Title: Open abdomen and entero-atmospheric fistulae: An interim analysis from the International Register of Open Abdomen (IROA)

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Open abdomen and entero-atmospheric fistulae: An interim analysis from the International Register of Open Abdomen (IROA)

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Research Highlights

- Entero-atmospheric fistula developed in 9% of the patients
- Techniques for temporary closure did not affect fistula formation
- Days of open abdomen, cancer and time to nutrition are related to EAF

ABSTRACT

Introduction: No definitive data describing associations between cases of Open Abdomen (OA) and Entero-atmospheric fistulae (EAF) exist. The World Society of Emergency Surgery (WSES) and the Panamerican Trauma Society (PTS) thus analyzed the International Register of Open Abdomen (IROA) to assess this question.

Material and Methods: A prospective analysis of adult patients enrolled in the IROA.

Results: Among 649 adult patients with OA 58 (8.9%) developed EAF. Indications for OA were peritonitis (51.2%) and traumatic-injury (16.8%). The most frequently utilized temporary abdominal closure techniques were Commercial-NPWT (46.8%) and Bogotà-bag (21.9%). Mean OA days were 7.9±18.22. Overall mortality rate was 29.7%, with EAF having no impact on mortality. Multivariate analysis associated cancer (p=0.018), days of OA (p=0.003) and time to provision-of-nutrition (p=0.016) with EAF occurrence.

Conclusion: Entero-atmospheric fistulas are influenced by the duration of open abdomen treatment and by the nutritional status of the patient. Peritonitis, intestinal anastomosis, negative pressure and oral or enteral nutrition were not risk factors for EAF during OA treatment.

Key words: Open Abdomen; Entero-atmospheric fistula; Fistula; IROA;

Introduction:

Entero-atmospheric fistulae (EAF) are devastating and frightening complications of

abdominal surgery in general and are particularly feared in the use of open abdomen (OA) management as part of damage control treatment philosophies. In current practice, the indications for OA are diverse encompassing many forms of severe physiological derangement and injury[1–6].The World Society of Emergency Surgery (WSES) and the Abdominal Compartment Society (WSACS) thus recently published guidelines and indication for OA management[4,6–8]. Abdominal sepsis and trauma were two of the main indications for leaving the abdomen temporarily open after damage control management[9,10]. Further, a recent consensus conference conducted among an international subject-matter experts suggested the OA as one of potential preferred options in managing patients with severe peritonitis and severe sepsis/septic shock under the following circumstances*:* "abbreviated laparotomy due to severe physiological derangement, the need for a deferred intestinal anastomosis, a planned second look for intestinal ischemia, persistent source of peritonitis (failure of source control), or extensive visceral oedema with the concern for development of abdominal compartment syndrome"[2]. OA management was also recommended for use in trauma patients with "persistent hypotension, acidosis, hypothermia and coagulopathy and/or risk factors for abdominal compartment syndrome and/or the inability to definitively control the source of contamination and/or the necessity to evaluate the bowel perfusion"[2].

Besides a general need for great caution in avoiding rough handling of the viscera with the OA, being aware of further risk factors would greatly assist clinicians in avoiding the occurrence of the OA. However there is little established data regarding the epidemiology of EAF in OA patients. What little is known suggests that intra-abdominal sepsis (IAS) itself is bone of the associated factors for EAF in presence of an OA[11]. Further, intestinal ischemia such as reflected by raised serum lactate have been proposed as risk factors for EAF in OA patients [12–20]. Finally, in a large series of 517 OA after large bowel resections for trauma, the number of operative re-explorations and high volumes (>5L) fluid

resuscitation were identified as predictors of EAF and IAS [13].

The present study thus aims to investigate the relationship between OA and EAF amongst the patients enrolled in the International Register of Open Abdomen (IROA).

Materials and methods:

The International Register of Open Abdomen IROA is a prospective observational international cohort study that enrolled patients worldwide using the major inclusion criteria of an OA. The Registry, sponsored by the WSES and PTS, was launched in September 2015[21]. Patients included in the present analysis are adult (with more than 14 years old) with an OA treatment collected from September 2015 to October 2017. Besides an analysis of the entire study population, subgroups with OA utilized after either peritonitis or trauma were studied separately. The IROA data was uploaded to and maintained on a specially constructed web platform (Clinical Registers®) through a dedicated web site: www.clinicalregisters.org. The study protocol was approved by the coordinating center Ethical Committee and also registered to ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT02382770).

The data collected for each patient included: demographical data, comorbidities, indication for treatment, temporary abdominal closure technique (TACT) and duration of the treatment, complications, rates and time to primary fascial closure, fistula, and mortality before and after closure. The study focused on the development of an entero-atmospheric fistula during the open treatment. In case of different TACT adopted during the treatment for each patient was chosen the most relevant based on the duration of the treatment; primary fascial closure was defined as the closure of the abdominal fascia without the implantation of a prosthesis. A detailed description of the study protocol is available at www.clinicalregisters.org/IROA.

Statistical analysis

The results were analyzed for the entire study population and for septic and traumatic. Continuous variables were expressed as mean and standard deviation; categorical data were expressed as proportions and percentages. Univariate analysis was performed with the ANOVA test for continuous variables and with the chi square test for the categorical; linear associations were tested with the Pearson's correlation. Multivariate models were calculated with the linear logistic regression method including all the variables resulted significantly associated ($p<0.05$) with the selected outcome at the univariate analysis. Results of the uni- and multivariate analysis were shown with the Odd Ratio (OR) and the 95% confidence intervals. All the statistical analysis was performed with IBM SPSS 20 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

Results:

Entire population

Six hundred and forty-nine (649) adult patients were included in the final analysis, 58 of whom (8.9%) patients developed EAF. Detailed results of these EAF are presented in Table 1. Definitive fascial closure was reached in 529 (81.5%) patients and the mean days of open abdomen were 7,9±18.22. Data regarding nutrition were available for 391 (60.1%) patients; however no significative association between type of nutrition administered and development of EAF was observed.

Data regarding intestinal anastomosis were available for 532 (82%) patients, among which 191 (35.9%) had an intestinal anastomosis and 18 (9.4%) developed EAF. Comparatively, among 341 (64.1%) patients who did not undergo intestinal anastomosis, 29 (8.5%) patients developed an EAF ($p=0.72$). Among the 52 patients who had a large bowel anastomosis, 2 (3.8%) developed EAF; 89 patients had small bowel anastomosis and 8 (9%) developed EAF, 41 patients had combined small and large bowel anastomosis with 6 (14.6%) EAF ($p=0.001$).

Nine (9) patients had gastro-esophageal and urological anastomosis either separate or combined. The overall mortality rate in the entire population was 29.7% (193 patients), however among the 58 patients with EAF, 23 (39%) died compared with 170 (28.8%) among the 591 without EAF (p=0.08) (Table3).

There was a linear correlation between the days of open abdomen and time to nutrition with the development of EAF (Pearson coefficient 0.142 and 0.149 respectively, p<0.001 for both).

At univariate analysis patient factors associated with EAF were: the presence of cancer (p=0.001), previous stoma (p=<0.001), peritonitis (p=0.004), days of open abdomen (as a continuous variable) (p=<0.001) and time to nutrition (continuous variable) (p=0.005). At multivariate analysis factors related to EAF were: presence of cancer (p=0.018), days of open abdomen (p=0.003) and time to provision of nutrition (p=0.016) (Table 2).

Intra-abdominal sepsis patients

The subgroup analysis for peritonitis included 332 adult patients, of whom 40 patients (12%) developed EAF. No difference in EAF rate was recorded among the different temporary abdominal closure techniques, nor did the presence of EAF did not affect the definitive fascial closure rate. The type of nutrition administered and the presence of an intestinal anastomosis did not affect the development of EAF. Overall mortality was 28.3% (94 patients) among all patients; and among the 58 patients with EAF, 17 (42%) died versus 77 (26%) without EAF (p=0.03) (Table3).

Both Uni- and multivariate analysis of factors linked to fistula formation were performed. With univariate analysis, days of open abdomen, time to nutrition provision, and previous stoma were significant, however with at multivariate analysis no factors significantly predicted EAF developing.

Trauma patients

Data for 109 adult victims of trauma was available, among whom 5 patients (4.6%) developed EAF. No associations were noticed between the development of EAF and the type of temporary closure technique or the type of nutrition provision. Nor did the presence of EAF significantly affect the definitive fascial closure rate. Due to the presence of only 5 EAF no inferential analysis were performed.

Discussion:

EAF is a known and dangerous complication of the open abdomen for which preemptive measures are mandatory as the developing of EAF increase mortality, length of stays and costs.. General and emergency surgeons are well aware of the risk factors especially in utilizing OA for damage control procedures in severely injured patients. Previous work has described that delayed abdominal closure, presence of bowel injury requiring repairs and/or anastomosis, colon resection during damage control procedures, large volume fluid resuscitation volume, presence of intra-abdominal sepsis/abscess, non-protection of bowel loops during OA and the use of polypropylene mesh directly over the bowel are all known risk factors for EAF[2,10,22–24]. The epidemiology of EAF in cases of peritonitis is not as well described however. There does appear to be an association between peritonitis as a general factor favoring EAF development when the open abdomen is especially if associated to OA[11,13]. Few studies suggest a relation between the presence of peritonitis and a higher EAF rate among those who experienced OA treatment. Some other studies found different risk factors for EAF[12–20]. The present study therefore aimed to identify among the largest existing cohort of OA patients, risk predicting the development of EAF. A number of conclusions thus arose from this study. First, it was identified that patients requiring the OA for peritonitis constituted a larger cohort of patients than those suffering traumatic injury treated with OA throughout the world: in fact more than half of OA recorded

in IROA were performed for peritonitis and abdominal sepsis. This trend is only likely to continue ad become more pronounced as the OA is used less and less for trauma and more frequently for intra-abdominal sepsis [25] Further study will be required in this area, as despite an higher fistula rate in patients with peritonitis compared to other indication for open abdomen, multivariate analysis did not confirm that peritonitis was not related to the development of EAF. Even the different temporary abdominal closure techniques seemed to not influence the EAF rate, with similar results among techniques with or without negative pressure. Therefore, despite the previous suspicious and caution regarding untoward effect of negative pressure on hollow viscera, the present study failed to demonstrated an existing link among negative pressure and developing of EAF in this cohort of patients.

Further, despite the evidences of previous studies [13], the presence of intestinal anastomosis were not a significant risk factor for EAF developing in the overall OA population. However, again future research should continue to further refine this question. When analyzed separately, the different kinds of anastomoses showed different and significant EAF incidence. Multiple anastomoses are inherently at higher risk, as in fact patients who underwent to either large either small bowel anastomosis in the same intervention are at higher risk of EAF than those who have only one small or large bowel anastomosis. Interestingly, in this population, isolated small bowel anastomosis were at higher risk to develop EAF then isolated large bowel ones. In any case from the present data seems that intestinal anastomosis can be performed in OA population without fear of an increased EAF rate.

The multivariate analysis identified three factors associated with EAF development: the presence of cancer, the time between first intervention and the start of nutrition and the duration of open abdomen treatment. The presence of cancer as a factor influencing the development of EAF could be interpreted as a “marker” of a patient’s frailty or reduced

functional status; cancer patients are characterized by a catabolic state with a constant inflammatory state and pre-operative malnutrition; these factors seem to play a role in the patient's response to the dramatic situation of the open abdomen, favoring the development of EAF. The relation between time to provision of nutrition and development of fistula suggests the importance of feeding in critically ill patients. The longer a patient remains without nutrition, the more likely a fistula may develop. Different nutritional regimens have been observed with no differences in EAF rate within them. This data suggests that enteral and oral feeding regimens should be initiated as soon as possible even in patients with OA, once provided that the bowel is viable with no major contraindications. Therefore, the authors suggest that as , nutrition seems to play a key role in the management of patients with an open abdomen, there may be promise in using enteral nutrition earlier to prevent the development of EAF. As the feeding route did not influence EAF rates so to reduce, patients should be fed per os or via enteral nutrition as soon as possible to avert the well-known consequences of prolonged bowel rest [26,27]. However, it must be cautioned that the relatively small number of patient in this cohort could lead to a II type error with a misinterpretation of the results and this is another topic for continued future study.

Finally, the days of open abdomen seemed to be one of the most important factors influencing the development of EAF. As previously noticed and demonstrated complications and fistulas are significantly influenced by the duration of the OA treatment[10,28]. Available data suggest this strong correlation between the two factors even if it not possible to determine if the time with OA favors the development of the EAF or, on the contrary, the development of fistula prolongs the time of OA. The fact that the presence of EAF does not influence the definitive closure rate and the mortality in general population suggest the role of time as a factors favoring the development of the fistula and not the contrary, even if a definitive evidence is quite impossible to reach.

Definitive abdominal fascial closure was generally reached in almost the 80% of patients in the overall population. In peritonitis group this rate was lower than in trauma patients. The development of EAF during the open treatment significantly influenced the duration of the open treatment, as shown in table 2, but seems not to influence the definitive fascial closure rate (table 3). The duration of the treatment has been detected as a factor significantly related to the developing of an EAF: at the same time it could be considered as a cause and a consequence of the fistula formation, with a reflecting effect.

In general study population the development of an EAF seems not to influence the mortality; on the other hand, among patients with open abdomen for peritonitis the development of EAF was associated with an increased mortality (Table3).

The present study presents the results of the largest cohort analysis in OA, with an international, worldwide, prospective cohort of patients. The strength of the very large study population and the multicenter nature of the study is unavoidably weakened by the lack of complete information for all patients with some missing data, sometimes important as the fluid balance information or the fistula management strategy. Moreover some considerations could be affected by the II type error due to the number of patients included. However the study, with only initial results of the IROA project, is the largest existing case series of patients with open abdomen and it represents a good attempt to answer to all the OA questions. Further data will be available increasing IROA numbers and researches with more patients are needed to confirm these results.

Conclusion:

Entero-atmospheric fistulas are influenced by the duration of open abdomen treatment, the patients' characteristics and by the time to nutrition start. Peritonitis is not by itself a risk factor for fistula. Intestinal anastomosis, negative pressure and oral or enteral nutrition are not risk factors for EAF during OA treatment.

Competing interest: All authors declare to have no competing interests

Conflict of interest: all authors declare to have no conflict of interest

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Ethics Approval and Consent to Participate: Study has been approved by the coordinating center Ethical Committee (Papa Giovanni XXIII Hospital, Bergamo, Italy) (Protocol number 0020776/15).

Availability of data and supporting materials: Not applicable

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Authors' contribution: FC study and manuscript conception and draft, FC, GM, MC, FS, AK, FCa, PF, MT, patients accrual and data insertion, FC, MC, MS, data analysis critically revised the manuscript, all authors read and gave the final approval.

List of abbreviations:

Open Abdomen (OA)

World Society of Emergency Surgery (WSES)

Panamerican Trauma Society (PTS)

International Register of Open Abdomen (IROA)

Temporary Abdominal Closure Technique (TACT)

Abdominal Compartment Syndrome (ACS)

Negative Pressure Wound Therapy (NPWT)

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Table legends:

Table 1: Characteristics of the included patients expressed as Number (%) or Number (±SD) as appropriate; (BMI: Body Mass Index; EAF: Entero-Atmospheric Fistula; TACT: Temporary Abdominal Closure Technique; ACS: Abdominal Compartment Syndrome; NPWT: Negative Pressure Wound Therapy; ICU: Intensive Care Unit; ISS: Injury Severity Score; MPI: Mannheim Peritonitis Index)

		All patients		peritonitis		trauma
n		649		332		109
mortality		193(29,7%)		94(28%)		19(17%)
definitive closure		529(81,5%)		279(84%)		94(86%)
EAF		58 (8,9%)		40 (12%)		5(4,6%)
Male gender		375(57,8%)		173(52%)		87(80%)
indication						
	peritonitis	332 (51,2%)		332 (100%)		
	pancreatitis	37(5,7%)				
	hemorrage and vascular emergencies	77 (11,9%)				
	ischemia	53(8,2%)				
	trauma	109(16,8%)				109(100%)
	post-op ACS	19(2,9%)				
	other	22(3,5%)				
TACT						
	Bogotà bag	142(21,9%)		69(21%)		24(22%)
	Skin Closure	58(8,9%)		13(4%)		31(28%)
	Wittmann Patch	51(7,9%)		40(12%)		1(1%)
	Barker vacuum pack	66(10,2%)		22(7%)		18(16%)
	Commercial NPWT	304(46,8%)		171(51%)		31(29%)
	Commercial NPWT+dynamic tension	28(4,3%)		19(5%)		7(4%)
nutrition during tretament						
	enteral	30(4,6%)		17(5%)		6(5%)
	parenteral	283(43,6%)		142(43%)		45(41%)
	enteral+parenteral	78(12%)		44(12%)		8(7%)
	missing	258(39,8%)		129(40%)		50(47%)
days of open abdomen		7,9(18,22)		7,87(±14,21)		8,07(±21,8)
age		60,19(±17,8)		63,81(±14,85)		41,99(±18,6)
BMI		27,06(±5,01)		27,46(±5,15)		26,3(±3,78)
ICU lenght of stay		13,85(±19,67)		12,51(±15,05)		15,49(±31,7)
Ventilation days		11,79(±18,24)		11,72(±20,64)		11,60(±14,4)
time to nutrition		1,43(±1,17)		1,33(±1,9)		2,11(±2,14)

MPI				23,63(±8,56)		
ISS						29,46(±16,2)

Table 2: Uni- and Multi-variate Analysis for factor influencing Entero-Atmospheric Fistula. Results are expressed as Number (%) or Number(±SD) as appropriate, Odd ratios (OR) were expressed along with the 95% confidence interval. (BMI: Body Mass Index; EAF: Entero-Atmospheric Fistula; TACT: Temporary Abdominal Closure Technique; ACS: Abdominal Compartment Syndrome; NPWT: Negative Pressure Wound Therapy;)

				univariate analysis		**multivariate analysis**	
		no EAF	EAF	OR	p	OR	p
All patients		591 (91%)	58 (8,9%)				
number of enrolled patients for each centre	<10	82(86%)	13(14%)	1	0,079		
	>10	509(91,9%)	45(8,1%)	0,558(0,28-1,07)			
gender	F	246(89,8%)	28(10,2%)	1	0,328		
	M	345(92%)	30(8%)	0,764(0,44-1,31)			
Cancer	no	437(93%)	31(7%)	1	0,001	2,44(1,98-3,64)	0,018
	yes	154(85%)	27(15%)	2,47(1,42-4,27)			
Ischemic cardiomyopathy	no	379(90%)	43(10%)	1	0,127		
	yes	212(93%)	15(7%)	0,624(0,33-1,14)			
diabetes	no	508(90%)	51(9,1%)	1	0,678		
	yes	83(92%)	7(8%)	0,84(0,36-1,91)			
immunosuppression / steroids	no	544(90%)	55(10%)	1	0,449		
	yes	47(94%)	3(6%)	0,631(0,19-2,09)			
malnutrition (wheight loss>10% in the last 6 months)	no	569(92%)	53(8%)	1	0,075		
	yes	22(82%)	5(18%)	2,440(0,88-6,70)			
previous stoma	no	565(92%)	49(8%)	1	<0,001	2,66(0,67-4,62)	0,101
	yes	26(74,3%)	9(25,7%)	3,991(1,77-8,99)			
nutrition during treatment					0,081		
	missing	244(94%)	14(6%)				
	enteral	26(86%)	4(14%)	1,087(0,69-1,32)			
	parenteral	251(88%)	31(12%)	1,021(0,45-1,35)			
	parenteral+enteral	70(90%)	8(10%)	0,987(0,68-1,41)			
intestinal anastomosis	no	312(91%)	29(9%)	1	0,72		
	yes	173(90%)	18(10%)	1,119(0,604-2,074)			
indication							
	peritonitis	292(88%)	40(12%)	2,27(1,27-4,06)	0,004	1,334(0,78-1,47)	0,456
	pancreatitis	32(94%)	2(6%)	0,567(0,13-2,44)	0,438		
	hemorrage and vascular	75(97%)	2(3%)	0,246(0,05-1,02)	0,058		
	ischemia	47(88%)	6(12%)	1,336(0,54-3,27)	0,526		

	trauma	104(95%)	5(5%)	0,442(0,17-1,13)	0,081		
	post-op ACS	17(89%)	2(11%)	1,206(0,272-5,35)	0,805		
	other	20(95%)	1(5%)	0,765(0,23-1,24)	0,754		
TACT							
	bogotà bag	134(94%)	8(6%)	0,546(0,25-1,17)	0,119		
	wittmann patch	43(84%)	8(16%)	2,039(0,90-4,57)	0,078		
	Barker vacuum pack	64(97%)	2(3%)	0,294(0,70-1,23)	0,076		
	commercial NPWT	271(89%)	33(11%)	1,559(0,90-2,68)	0,108		
	NPWT+dynamic	26(93%)	2(7%)	0,776(0,17-3,35)	0,734		
	Skin closure	53(91%)	5(9%)	0,958(0,36-2,49)	0,93		
Negative pressure	no	230(92%)	21(8%)	1	0,686		
	yes	361(91%)	37(9%)	1,12(0,11-1,96)			
Days of open abdomen		7,12(±16)	16,4(±30,4)	1,014(1,02-1,04)	<0,001	1,008(1,002-1,010)	0,003
age		60,14(±17,8)	60,71(±17,4)	1,002(0,98-1,01)	0,816		
BMI		27,03(±4,9)	27,44(±5,63)	1,01(0,96-1,07)	0,547		
time to nutrition		1,32(±1,99)	2,37(±3,22)	1,175(1,04-1,32)	0,005	1,170(1,09-1,21)	0,016

Table 3: Contingency Tables between Entero-Atmospheric Fistula and Definitive closure rate, Mortality, Intensive Care Unit length of stay and Number of Ventilation days. Data are expressed as Number (%) or Number (±SD) as appropriate. (EAF: Entero-Atmospheric Fistula; ICU: Intensive Care Unit)

	n	definitive closure	p	mortality	p	ICU lenght of stay	p	ventilation days	p
All patients									
no EAF	591 (91%)	482(81%)	0,457	170(28%)	0,083	13,91(±20,02)	0,83	11,80(±17,07)	0,96
EAF	58 (8,9%)	47(81%)		23(39%)		13,23(±15,85)		11,64(±27,18)	
peritonitis									
no EAF	292(88%)	247(84%)	0,457	77(26%)	0,034	12,42(±14,66)	0,808	11,39(±18,41)	0,52
EAF	40(12%)	32(77%)		17(42%)		13,13(±17,88)		14,03(±32,43)	