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ORIGINAL SCIENTIFIC REPORT (INCLUDING PAPERS PRESENTED AT SURGICAL CONFERENCES)

Outcome of Self-Expanding Metal Stents in the Treatment of Anastomotic Leaks After Ivor Lewis Esophagectomy

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Abstract

Background Esophageal anastomotic leakages after Ivor Lewis esophagectomy are severe and life-threatening complications. We analyzed the outcome of using self-expanding metal stents (SEMS) in the treatment of postoperative leakage after esophagogastrostomy.

Methods Seventy patients with esophageal anastomotic leakage after Ivor Lewis esophagectomy for esophageal cancer who had received SEMS treatment between January 2006 and December 2015 at our clinic were identified in this retrospective study. The patients were analyzed according to demographic characteristics, risk factors, leakage characteristics, stent characteristics, stent-related complications, sealing success rate and mortality.

Results Over a 10-year period, 70 patients received SEMS as treatment for postoperative anastomotic leakage after esophagectomy. Technical success of esophageal stenting in anastomotic leakage was achieved in 50 out of 70 cases (71.4%). Sealing success rate was 70% (n = 49) with a median treatment of 28 days (range 7–87). In 20 patients (28.6%), stent-related complications, such as stenosis, dislocation, leakage persistence, perforation or esophagotracheal fistula occurred after the SEMS treatment. Sixty-one patients (87.1%) survived SEMS treatment of esophagogastric anastomotic leakage. Mean follow-up for all patients was 38 months (IQR 10–76), and no significant difference was found in a comparison of the long-term survival rate between patients with successful and unsuccessful SEMS treatment.

Conclusions The management of esophageal anastomotic leaks after Ivor Lewis esophagectomy with SEMS is effective, safe and technically feasible. Aggressive non-surgical management should be considered when developing a treatment plan for stenting.

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Introduction

The incidence of upper gastrointestinal cancers is still rising in the Western world [1]. Since the only curative treatment of this disease has been surgical resection until now, the number of esophagectomies is increasing. Further standardization and implementation of innovative technologies like minimally invasive approaches improved the existing surgical procedures. This consecutively leads to rates of anastomotic leakages between 0 and 2.7% in specialized facilities [2, 3]. However, there are still reports in the literature, presenting the occurrence of anastomotic leaks in about 8.2–15.0% [4–7]. When considering the 30-day in-hospital mortality rate of 2.1–35.7%, the clinical relevance is even more devastating [4, 8, 9]. These heterogeneous numbers can be explained by different tumor stages, occurrence of neoadjuvant therapy or the center volume where the surgery was performed (high- vs. low-volume centers).

Several new endoscopic procedures, such as the endoscopic vacuum sponge, have been developed in addition to surgical revision with reanastomosis or suture of the leakage [10–12]. The application of self-expanding metal stents (SEMS) has become another established method for treating anastomotic leakage after oncological surgical resections [13–21].

However, the majority of studies included a variety of heterogeneous benign and malignant diseases and dealt with several different surgical approaches for passage reconstruction such as cervical esophagogastrostomy, intrathoracic esophagogastrostomy and mediastinal/abdominal esophagojejunostomy [16, 22]. The amount of data focusing on anastomotic complications after oncological upper gastrointestinal surgery was limited and only based on small cohorts [15]. Therefore, we reviewed our experiences with SEMS in the therapy of anastomotic leakage after oncological Ivor Lewis esophagectomy at a high-volume upper gastrointestinal tract center. The aim was to analyze the efficacy and limitations of SEMS after leakages in this subgroup of tumor patients who underwent highly standardized surgery.

Patients and methods

Patient inclusion

From January 2006 to December 2015, all patients with leakage of esophagogastrostomy after oncological surgery were identified at our department (Head of Department during that time: Prof. Dr. med. A.H. Hölscher) (total number of oncological resections 2006–2015: esophagectomies $n = 1.266$). This retrospective analysis only includes patients who underwent SEMS placement for type-II leakages according to the Esophagectomy Complications Consensus Group (ECCG) classification for anastomotic leaks [23]. That definition considers such postsurgical leaks that require interventional but not surgical therapy. Demographics, details of disease, surgical outcome, leakage characteristics, stent specification and stent-related complication were analyzed. Data were retrospectively collected from "Clinic WinData", (version 8.05; E&L medical system GmbH, Erlangen, Germany) (prospective endoscopic database) and from the "Orbis" (version 08042702; Agfa HealthCare N.V., Belgium) hospital database. Clinical data from our follow-up care and the department's quality management were included. The study was performed according to the criteria of the local ethics committee (No. 17-320).

Surgery

Anastomotic leakages occurred in trans-thoracic esophagogastrostomies detected after Ivor Lewis esophagectomy [24]. Surgery was highly standardized and performed in our department. Lymph nodes were removed from the resected esophageal specimens according to a standardized protocol for further histopathological examination [24]. All specimens were histopathologically analyzed and classified by experienced gastrointestinal pathologists according to the seventh edition of the Union for International Cancer Control/TNM classification of malignant tumors including tumor localization, depth of tumor infiltration, grading, residual tumor as well as total number of resected and infiltrated lymph nodes [25].

Leakage detection and management

All leakages were identified by video esophagogastroduodenoscopy (e.g., Pentax Medical, Japan; Olympus Corporation, Tokyo, Japan) or contrast-enhanced computed tomography (CT). All interventions were performed by two surgical endoscopists (T.H. and H.S.) with experience averaging more than 10.000 examinations in total. Therapeutic decisions were based on the leakage size and severity of the associated systemic response. SEMS were inserted using a guidewire under direct endoscopic guidance, but without radiological control. The position of the stent was checked endoscopically. We utilized the following stent models: aixstent® OEL (Leufen Medical GmbH, Germany), Ultraflex Esophageal NG Stent (Boston Scientific, USA) and Niti-S™ Esophageal Stent (TaeWoong Medical, South Korea). Aggressive non-operative management in all patients consisted of endoscopically placed double-lumen nasogastric feeding tube (e.g., Freka® Sonde, Fresenius Kabi

Germany GmbH) for decompression, enteral nutrition by a triple-lumen diverted nasogastric feeding tube (e.g., Freka® Trelumina, Fresenius Kabi Germany GmbH) and intravenous antimicrobials (including antifungals). The leaked fluid was drained externally in the cases of mediastinal, pleural or abdominal collections. A swallow X-ray, computed tomography (CT) or endoscopy was used to identify persistent leakage after endoscopic insertion. The procedure of SEMS removal was as follows: SEMS were extracted after 4 weeks, and leakage sealing was controlled endoscopically. If there was any persistent leakage, SEMS implantation was repeated for another 4 weeks.

Outcome detection

Successful closure was defined as the state in which the endoscopic imaging showed complete closure, and the patient no longer had any clinical signs of persistent leakage. Routinely, contrast esophagograms were only used for control of the sufficient stent placement, but not for the evaluation of the definitive successful closure since there are conflicting data considering its value within the diagnosis of anastomotic leaks [26–28]. SEMS failure was defined as the following: persistent leakage or fistula, death before confirmation of healing, need for surgical revision of the anastomotic leak after the stent placement and referral of the patient to another hospital before the stent could be extracted. Not considered as failure were both SEMS repositions and replacements due to migration.

Statistics

Data were expressed as numerals with percentages, mean values with an interquartile range or as median values with a range or interquartile range. Data were compared by referring to the Mann–Whitney *U* test. Qualitative variables were summarized by count (percentage) and were compared by chi-square test. A two-sided p value <0.05 was considered statistically significant, in compliance with the explorative kind of interpretation of the p values. The comparative survival analysis with Kaplan–Meier curves was based on the Breslow test. Because of the small number of cases, a multiple regression was not performed. All data were managed with the SPSS Statistics Version 24 (IBM Corp., Armonk, NY, USA) for Windows (Microsoft Corp, Redmond, WA, USA).

Results

Demographics and endoscopic results

We identified 70 patients, 58 (82.9%) of whom were males, with postoperative anastomotic leakage who had received a fully (FC) or partially covered (PC) SEMS. The median age was 62.5 years (IQR 56–69). Table 1 shows details of demographics. All 70 patients underwent Ivor Lewis esophagectomy with two-field lymphadenectomy. Table 2 summarizes the histopathological results of the resected surgical specimens. All tumors were resected completely (R0). Leakages occurred in 70 thoracic esophagogastrostomies. The leakage size ranged from 1/4 ($n = 57$, 81.4%) over 1/3 ($n = 10$, 14.3%) to 1/2 ($n = 2$, 2.9%) of the circumference of the esophagus [no description ($n = 1$, 1.4%)]. Sixty-eight leakages (97.1%) were located directly at the circular anastomosis of the remaining esophagus to the pulled-up gastric tube, and two leakages ($n = 2.9\%$) were in the pulled-up gastric tube along the longitudinal staple line. The time between surgery and leakage detection ranged from 1 to 58 days with a median of 9 days (IQR 6–12) (see Fig. 1). Prior leakage treatment was operative in 11 patients and non-operative in 15 patients with 3 requiring radiologically guided drainage of pleural, mediastinal or abdominal collections. The days of latency between diagnosis and stent treatment varied between 0 and 37 days (median 0 days, IQR 0–1). Postinterventionally, stent placement was controlled by either endoscopy ($n = 9$), computed tomography ($n = 23$), contrast esophagogram ($n = 29$) or X-ray of the chest ($n = 9$). There was no routinely performed computed tomography or contrast esophagogram for detection of stent success after stent removal. This evaluation was performed endoscopically.

Stent treatment

Forty-five patients (64.3%) underwent SEMS placement on the same day the leakage was diagnosed. SEMS were used as a secondary treatment in 14 cases (20%) after failure of surgical revision ($n = 11$) or vacuum therapy ($n = 3$). Fifty-five patients (78.6%) received one stent, 13 patients (18.6%) received 2 stents, and 2 patients (2.9%) received 3 or more consecutive stents. In 20 cases (28.6%), a drain was placed additionally for the management of coexisting empyema in the pleural, mediastinal or abdominal cavities. The most common additional procedure was escalation of antimicrobial therapy in 55 cases (78.5%). Table 3 presents the several additional treatment concepts for management of the leakage. In 63 cases (90%), the SEMS were removed after 1–152 days (median 27 days), with seven exceptions. Six of these 7 patients died in hospital, and 1 patient was referred to another clinic.

Complications related to the SEMS treatment

SEMS-associated complications were classified according to their moment of occurrence: Complications were classified as complications during stent treatment when they

Table 1 Study population by success of treatment

	Success	Failure	*p* value
Number of patients	49	21	
Gender (male:female)	42:7	16:5	0.489
Age	62 (43–78)	63 (45–83)	0.438
Smoker (yes:no)	21:28	9:12	1.00
BMI	26 (16–46)	26 (19–33)	0.285
ASA score	3 (1–4)	2 (1–3)	0.751
Neoadjuvant therapy (yes:no)	31:18	15:5[a]	0.410
Histopathology			0.307
Adenocarcinoma	30 (61.2)	10 (47.6)	
Squamous cell carcinoma	19 (38.8)	11 (52.4)	
Days between surgery and leakage detection	9 (2–58)	9 (1–22)	0.817
Days between diagnosis of leakage and stenting	0 (0–14)	0 (0–37)	0.664
Number of stents	1 (1–3)	1 (1–3)	0.114
Days on ICU	7 (0–105)	30 (0–295)	0.117
Hospitalization	33 (14–150)	59 (17–296)	0.110
Duration of treatment	28 (7–87)	23 (1–152)	0.116
30 day mortality (deceased:alive)	1:47[a]	2:19	0.218

Values given as number (percentage) or median (range)
[a]Information was not available for one patient

Table 2 Patient cohort by success of treatment after 7th edition of TNM classification of malignant tumors for esophageal cancer

	Success		Failure		*p* value
	n	%	*n*	%	
Total	49	100	20[a]	100	
Pathology (neoadjuvant:no neoadjuvant)					
pT0	1:0	2	3:0	15	0.390
pT1	7:9	32.7	5:3	40	
pT2	10:4	28.6	3:0	15	
pT3	12:6	36.7	4:2	30	
pN0	18:13	63.2	10:5	75	0.987
pN1	7:4	22.5	3:1	20	
pN2	2:2	8.2	1:0	5	
pN3	2:1	6.1	0:0	0	

[a]Information was not available for one patient

were detected when the stent was in situ while postinterventional complications were defined as complications detected during the follow-up endoscopies after definitive stent removal.

Stent-related complications during the treatment (e.g., dislocation, leakage persistence or esophagotracheal fistula) occurred in 20 of 70 cases (28.6%). The most frequent complications were dislocation ($n = 13$, 18.6%) and persistent leakage ($n = 6$, 8.6%) (compare Table 3). In the case of dislocation due to stent migration, an endoscopic replacement was performed. Here, between one and eleven interventions (median 2) were necessary for the correct placement of the stent in situ.

Eighteen patients (18.3%) developed postinterventional complications. The most frequent complications were persistent leakage ($n = 10$, 14.3%), stenosis ($n = 5$, 7.1%) and esophagotracheal fistula ($n = 3$, 4.3%). Table 3 illustrates the complications detected after SEMS therapy. A comparison between PC-SEMS and FC-SEMS did not show any significant differences in the occurrence of stent-related complications during and after SEMS treatment ($p = 0.142$, $p = 0.842$). All patients with esophagotracheal fistula survived. Here, leakage sealing was finally achieved by surgical revision. After stent treatment, 5 patients (7%) developed a stenosis of the anastomosis and needed further endoscopic management. In these cases, endoscopic bougienage was performed. After 1–14 interventions (median 3), the post-stent stricture was solved and there was no dysphagia problem in the follow-up.

Technical success and outcome

Technical success of stenting in anastomotic leakage was achieved in 50 cases (71.4%). Table 1 illustrates the results detected. The mean length of stay in the intensive care unit (ICU) after stent placement was 8.5 days (IQR 0–38). Patients were hospitalized for a mean of 37 days (IQR 25.75–70.25). The mean total days of stent treatment were 27 days (IQR 22.5–32). There was no significant difference considering the ICU stay and in-hospital stay when comparing the patients with SEMS success to those with SEMS failure. Successful leakage closure was achieved in 49 cases (70%). There were no significant differences in sealing rates between the type and size of leakage ($p = 0.35$, $p = 0.347$) and between patients with and without neoadjuvant therapy ($p = 0.519$). Reasons for failure were persistent leakage ($n = 10$, 14.3%) or esophagotracheal fistula ($n = 3$, 4.2%) (unclear $n = 1$, 1.4%). Nine patients (12.9%) died as a direct consequence of leakage and uncontrolled sepsis. Sixty-one patients (87.1%) survived the SEMS treatment. The overall mean follow-up was 38 months (IQR 10–76). No significant difference was found in the comparison of the long-term survival between patients with successful treatment and unsuccessful treatment ($p = 0.116$). Early differences in survival rate were only observed in the first year after surgery. This is illustrated in Fig. 1. The day of the leakage detection showed no significant differences considering the success of the SEMS treatment (see Fig. 2) ($p = 0.817$).

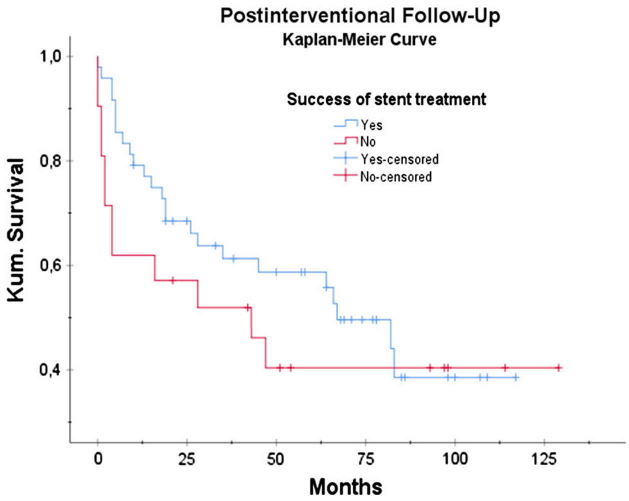

Fig. 1 Patients' outcome within the postinterventional follow-up. The mean follow-up for all patients was 38 months (IQR 10–76). There was no significant difference between patients with successful SEMS treatment (blue line) and to those with unsuccessful SEMS treatment (red line) when regarding the long-term survival. However, there is an observable (nonsignificant) difference in the survival rate within the first year after surgery ($p = 0.116$)

Discussion

Anastomotic leakage is a severe complication after upper gastrointestinal surgery and leads to high perioperative mortality and morbidity as well as a need for further surgical or endoscopic therapy [8, 23].

We identified successful SEMS-associated leakage sealing in 70%. This corresponds to the data by Fernández et al. [14], Schweigert et al. [20] and Feith et al. [29], who report complete anastomotic healing in 69.3%, 77%, respectively, 70%. There are also studies showing higher success rates of stent treatment of about 81–100% [17, 18, 22, 30]. The discrepancy may result from the relatively small cohorts of about 12, 14 or 20 patients per study [17, 18, 20, 22, 29, 30]. Furthermore, the definition of successful stent treatment differs between the studies: We considered complete leakage sealing to be successful in SEMS therapy; while, in other studies, the absence of reoperation was evaluated as successful therapy and complications (e.g., fistulas or persistent leaks) were not taken into account [30].

Putative predictive factors for the success or failure of SEMS therapy could not be identified here although we took into account the patients' comorbidities, neoadjuvant treatment, time delay between diagnosis of anastomotic leakage, beginning of SEMS treatment, stage of disease, type of stent, duration of stent therapy and its complications. The literature differs on this issue: On the one hand, the data of Aryaie et al. [22] from an analysis of 20 patients with anastomotic leakages after surgery due to different indications correspond with our findings showing that demographic factors, comorbidities and type of surgery are not predictive for the SEMS outcome. On the other hand, Persson et al. [13] described persistent leakage after stent application, decreased physical preoperative performance and concomitant esophagotracheal fistula as independent risk factors for SEMS failure within a series of 46 leakages treated with SEMS between 2003 and 2014. Our study did not confirm the findings of El Hajj et al. [31], who identified a positive predictive value of a brief delay between leakage diagnosis and primary stent insertion in their cohort of 54 patients after surgery, fistulas and perforations. It is not possible to make a clear statement based on the data currently available.

Although SEMS treatment produces good leakage sealing after upper gastrointestinal surgery, SEMS usage does not appear to decrease the duration of hospital stay compared with other conservative procedures, such as drainage placement and enteral nutrition by feeding jejunostomy [32]. With a median SEMS treatment period of 27 days and a median hospital stay of 37 days, our data confirm the literature as summarized by Dasari et al. [33]. In 21.4% of the cases, SEMS-related complications (e.g., dislocation, leakage persistence or esophagotracheal fistula) occurred in our cohort. This reflects the actual problems/limitations of SEMS usage for anastomotic leakage although bleeding complications deriving from vascular erosion such as esophagoaortic fistulas did not develop under stent therapy in this series [16, 22, 29, 31, 33]. According to Freeman et al. [34], a stent should be removed 2 weeks after implantation in order to minimize the incidence of complications associated with SEMS insertion. However, we continued SEMS therapy for persistent leakage rather than removing the stent at that time.

As expected, we found that patients who had no successful sealing showed nonsignificantly longer stays on the ICU or a hospitalization in general. Furthermore, the in-hospital mortality was nonsignificantly increased compared to those patients with successful SEMS therapy. This might be explained by the fact that a persistent leakage can result in further comorbidities/complications acquired during the hospital stay, especially when patients are critically ill. Since the duration of stent treatment was significantly shorter when patients failed the endoscopic therapy, it seems that SEMS intervention was interrupted early if the endoscopist mistrusted its success.

However, we demonstrated a significant impact of aggressive conservative management consisting of gastral decompression via feeding tube, abstinence from food, placement of drainages for secretions and intravenous antibiotics/antifungal agents on stent success for additional therapy besides SEMS insertion. Leakage sealing was less successful if only some of these procedures were used.

Table 3 Course of treatment and complication management of the study cohort

	Success	Failure	*p* value
Additional treatment of leakage			0.001
Surgical revision with anastomotic suture	0 (0.0)	4 (19.0)	
Feeding tube	6 (12.2)	0 (0.0)	
Antimicrobial therapy	3 (6.1)	3 (14.3)	
Antimicrobial therapy + feeding tube + drain	17 (34.7)	3 (14.3)	
Vacuum therapy	0 (0.0)	2 (9.5)	
Antimicrobial therapy + feeding tube	20 (40.8)	9 (42.9)	
None	3 (6.1)	0 (0.0)	
Complications of stent treatment			0.211
Dislocation	9 (18.4)	4 (19.0)	
Persisting leakage	2 (4.1)	4 (19.0)	
Gastrotracheal fistula	1 (2.0)	0 (0.0)	
None	37 (75.5)	13 (62.0)	
Complications after stent treatment		[a]	<0.001
Persisting leakage	0 (0.0)	10 (50.0)	
Stenosis	5 (10.2)	0 (0.0)	
Gastrotracheal fistula	1 (2.0)	2 (10.0)	
None	43 (87.8)	8 (40.0)	

Values given as number (percentage)
[a]Information was not available for one patient

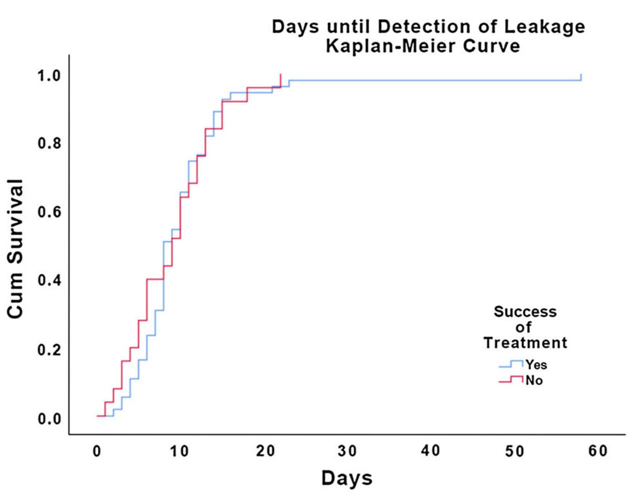

Fig. 2 Time-to-event analysis of the study cohort considering the time span between surgery and leakage detection. There was no significant difference between those patients with and without successful SEMS treatment ($p = 0.817$)

Therefore, we always tried to use all of the procedures as prescribed by our internal standards, which are continuously updated according to the literature [32, 35].

To our best knowledge, this study analyzed the long-term outcome of patients after SEMS therapy for anastomotic leakage for the first time. When taking into account long-term follow-up, there was no significant prognostic difference between patients with successful SEMS treatment compared to those with unsuccessful treatment. Notably, we found a tendency toward a poorer short-time prognosis after initial stent failure ($p = 0.116$). However, the statistical power of this comparison of 49 patients with successful SEMS treatment versus 21 patients who failed SEMS therapy is too low to confirm a significant prognostic difference. Therefore, this analysis cannot provide a definitive answer considering this issue.

The main strengths of this study are the large cohort size and its homogeneity considering only patients who underwent standardized Ivor Lewis esophagectomy due to esophageal cancer and excluding benign causes. In our opinion, focusing on this subgroup increases the study's reliability. Furthermore, all data were processed, especially stringently and comprehensively.

Nevertheless, this study has some weaknesses that need to be considered carefully. Our analysis has limitations due to its retrospective character. The individual investigator's clinical experience with anastomotic leakages along with his evaluation and skills in the use of non-surgical treatment methods are likely to influence how the detected leakage is handled. As already mentioned, we do not have a comparative cohort treated without SEMS but only with aggressive conservative management. As SEMS insertion is only one option among many other interventional procedures, systematic analysis of the different endoscopic or conservative approaches in the complication management of upper gastrointestinal leakages surely will improve our understanding about this clinically highly relevant issue.

Conclusion

In conclusion, the study delivers evidence that SEMS are a feasible treatment option of anastomotic leakages after Ivor Lewis esophagectomy. Specific predictive factors for the success/failure of stent therapy were not identified. However, stent complications, e.g., dislocation or persistent leakage, remain common problems. Furthermore, SEMS insertion should be accompanied by aggressive, non-surgical management including feeding tube, intravenous antibiotics/antifungal agents, abstinence from food and drainage placement. Regular endoscopic controls after SEMS implantation are necessary and should be performed by an experienced interventional endoscopist.

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Compliance with ethical standards

Conflict of interest The authors declare that they have nothing to disclose.

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