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Management of esophageal perforations: proposal of a decision-making algorithm and validation of a severity score

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Management of esophageal perforations: Proposal of a decision-making algorithm and validation of a severity score

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ao Hugo e à Joana pelo grande exemplo

Inês

os meus pais

os meus irmãos

por me aturarem

MANAGEMENT OF ESOPHAGEAL PERFORATIONS: PROPOSAL OF A DECISION-MAKING ALGORITHM AND VALIDATION OF A SEVERITY SCORE

Esophageal Perforations

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ABSTRACT

Introduction: Esophageal perforation (EP) is a rare, often life-threatening condition, and its management is still challenging. The Pittsburgh group has suggested a perforation severity score (PSS) for better decision-making in the management of EP. The aim of this study was to propose a decision-making algorithm based in our experience of a quarter of century and to analyze the usefulness of the PSS in an independent study population.

Material and Methods: Analysis of a prospective database with cases of EP (n=71) treated in an Upper GI Surgery Unit, between January 1991 and October 2014.

Results: The majority of perforations were traumatic (60.6%) and thoracic (62.0%), and 22.5% were treated non-operatively. Morbidity and mortality were 40.8% and 15.5%. PSS was significantly higher in patients with fatal outcome (7.36 vs. 3.93;p=0.009), morbidity (6.55 vs. 3.02;p<0.001) and operative cases (5.13 vs. 2.19;p<0.001). PSS presented an OR of 2.87 (95%CI:1.06-7.75;p=0.037) for mortality, 5.10 (95%CI:2.19-11.91;p<0.001) for morbidity and 4.70 (95%CI:1.78-12.35;p=0.002) for operative treatment. Most significant outcome predictors were PSS, clinical stability, non-contained leak, prior esophageal pathology, etiology and location of perforation.

Conclusions: Based on these results, we propose a decision-making algorithm to best assist in the choice of EP treatment. The PSS reliably correlates with the seriousness of EP and is a useful tool to identify appropriate candidates for non-operative management.

KEY WORDS: Esophageal perforation, Severity score, Decision-making algorithm, Outcomes, Non-operative management

INTRODUCTION

Esophageal perforation (EP) is an uncommon condition of increasing incidence. This is mainly due to iatrogenic perforations, which have been reported as its leading cause, at least, since 1970 [3, 4], despite the shift from rigid to flexible endoscopy [1-3]. The rising applicability and advantages of endoscopic procedures enhanced this tendency [5]. EP is associated to high mortality (10-40%) [6, 7] that, despite diagnosis, support and treatment developments, has shown few or no improvements for almost 50 years [4]. It is important to notice that these values are highly variable due to the limited number and high heterogeneity regarding patients, and lack of universally consistent approach. EP shows a great clinical heterogeneity due to its variability concerning location, cause, extent of lesion and the fact that it can mimic more common pathologies, such as: aortic dissection, myocardial infarction, acute pancreatitis, perforated ulcer, pneumothorax or pulmonary disease [7]. Hereupon, EP may present itself as a challenging diagnosis, explaining the extended time between presentation and diagnosis (more than 24 hours in 60% of the cases [8]). This delay, along with mediastinitis, sepsis and the initial diagnosis being incorrect in 50% of the cases, [7, 8], may partially explain the great morbidity and mortality of EP. [6, 7, 9-12] The approach and management of EP, depends greatly on medical experience and subjectivity, ranging from conservative treatment to radical esophagectomy. In 2009, *Ghulam Abbas, MD et al.[9]* proposed a “perforation score” to evaluate the ability some clinical factors could have in the decision-making process in order to generate an optimal therapeutic approach and better patient outcomes. They concluded that injury severity, degree of mediastinal and pleural contamination should greatly head approach to EP. They also concluded that non-operative management might be successfully implemented in selected patients with a low morbidity and mortality if favorable radiographic and clinical characteristics are present. In the current study, we evaluate the presentation, treatment and outcome of all cases of EP treated in a tertiary hospital during 24 years. We have applied the perforation severity score (PSS), evaluated its

feasibility and capability to guide clinical diagnosis and management in an independent study population. A decision-making algorithm is also proposed based in the analysis of our series and the lessons taken from our experience.

MATERIALS AND METHODS

A prospective database with EP cases (n=71) treated in the Upper GI Surgery Unit of Centro Hospitalar São João (Porto, Portugal), between January 1991 and October 2014, was retrospectively reviewed. Institutional review board approval was obtained for this study (CES 04-13). The following clinical and pathological parameters were evaluated: gender, age, etiology (spontaneous, iatrogenic or traumatic), type of traumatic lesion (fishbone, chicken bone, teeth prosthesis, aliment impaction, trauma or other), prior esophageal pathology (stricture, cancer, diverticulum or other), location (cervical, thoracic or abdominal), time to diagnosis (hours), type of management (operative or non-operative, including endoscopic treatment), type of surgery (primary repair, repair over drain, exclusion, esophagectomy, drainage only or other), minimally invasive approach, endoscopic stent insertion, need of surgery after non-operative management, morbidity, type of complications (empyema, mediastinitis, pneumonia, sepsis, leakage of the repair, stricture after repair or other), mortality, length of stay (LOS) [days] and follow-up. When the patient presented with more than one complication, the most severe (life-threatening) complication was accounted. In order to evaluate the PSS (range 0-18), ten clinical variables were obtained for each patient (Table 1). Variables were defined as suggested by *Abbas et al [9].* The performance of PSS was assessed according to its capability to predict mortality, morbidity and type of management using the cut-off that presented better sensibility and specificity. In order to create a decision algorithm, patients were divided in 3 groups, as suggested by the Pittsburgh group, according to percentiles 25 and 75 of PSS: ≤2; 3-5; ≥6. Univariate and multivariate analysis were performed to correlate variables and outcome with PSS groups and assess the variables that could better guide decision.

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics for Macintosh, Version 21.0. (Armonk, NY, USA: IBM Corp). Analyzing categorical variables, Pearson's chi-square test or Fisher's exact test were used when appropriate. Normal distribution was assessed using normality plots (visual assessment of histograms with the normal distribution curve and normal Q-Q plots) and tests (Kolmogorov-Smirnov and Shapiro-Wilk tests). Continuous variables were analyzed using t-Student test or non-parametric tests (Mann–Whitney U and Kruskal-Wallis tests) whenever appropriate. Receiver operating characteristic (ROC) curves were used to assess the performance of PSS in appropriate situations. Multivariate analysis used logistic regression to compare variables that had shown differences (p-value <0.2) related to mortality, morbidity or type of treatment in univariate analysis. All 3 analyses using forward stepwise method were performed twice: the first one considered PSS groups and not the variables that compose PSS, the second one considered the variables that compose PSS, but not PSS groups. The p-value considered statistically significant was <0.05. All p values given are results of 2-sided tests.

RESULTS

The study comprises a total of 71 adult (≥18 year-old) patients. The median age at presentation was 62 (19-89) years, with 83.1% being ≤75 year-old. Thirty-six (50.7%) patients were female. No association was found between gender and morbidity (p=0.734) or mortality (p=0.705). Fifty-nine (83.1%) patients had no prior pathology, 4.2% and 1.4% had been previously diagnosed with esophageal cancer or stricture, respectively. The median timing of diagnosis was 24 (1-336) hours and 50.7% were diagnosed in the first 24 hours. The median LOS was 26 (4-266) days. The most common etiology was traumatic (60.6%) followed by iatrogenic (21.1%) and spontaneous (Boerhaave) accounting for 18.3%. Fish and chicken bones caused 74.4% of all traumatic perforations (39.5% and 34.9%, respectively). Most lesions were thoracic (62%). Operative treatment (77.5%) was more common than non-operative management. Primary repair was the most common option (52.7%) in operative treatment. The morbidity and mortality rates were 40.8% and 15.5%, respectively. In the non-operative group, out of 16 treated patients, none died and only one needed posterior operative treatment. Empyema (9.9%) and sepsis (9.9%) were the most common complications.

Morbidity was significantly associated to etiology (p=0.003), type of management (p=0.001) and PSS (p<0.001) [presence at presentation of tachycardia (p=0.001), pleural effusion (p<0.001), non-contained leak (p<0.001), respiratory compromise (p<0.001) and hypotension (p=0.012)]. No statistic significant association was found between morbidity and location of perforation (p=0.058). Mortality was significantly associated to age (p=0.007), etiology (p=0.02), esophageal pathology (p=0.002), location (p=0.004) and PSS (p=0.009) [age >75 years (p=0.016), presence at presentation of tachycardia (p=0.002), hypotension (p=0.006) and cancer (p=0.035)]. Type of management did not significantly affect mortality (p=0.052). The timing of diagnosis didn't significantly influence morbidity or mortality (p=0.699 and 0.389 respectively). Type of management was significantly associated to periods (p=0.03), LOS (p<0.001) and PSS (p<0.001) [presence at presentation of tachycardia (p=0.020), pleural

effusions (p=0.016), non-contained leak (p=0.004) and respiratory compromise (p=0.003)]. A more detailed description of the demographics and univariate analysis according to morbidity, mortality and type of management are depicted in Table 2. Cases were divided in 8-year periods (1991-1998; 1999-2006; 2007-2014) and no association was found (Table 3) between the periods and mortality (p=0.617), morbidity (p=0.381), LOS (p=0.054) or PSS (p=0.394). Association was significant between 8-year periods and type of treatment (p=0.03).

The median PSS was 4 (range 0-14). The 25 and 75 percentiles were 2 and 6, respectively (Figure 1). PSS was significantly higher in patients with fatal outcome (7.36 ± 4.13 vs. 3.93 ± 2.69; p=0.009) and in morbidity cases (6.55 ± 3.52 vs. 3.02 ± 1.88; p<0.001). Moreover PSS was significantly higher in operative cases (5.13 ± 3.22 vs. 2.19 ± 1.64; p<0.001). Dividing all patients according to PSS (cut-off in the middle possible value: <9 and ≥9), the first group showed over 10 higher odds of survival (OR: 10.86; 95% CI: 2.00-58.86; p=0.006). The ROC curves for PSS showed a good prediction of morbidity (AUC=0.801; p<0.001), mortality (AUC=0.745; p=0.010) and type of management (AUC=0.795; p<0.001) (Figures 2, 3 and 4). Regarding mortality and morbidity, PSS cut-off that has shown the best likehood ratios (1,488 and 1,753, respectively) was the value 4. About mortality, PSS ≥4 showed sensibility and specificity of 81.8% and 45.0%, respectively and diagnostic OR of 3.682. Concerning morbidity, PSS ≥4 showed sensibility and specificity of 79.3% and 54.8%, respectively, and a diagnostic OR of 4.640. As for the ROC curve of PSS and type of management, the best cut-off was 4, with likehood ratio of 2.426. PSS <4 was related with non-operative treatment with a sensibility of 75% and specificity of 69.1%, and a diagnostic OR of 6.706.

As suggested by the Pittsburgh group [9], patients were divided in three groups: PSS ≤2; PSS 3-5; PSS ≥6 (cut-offs based in percentiles 25 and 75). Groups were named 1 (low risk), 2 (moderate risk) and 3 (high risk), respectively. Twenty patients were allocated to group 1 (28.2%), and the same for group 3. In group 2 were the remaining 31 patients (43.6%). Groups were significantly associated to morbidity, type of management and LOS (p<0.001, p=0.003

and p<0.001, respectively), but not to mortality (p=0.080) (Table 4). Univariate analysis was performed to compare those groups regarding mortality and morbidity. Results are resumed in Table 5. The analysis of the PSS groups presented an OR of 2.87 (95% CI: 1.06-7.75; p=0.037) for mortality, OR of 5.10 (95% CI: 2.19-11.91; p<0.001) for morbidity and OR of 4.70 (95% CI: 1.78-12.35; p=0.002) for type of management, with significant higher mortality, morbidity and operative treatment rate in group 3.

Multivariate analyses were performed to determine the variables that had most influence on mortality, morbidity and type of management. As explained above, 2 models with different variables included were analyzed for each outcome. The 2 models for morbidity included: etiology, location, PSS and the following PSS parameters: age >75 years, tachycardia, pleural effusion, non-contained leak, respiratory compromise and hypotension. The 2 models for mortality included: etiology, prior esophageal pathology, location, PSS and the following PSS parameters: age >75 years, tachycardia, pleural effusion, non-contained leak, hypotension and cancer. The 2 models for type of treatment included: PSS groups and the following PSS parameters: tachycardia, pleural effusion, non-contained leak, respiratory compromise and hypotension. The variables that showed to be significant outcome predictors are detailed in Table 6.

DISCUSSION

Demographics

The current data shows that EP remains a challenging diagnosis with highly variable presentation. It affects all ages, genders and, regardless medicine development, morbidity and mortality rates show no significant improvement. It is important, although, to notice that some substantial differences have been brought to light in this population. Regarding etiology, it is of great importance the fact that traumatic cause is, by far, the most common (60.6%) and iatrogenic perforations, which have been described as leading cause at least for the last 50 years [4, 6, 7, 12-15], account for only 21.1%. No obvious cause or bias yields up, once all patients treated in a tertiary hospital are included (apart from pediatric population). A possible cause could be the Portuguese alimentary habits, since 74.4% of traumatic perforations were caused by chicken or fish bones, especially codfish bones. Further conclusions would be highly speculative since, although fish and chicken bones are generally reported among the most common causes [5, 7], the specific cause of traumatic perforations is not specified in most studies.

Management

Interestingly, despite the differences in etiology distribution of this series, the outcomes (mortality and morbidity rates, operative/non-operative treatment ratio, LOS) were similar to those described in the literature [3, 6, 7, 11-14, 16, 17]. Time to diagnosis, that is widely referred as a important outcome predictor[7, 12, 18-23], being associated, when over 24 hours, with up to 5 fold increase in mortality[3, 7, 23], was not significantly associated with increased mortality or morbidity ($p=0.389$ and $p=0.699$, respectively) in the present study. Such difference shows no evident cause, given that the number of patients with time to diagnosis ≤24h (50.7%) is comparable to most literature reports [7, 8, 13, 14]. We hypothesize that this may be due to the major difference in the etiology of EP referred above.

Decision between operative or non-operative treatment is an important choice for each patient, and it's, many times, empirically based on surgeon's experience and knowledge. Non-operative management, which includes, in recent years, an increasing use endoscopic treatment [24-27], is generally associated with better prognosis, depending on being rightly adjudicated to select patients [7, 15, 17, 25, 28]. As reported in most recent series, about one in every four patients might be treated non-operatively [6, 7]. This is similar to what reports our study (22.5%). As expected, according to the relatively recent interest and knowledge regarding non-operative management, this approach has shown to be an increasing option in our hospital, accounting for 9.5% of EP patients treated in 1991-1998, 16% in 1999-2006 and 40% in 2007-2014. However, this increase was not accompanied by a significant difference regarding LOS neither mortality and morbidity rates (Table 3). It should be pointed out that the use of stents in patients with cancer as a palliative treatment may be a cause of bias, since patients with worse prognosis *a priori* are included in the non-operative group. In our study, no patient with cancer was treated non-operatively. In our series, one patient was treated with stent (had no diagnosis of cancer) and non-operative management was associated with better outcome regarding morbidity (p=0,001), but not regarding mortality (p=0.052), although no patients treated non-operatively (n=16) died. Several factors have been suggested as guidance to decide between operative and non-operative treatment [7, 29]. Among them is the PSS [9], that we apply and evaluate here.

Perforation Severity Score

PSS has shown to be a useful tool guiding decision on EP management [9, 13]. In our series, PSS was significantly higher in patients with a fatal outcome (7.36 ± 4.13 vs. 3.93 ± 2.69; p=0.009) and in morbidity cases (6.55 ± 3.52 vs. 3.02 ± 1.88; p<0.001). Accordingly, PSS was significantly higher in operative cases (5.13 ± 3.22 vs. 2.19 ± 1.64; p<0.001). We also found that the ones with PSS <9 showed over 10 higher odds of survival (OR: 10.86; 95% CI: 2.00-58.86;

p=0.006). All this data is in favor of PSS utility even in a particular population as ours. In order to evaluate PSS strength to envisage outcome, ROC curves analyzing PSS as predictor of mortality, morbidity and type of management were elaborated. The ROC curves showed a good prediction of all 3 variables evaluated according to their AUC. The PSS cut-off of 4 for morbidity, mortality and type of management has shown good accuracy regarding sensitivity and specificity: 81.8% and 45.0%, for mortality; 79.3% and 54.8% for morbidity; 75% and 69.1% for type of management. Our data show that PSS highly correlates with seriousness of EP. A comparison of PSS values between non-operative patients and non-operative patients that had conversion to operative treatment would be interesting to see if those patients, according to PSS, should have been submitted to operative treatment in the first place. That analysis is not possible in the current series since only one patient needed the conversion from non-operative to operative management.

Decision algorithm

Decision algorithms in EP are always limited by the great heterogeneity of cause, presentation and patient background. However, a validated algorithm would be of great interest guiding management in EP, given the lack of universal consensus in treatment options and the rarity of the condition, both contributing to a lack of solid evidence-based medicine. We propose a decision-making algorithm (Figure 5), requiring further validation, based on PSS and clinical signs, which have shown consistently good prognosis association in patient treatment [9, 13]. The correlation between PSS and EP management is in favor of its usefulness in directing patient treatment. Converting PSS to a dichotomous variable (using 4 as cut-off, as seen above) shows good correlation with outcome, but the amount of false negative cases suggests it may not be enough to guide management *per se*. The Pittsburgh group suggested patients to be divided in three groups [9]. Based in the 25 and 75 percentiles of our PSS distribution, 3 groups were formed (low, moderate and high risk). Distribution of patients among groups was

as follows: 28.2% in group 1, 43.6% in group 2 and 28.2% in group 3. Mortality and morbidity increased, and percentage of non-operative treatment decreased, from group 1 to group 3. Those differences were statistically significant for morbidity and type of treatment, but not for mortality. However, the analysis of the PSS groups presented an OR of 2.87 (95% CI: 1.06-7.75; p=0.037) for mortality, OR of 5.10 (95% CI: 2.19-11.91; p<0.001) for morbidity and OR of 4.70 (95% CI: 1.78-12.35; p=0.002) for operative management, with significant higher mortality, morbidity and operative treatment rate in group 3. Those statistically significant differences were not as striking or always significantly different when comparing groups individually (Table 5). Those main differences are mostly seen when comparing groups 1 or 3 with group 2, although the mortality rate difference between groups 3 and 1 was not statistically significant (p=0.065) (what might be seen as a considerable trend toward significance). Those data strongly suggest PSS utility in guiding management of EP, although group 2 patients should go under a further decision chain. In order to do so, multivariate analyses were performed in order to assess the variables that presented as stronger prognosis predictors regarding mortality, morbidity and type of management (Table 6). Therefore, those variables (non-contained leak, clinical stability - respiratory compromise and tachycardia, location of EP and previous esophageal pathology) would be the better option to guide patients through the algorithm in groups 2. The subsequent steps of the algorithm were based on multivariate analyses and clinical experience, and turned out to be substantially similar to most algorithms suggested by various studies [1, 3, 5-7, 11, 13-15, 30].

CONCLUSION

Based on these results, we propose a decision-making algorithm to best assist in the choice of EP treatment. The PSS reliably correlates with the seriousness of EP and is a useful tool to identify appropriate candidates for non-operative management. Although the possible catastrophic prognosis, the opposite is also true. The avoidance of unnecessary interventions with consequent morbidity is a must, but should not compromise aggressive treatment when needed.

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TABLES AND FIGURES

Table 1. Perforation severity score	
Variable	**Value**
Age >75 years	1
Tachycardia (>100 bpm)	1
Leukocytosis (> 10,000 WBC/ml)	1
Pleural effusions (on chest X-ray, CT, or barium swallow test)	1
Fever (>38.5°C)	2
Non-contained leak (on barium swallow test or CT)	2
Respiratory compromise (respiratory rate >30, increasing oxygen requirement, or need for mechanical ventilation)	2
Time to diagnosis >24 hours	2
Presence of hypotension at presentation	3
Presence of cancer	3

Table 2. Demographics and univariate analyses according to the presence of morbidity, mortality and non-operative treatment				
	All patients, n (%)	Morbidity, n (%)	Mortality, n (%)	Non-operative treatment, n (%)
Age		NS (p=0.06)*	p=0.007*	NS (p=0.405)*
Mean ± SD	61.06 ± 14.86			
Presence vs. absence		65.03 ± 11.84 vs. 58.31 ± 16.19	72.00 ± 8.15 vs. 59.05 ± 14.97	58.31 ± 13.87 vs. 61.85 ± 15.16
Gender		NS (p=0.734)	NS (p=0.705)	NS (p=0.230)
Female	36 (50.7)	14 (38.9)	5 (13,9)	6 (16.7)
Male	35 (49.3)	15 (42.9)	6 (17.1)	10 (28.6)
Etiology of perforation		p=0.003	p=0.02	NS (p=0.3)
Spontaneous	13 (18.3)	10 (76.9)	5 (38.5)	1 (7.7)
Iatrogenic	15 (21.1)	2 (13.3)	3 (20.0)	3 (20.0)
Traumatic	43 (60.6)	17 (39.5)	3 (7.0)	12 (27.9)
Esophageal pathology		NS (p=0.306)	p=0.002	NS (p=0.241)
No prior pathology	59 (83.1)	25 (42.4)	6 (10.2)	16 (27.1)
Stricture	1 (1.4)	1 (100)	1 (100)	0 (0.0)
Cancer	3 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Others	8 (11.3)	3 (37.5)	4 (50.0)	0 (0.0)
Location of perforation		NS (p=0.058)	p=0.004	NS (p=0,759)
Cervical	17 (23.9)	3 (17.6)	1 (5.9)	3 (17.6)
Thoracic	44 (62.0)	20 (45.5)	5 (11.4)	10 (22.7)
Abdominal	10 (14.1)	6 (60.0)	5 (50.0)	3 (30.0)
Type of management		p=0.001	p=0.052	-
Operative	55 (77.5)	28 (50.9)	11 (20.0)	-
Non-operative	16 (22.5)	1 (6.3)	0 (0.0)	-
Type of operative management		p=0.342	p=0.437	-
Primary repair	29 (52.7)	16 (55.2)	8 (27.6)	-
Exclusion	21 (38.2)	11 (52.4)	3 (14.3)	-
Esophagectomy	2 (3.6)	1 (50.0)	0 (0.0)	-
Drainage only	3 (5.5)	0 (0.0)	0 (0.0)	-
LOS (days)		p<0.001**	NS (p=0.830)**	p<0.001**
Median [range]	26 [4-266]			
Mean ± SD, Presence vs. absence		63.97 ± 54.39 vs. 25.86 ± 26.84	36.18 ± 26.3 vs. 42.38 ± 46.94	11.94 ± 6.27 vs. 50 ± 26.89
PSS		p<0.001**	p=0.009**	p<0.001**
Median [range]	4 [0-14]			
Mean ± SD, Presence vs. absence		6.55 ± 3.52 vs. 3.02 ± 1.88	7.36 ± 4.13 vs. 3.93 ± 2.69	2.19 ± 1.64 vs. 5.13 ± 3.22
Age >75 years		NS (p=0.176)	p=0.006	NS (p=0.196)
Yes	12 (16.9)	7 (58.3)	5 (41.7)	1 (8.3)
No	59 (83.1)	22 (37.3)	6 (10.2)	15 (25.4)
Tachycardia		p=0.001	p=0.001	p=0.02
Yes	21 (29.6)	15 (71.4)	8 (38,1)	1 (4.8)
No	50 (70.4)	14 (28.0)	3 (6.0)	15 (30.0)
Leukocytosis		NS (p=0.678)	NS (p=0.735)	NS (p=0.757)
Yes	29 (40.8)	11 (37.9)	5 (17.2)	6 (20.7)
No	42 (59.2)	18 (42.9)	6 (14.3)	10 (23.8)

Pleural effusions		p<0.001	NS (p=0.178)	p=0.016
Yes	32 (45.1)	22 (68.8)	7 (21.9)	3 (9.4)
No	39 (54.9)	7 (17.9)	4 (10.3)	13 (33.3)
Fever		NS (p=0.319)	NS (p=0.789)	NS (p=0.682)
Yes	11 (15.5)	3 (27.3)	2 (18.2)	3 (27.3)
No	60 (84.5)	26 (43.3)	9 (15.0)	13 (21.7)
Non-contained leak		p<0.001	NS (p=0.166)	p=0.004
Yes	20 (28.2)	17 (85.0)	5 (25.0)	0 (0.0)
No	51 (71.8)	12 (23.5)	6 (11.8)	16 (31.4)
Respiratory compromise		p<0.001	NS (p=0.209)	p=0.003
Yes	21 (29.6)	16 (76.2)	5 (23.8)	0 (0.0)
No	50 (70.4)	13 (26.0)	6 (12.0)	16 (32.0)
Time to diagnosis >24 hours		NS (p=0.591)	NS (p=0.405)	NS (p=0.447)
Yes	34 (47.9)	15 (44.1)	4 (11.8)	9 (26.5)
No	37 (52.1)	14 (37.8)	7 (18.9)	7 (18.9)
Hypotension at presentation		p=0.007	p=0.001	NS (p=0.066)
Yes	10 (14.1)	8 (80.0)	5 (50.0)	0 (0.0)
No	61 (85.9)	21 (34.4)	6 (9.8)	16 (26.2)
Presence of cancer		NS (p=0.909)	p=0.035	NS (p=0.133)
Yes	7 (9.9)	3 (42.9)	3 (42.9)	0 (0.0)
No	64 (90.1)	26 (40.6)	8 (12.5)	16 (25.0)

SD, *Standard deviation*; PSS, *Perforation severity score*; NS, *Non-significant*

* t-Student test

** Mann-Whitney U test

Table 3. Outcomes univariate analysis according to 8-year periods				
	First period (1991-1998)	Second period (1999-2006)	Third period (2007-2014)	p-value
n	21	25	25	-
Morbidity, n (%)	9 (42.9)	11 (44.0)	9 (36.0)	NS (0.827)
Mortality, n (%)	2 (9.5)	4 (16.0)	5 (20.0)	NS (0.617)
Non-operative treatment, n (%)	2 (9.5)	4 (16.0)	10 (40.0)	0.03
LOS (days), mean ± SD	50.19 ± 39.90	47.80 ± 57.00	27.68 ± 28.94	NS (0.054)*
PSS, mean ± SD	4.95 ± 3.28	4.60 ± 2.92	3.92 ± 3.38	NS (0.394)*

LOS, *Length of stay*; PSS, *Perforation Severity Score*; SD, *Standard Deviation,* NS, *Non-significant*

* Kruskal-Wallis test

Table 4. Outcomes univariate analysis according to perforation severity score groups				
	Group 1 (PSS ≤ 2)	Group 2 (PSS 3-5)	Group 3 (PSS ≥ 6)	p-value
n	20	31	20	-
Morbidity, n (%)	3 (15.0)	10 (32.3)	16 (80.0)	<0.001
Mortality, n (%)	1 (5.0)	4 (12.9)	6 (30.0)	NS (0.08)
Non-operative treatment, n (%)	9 (45.0)	7 (22.6)	0 (0.0)	0.003
LOS (days), mean ± SD	20.15 ± 20.44	39.71 ± 37.25	65.35 ± 59.43	<0.001*

LOS, *Length of stay*; PSS, *Perforation Severity Score*; SD, *Standard Deviation,* NS, *Non-significant*

* Kruskal-Wallis test

Table 5. Univariate analysis of perforations severity score groups according to mortality and morbidity

PSS Groups	Mortality			Morbidity		
	OR	95% CI	p-value	OR	95% CI	p-value
3 vs. 2	2.890	0.699-11.972	0.143	8.400	2.223-31.744	0.002
3 vs. 1	8.143	0.878-75.749	0.065	22.667	4.374-117.468	<0.001
2 vs. 1	2.817	0.291-27.027	0.371	2.695	0.639-11.364	0.177

CI, *Confidence interval*; OR, *Odds ratio*; PSS, *Perforation severity score*

Table 6. Multivariate Logistic Regression Analyses (Forward Stepwise Method): Significant outcome predictors for each model			
	Model accuracy rate, %	OR (95%CI)	p-value
Morbidity			
Model 1 (PSS groups) [1]	76.1		
PSS Groups		5.10 (2.19-11.90)	<0.001
Model 2 (PSS variables) [2]	83.1		
Non-contained leak		12.59 (2.94-53.91)	0.001
Respiratory compromise		5.47 (1.43-20.94)	0.013
Mortality			
Model 1 (PSS groups) [3]	90.1		
Etiology of perforation		2.42 (1.03-5.68)	0.043
Location of perforation		3.89 (1.09-13.89)	0.036
Model 2 (PSS variables) [4]	87.3		
Previous esophageal pathology		1.70 (1.03-2.81)	0.040
Location of perforation		4.90 (1.16-20.83)	0.030
Tachycardia		9.30 (1.73-50.03)	0.009
Type of management			
Model 1 (PSS groups) [5]	77.5		
PSS Groups		4.69 (1.78-12.35)	0.002
Model 2 (PSS variables) [6]	-		
None		-	-

CI, *Confidence interval*; OR, *Odds ratio*; PSS, *Perforation severity score*

Variables included in the models (based in univariate analyses p-value <0.2):

1. *Etiology, location and PSS*
2. *Etiology, location, age, tachycardia, pleural effusion, non-contained leak, respiratory compromise and hypotension*
3. *Etiology, location, previous esophageal pathology and PSS*
4. *Etiology, location, previous esophageal pathology, age, tachycardia, pleural effusion, non-contained leak, hypotension and cancer*
5. *PSS*
6. *Tachycardia, pleural effusion, non-contained leak, respiratory compromise and hypotension*

Figure 1. Perforation severity score distribution in study population

Median PSS was 4 (0-14), percentiles 25 and 75 were 2 and 6, respectively

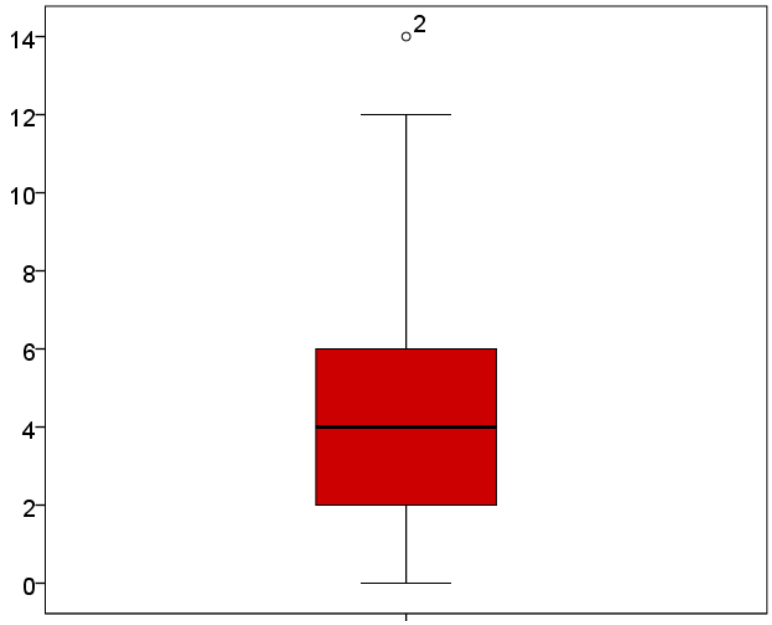


Figure 2. ROC curve for perforation severity score association with morbidity

The ROC curve for PSS showed a good prediction of morbidity (AUC=0.801; p<0.001). PSS cut-off value 4 has shown the best likehood ratio (1,753), sensibility of 79.3% and specificity of 54.8%, and diagnostic odds ratio of 4.640.

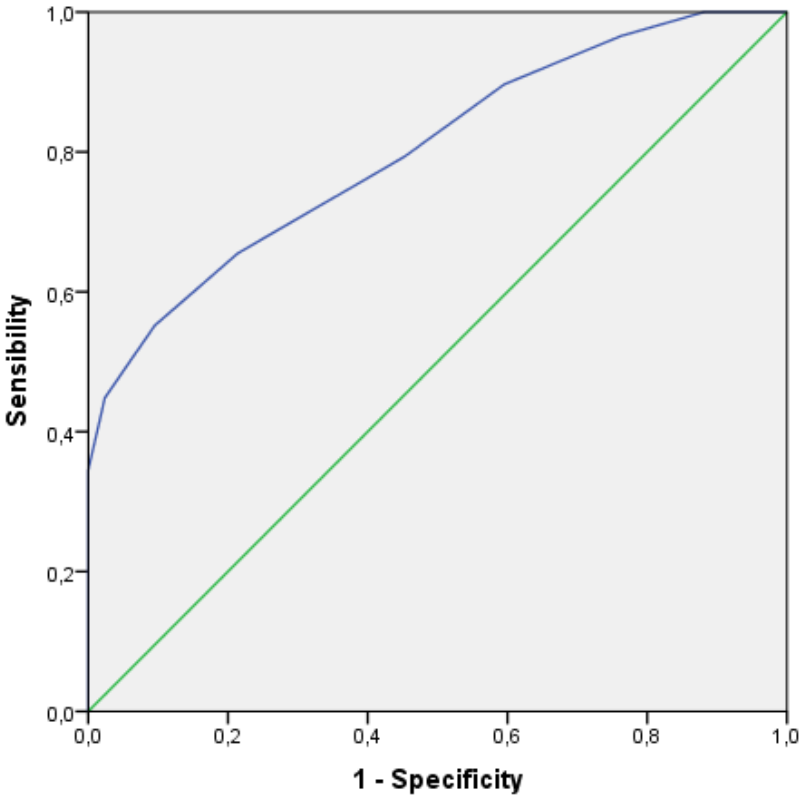


Figure 3. ROC curve for perforation severity score association with mortality

The ROC curve for PSS showed a good prediction of morbidity (AUC=0.801; p<0.001). PSS cut-off value 4 has shown the best likehood ratio (1,488), sensibility of 81.8% and specificity of 45.0%, and diagnostic odds ratio of 3.682.

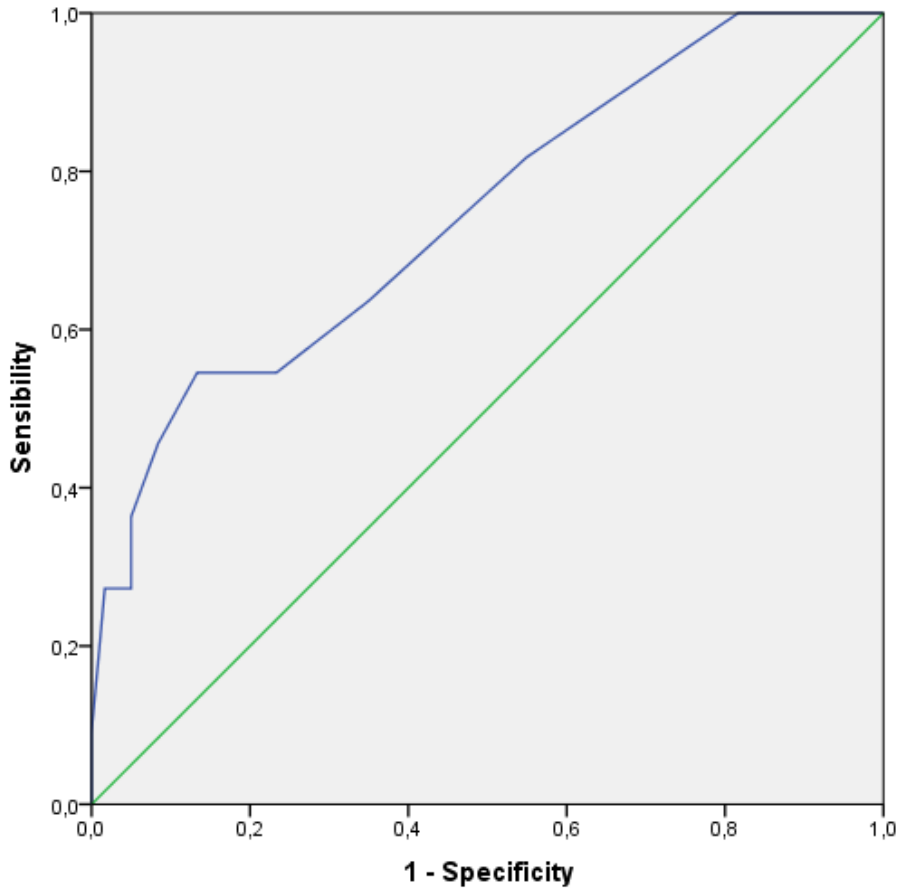


Figure 4. ROC curve for perforation severity score association with non-operative treatment

The ROC curve for PSS showed a good prediction of non-operative management (AUC=0.795; p<0.001). PSS cut-off value 4 has shown the best likehood ratio (2.426), sensibility of 75% and specificity of 69.1%, and diagnostic odds ratio of 6.706.

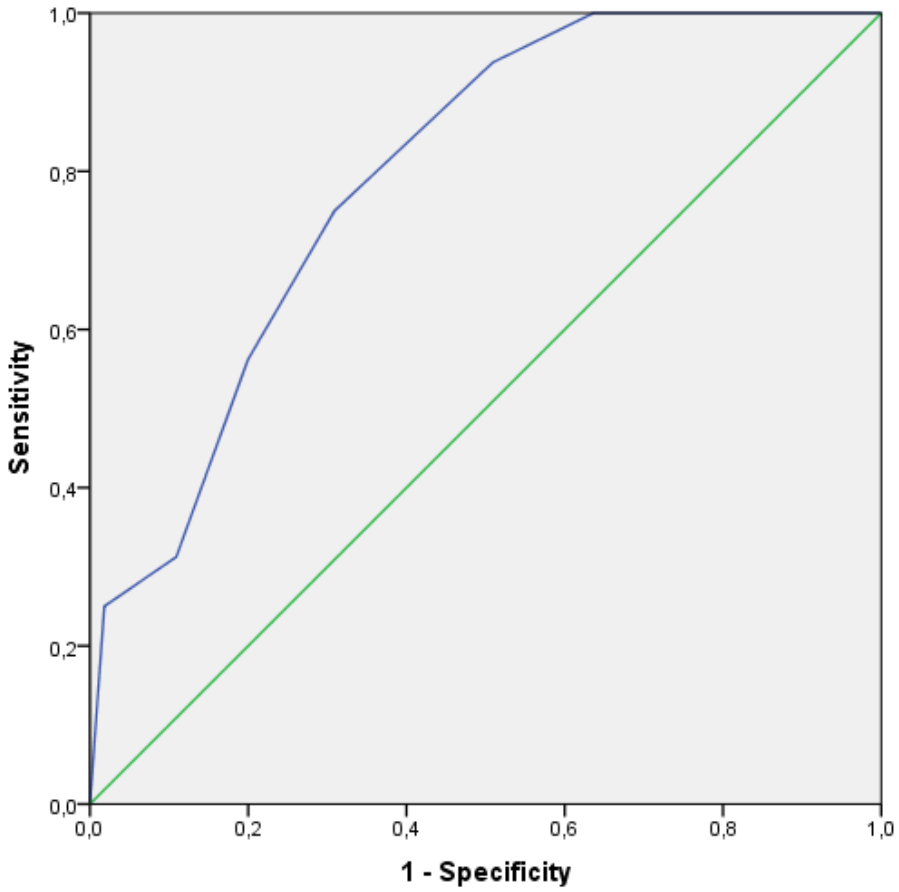
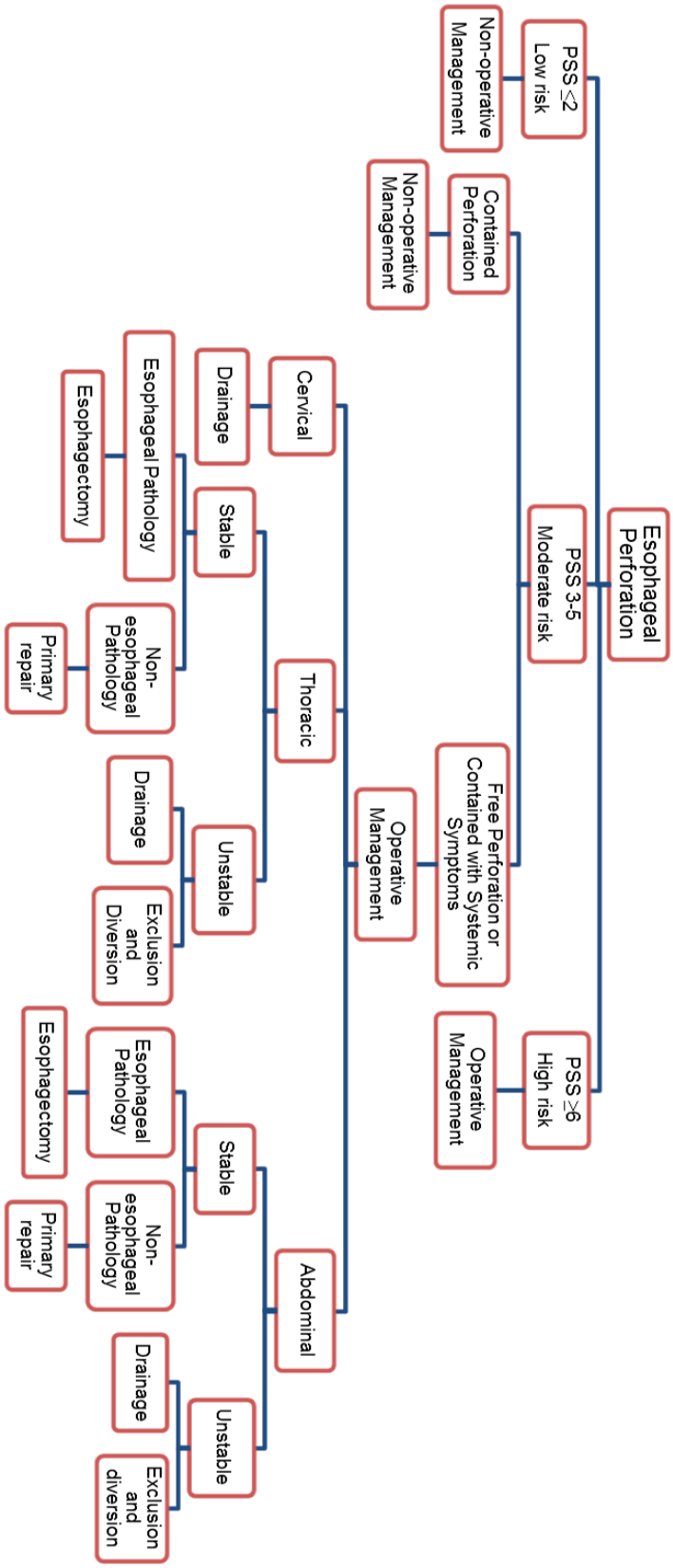


Figure 5. Proposed decision-making algorithm for EP management

Based in univariate and multivariate analyses according to morbidity, mortality, type of management and PSS. Most significant outcome predictors were PSS categorized in low (≤2), moderate (3-5) and high risk (≥6) groups, clinical stability (respiratory compromise and tachycardia), non-contained leak, prior esophageal pathology, etiology and location of perforation.



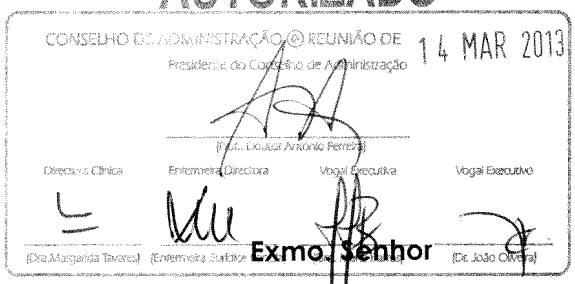
Anexos

1 - Autorização da Comissão de Ética

2- Normas do Journal of Gastrointestinal Surgery

CES 04-13

AUTORIZADO



Exmo. Senhor
Presidente do Conselho de Administração do
Centro Hospitalar de S. João – EPE

13.3.2013

Assunto: Pedido de autorização para realização de estudo/projecto de investigação

Nome do Investigador Principal: Hugo Miguel Teixeira Ferraz dos Santos Sousa

Título do projecto de investigação: Esophageal Perforation: A Multicentric Study for a Score Validation

Pretendendo realizar no(s) Serviço(s) de Cirurgia Geral do Centro Hospitalar de S. João – EPE o estudo/projecto de investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efectivação.

Para o efeito, anexa toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de S. João respeitante a estudos/projectos de investigação, à qual endereçou pedido de apreciação e parecer.

Com os melhores cumprimentos.

Porto, 14 / Dezembro / 2012

O INVESTIGADOR/PROMOTOR

Hugo [illegible]

Comissão de Ética para a Saúde – Centro Hospitalar São João

Parecer

Título do Projecto: Esophageal Perforation: A Multicentric Study for a Score Validation

Nome do Investigador Principal: Dr. Hugo Miguel Teixeira Ferraz dos Santos Sousa.

Local onde sera realizado o estudo: Serviço de Cirurgia Geral – CHSJ, havendo autorização do respectivo Diretor de Serviço para a realização do mesmo.

Objectivo do estudo: A multi-institutional prospective study is necessary to better define the selection criteria for operative versus nonoperative management and to establish the best operative approach for the management of esophageal perforation. A perforation severity score using clinical variables can be used to validate its effectiveness.
Hypothesis: discrete clinical factors con be identified at the time of presentation that might impact optimal operative approach and resulting patient outcomes. The initial clinical presentation may serve to identify the subset of patients amenable to nonoperative therapy.

Período previsto de conclusão: Dezembro 2014

Benefício / Risco: Não existem benefícios imediatos, nem riscos para os doentes.

Respeito pela liberdade e autonomia do sujeito do ensaio: Prevê-se a obtenção do consentimento informado, complementado por um suporte de informação escrita para os participantes, que refere os objetivos do estudo, os riscos/benefícios, bem como a liberdade em participar.

Confidencialidade dos dados: está garantida a confidencialidade dos dados e esta informação será restrita ao investigador principal.

O Investigador Principal dispõe de competência técnica e científica para a realização do estudo.

Não prevê a realização de questionário.

Custos: O estudo não prevê custos acrescidos para os participantes nem para a instituição.

Parecer: Em face da análise do protocolo de estudo, proponho a sua aprovação pela CES do CHSJ.

Porto, CHSJ, 22 de janeiro de 2013

O Relator

Dr. John Preto

7. SEGURO

a. *Este estudo/projecto de investigação prevê intervenção clínica que implique a existência de um seguro para os participantes?*

SIM ☐ (Se sim, junte, por favor, cópia da Apólice de Seguro respectiva)
NÃO ☑
NÃO APLICÁVEL ☐

8. TERMO DE RESPONSABILIDADE

Eu, Hugo Miguel Teixeira Ferraz dos Santos Sousa,
abaixo-assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (com as emendas de Tóquio 1975, Veneza 1983, Hong-Kong 1989, Somerset West 1996 e Edimburgo 2000) e da Organização Mundial da Saúde, no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo no decurso do actual internamento ou da mesma consulta.

Porto, 14 / Dezembro / 2012

O Investigador Principal

PARECER DA COMISSÃO DE ÉTICA PARA A SAÚDE DO CENTRO HOSPITALAR DE S. JOÃO

emitido na reunião plenária da CES de 25 / Janeiro / 2013

A Comissão de Ética para a Saúde APROVA por unanimidade o parecer do Relator, pelo que nada tem a opor à realização deste projecto de investigação.

O Doutor Filipe Alt
Presidente da Comissão de

Journal of Gastrointestinal Surgery publishes Original Articles, Review Articles, How I Do It articles (technique articles), Gastrointestinal Images, and other special categories of articles relevant to surgery of the digestive tract. Manuscripts must be prepared in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" developed by the International Committee of Medical Journal Editors (N Engl J Med 1991;324:424-428). Manuscripts submitted must not be under consideration for publication elsewhere. Material accepted for publication is subject to copyediting.

INFORMATION ABOUT ARTICLE TYPES

Original Articles

Original Articles are full-length reports of original research, either clinical or basic science. They most typically discuss topics relevant to the gastrointestinal tract (alimentary tract) and most commonly include organs such as the esophagus, stomach, duodenum, jejunoileum, colon, rectum, anus, appendix, liver, spleen, pancreas, peritoneal cavity, etc. Both adult and pediatric issues are considered. To be published, the work presented in the manuscript should be original, should include appropriate scientific content and should be appropriately analyzed with statistics. Considerations for acceptability of a submitted manuscript by the Editors and the Editorial Board will include its importance, the soundness and appropriateness of the experimental design, the validity of the methods, the appropriateness of the conclusions, and the overall quality of the presentation.

Original Articles submitted to the *Journal of Gastrointestinal Surgery* should not exceed 6,000 words, including the abstract, text, figure and table legends, and references. The editors reserve the right to publish excessively long tables as “on-line only” material.

Review Articles

Each issue of the *Journal of Gastrointestinal Surgery* may contain one or more Review Articles. Review Articles must not exceed a total of 6,000 words, and should typically have a

maximum of 100 references or less. Review Articles will be considered if they deal with relevant topics in either the clinical or the bench research realm, and provide an up-to-date synthesis of previously published material. Preference is given to reviews that are scholarly, systematic and critical (e.g. evaluation of quality and levels of evidence). Liberal use of illustrations, figures, or tables is encouraged.

How I Do It Articles

The *Journal of Gastrointestinal Surgery* will publish How I Do It articles that focus upon specific operations, interventions, or techniques. These articles should clearly describe an intervention in a step-by-step fashion, and provide appropriate illustrations (best not intraoperative photographs) that depict the intervention described in the text. Strong consideration will be given to How I Do It articles written by experts in the field, describing a technique used on large numbers of patients, with successful outcomes. Submissions as How I Do It manuscripts of single cases or novel interventions in small numbers of patients are discouraged. How I Do It articles should include some comment about the number of patients treated via the intervention, specific preoperative evaluation and postoperative care, and outcomes. If appropriate, a reference list should be provided.

Gastrointestinal (GI) Images

The *Journal of Gastrointestinal Surgery* will be pleased to publish GI Images that provide a striking clinical image meant to challenge and inform readers. This section is intended to illustrate and teach important medical or surgical points. Manuscripts in this section should be limited to no more than four (4) double-spaced manuscript pages, with a limited number of references. The GI Image submission should include one or two images, but no abstract. The images can be pathologic, endoscopic, or radiographic. Images should be of high quality and illustrate the diagnosis well. The case should be described in brief, with a short history and physical exam, with pertinent laboratory findings and clinical course. The images submitted should be described in a figure legend, with relevant structures labeled and explained. Figures should be in either TIFF (Tag ImageFile Format) or EPS (Encapsulated PostScript) format. The JPEG format is acceptable if the image is saved at the highest quality (without or with lossless compression). Images created in slide presentation programs, such as Microsoft PowerPoint, are not recommended. Charts
created with Microsoft Excel are not acceptable in any circumstances.

Case Reports

The *Journal of Gastrointestinal Surgery* no longer accepts simple case reports. Case reports, or better still, small case series that include extensive literature reviews, considered for publication will be of significant educational value, of timely relevance, a description of a unique case series, a description of a novel technique, or a presentation of an extremely unusual genetic disease or mechanism of disease. Manuscripts submitted as Case Reports should be limited to no more than eight (8) double-spaced manuscript text pages (excluding figures, figure legends and tables), with up to 15 references and must include a review of the literature in both text and tabular form.

Multi-Media Articles

The *Journal of Gastrointestinal Surgery* is pleased to consider multi-media articles, where the heart of the article is the video. As with Case Reports, simple anecdotal "interesting case" videos are usually not competitive. At a minimum an abstract and references should be included. Multi-media components to an Original Article, Review or How I Do It article may also be submitted, where supplementary electronic material is added to the normal text.

For those individuals interested in submitting multi-media or dynamic articles, please note that all submissions must be in English, and that additional information and requirements for submission are included subsequently in the "Instructions for Authors" section.

Evidence-Based Surgical Practice

The Journal, in collaboration with the Society for Surgery of the Alimentary Tract publishes an article type designated "Evidence-Based Current Surgical Practice" which represents an expert review of a gastrointestinal surgical topic identified through the annual SSAT Maintenance of Certification course or through its Continuing Medical Education Committee. Unsolicited manuscripts of this sort will NOT be considered outside of the work of a SSAT committee, and should instead be submitted as Review Articles."

Letters to the Editor

The editors of the *Journal of Gastrointestinal Surgery* invite comments in the form of Letters to the Editor that express differences of opinion or supporting views of previously published editorials or recently published papers in the *Journal of Gastrointestinal Surgery*. Each letter should not exceed 750 words, should be typed with double-spacing, and should include complete references. The editors reserve the right to accept, reject, or excerpt letters without changing the views expressed by the writers. Such correspondence is evaluated only for articles published within three months of submission of the Letter to the Editor. Those letters deemed of interest to the Journal are, if appropriate, sent to the authors of the original article for a response. The authors of the original article are given a short period of time to reply. A decision will then be made by the editors whether to publish the letter with or without its corresponding reply.

CONFLICT OF INTEREST FORM

Effective July 2012: Every contributing author must complete the official **ICMJE Conflict of Interest (COI) form,** which is available at http://www.icmje.org/coi_disclosure.pdf
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Each author must complete the form even if no conflict of interest exists.
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