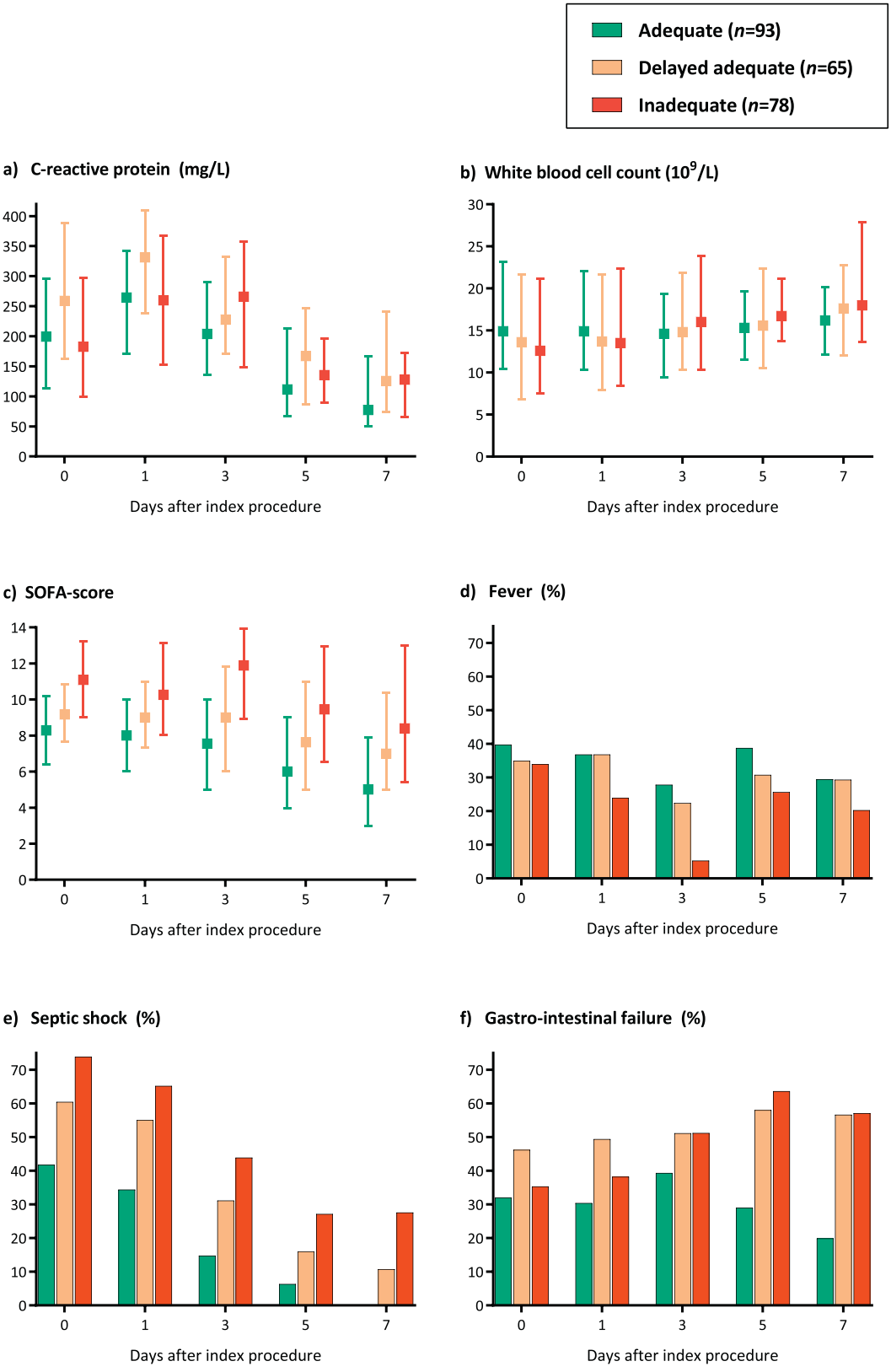

Fig. 2. Trend of disease severity markers stratified by adequacy of the index procedure ($n = 236$). Patients with an initial procedure that was performed within one day of ICU admission were divided based on adequacy of source control on day 14 after the index procedure. Fever was defined as core temperature > 38.0 °C. Gastrointestinal failure was defined as intolerance to enteral feeding (daily caloric intake <50% of calculated needs), use of prokinetic medication, presence of severe diarrhea/vomiting, or increased abdominal pressure (>25 mmHg or open abdomen treatment) [30]. Whiskers show medians with interquartile range, bars show proportions.

may have been influenced by informative censoring, as observations were conditional on patients remaining in the ICU.

5. Conclusions

This study provides detailed epidemiological data underpinning the complex associations between (the adequacy of) source control and clinical outcomes of ICU patients with IAI. Our findings may thus help clinicians to make better informed decisions in these patients.

Competing interests and funding

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.02.029.

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