

Efficacy and Safety of Endoscopic Primary Prophylaxis of Bleeding in Children With High-Risk Gastroesophageal Varices

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ABSTRACT

Objectives: Primary prophylaxis of bleeding is debated in children with gastroesophageal varices; one of the reasons is the limited number of studies concerning its efficacy and safety. We report our experience with endoscopic primary prophylaxis.

Methods: From 2006 to 2019, 145 children (median age, 3.5 years; cirrhosis, n = 116) with high-risk gastroesophageal varices underwent primary prophylaxis (banding, n = 114; sclerotherapy n = 31, primarily in smaller children).

Results: We observed the eradication of varices in 93% of children after a mean of 6 months, at least one recurrence of varices in 45% after eradication, and gastrointestinal bleeding in 17% of children. Irrespective of the cause of portal hypertension, grade 3 esophageal varices, presence of gastric varices along the cardia and a lower composite score of endoscopic severity were associated with a worse probability of eradication, a longer time to eradication and a lower risk of a first recurrence and of bleeding following the procedure, respectively. Ten-year probabilities of overall survival and of bleeding-free survival were 95% and 75%, respectively.

Conclusions: Endoscopic primary prophylaxis of variceal bleeding is reasonably effective and safe in children with high-risk gastroesophageal varices. Worse results are observed in children with more advanced endoscopic features. This pleads for endoscopic screening in children with portal hypertension and early detection of varices warranting primary prophylaxis.

Key Words: biliary atresia, endoscopic management, gastrointestinal bleeding, liver disease, portal hypertension

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In children with portal hypertension, the question of endoscopic primary prophylaxis of bleeding from gastroesophageal varices is debated among pediatric gastroenterologists (1,2). In Europe and

What Is Known

- Bleeding from gastroesophageal varices carries severe risks in children.
- Endoscopic primary prophylaxis of bleeding is debated among pediatric gastroenterologists.
- One of the reasons is the relatively limited number of reports concerning efficacy and safety.

What Is New

- A study of endoscopic primary prophylaxis in 145 children with high-risk varices.
- Two-thirds of children under the age of 3 had a platelet count $\geq 150,000/\text{mm}^3$.
- Eradication of varices in 93% of children, recurrence in 45%, gastrointestinal bleeding in 17% and a 10-year overall probability of survival of 95%.
- Efficacy depends on the initial severity of the endoscopic features.

Brazil, there is a growing trend towards endoscopic screening and primary prophylaxis of varices at risk of bleeding, whereas this approach is not commonly used in North America (1–10). One of the issues is the relatively limited availability of data on the efficacy and safety of the primary prophylaxis method (11); there have been papers reporting primary prophylaxis by endoscopic management, albeit with various numbers of patients in each report, various age ranges, different levels of detail, various endoscopic criteria for deciding upon treatment, some encompassing many causes of liver

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disease and others limited to one cause (3–8,12–16). We have previously reported the feasibility and safety of endoscopic primary prophylaxis of bleeding in small children with biliary atresia and high-risk gastroesophageal varices (17,18). Here, we extend this study to a larger number of children with high-risk varices, including children with biliary atresia of all ages and children with other causes of portal hypertension. Our aim was to take advantage of this relatively large population in a single center to try to identify factors combined with the success or failure of these procedures.

PATIENTS AND METHODS

This is a retrospective analysis of 145 children with portal hypertension and high-risk gastroesophageal varices who underwent endoscopic primary prophylaxis of bleeding in our unit between January 2006 and December 2019.

Selection of Children With High-Risk Varices

Children with palpable splenomegaly and ultrasonographic signs of portal hypertension (19) underwent one or more episodes of upper gastrointestinal diagnostic endoscopy. The endoscopic signs were recorded as follows: (1) number and grade of esophageal varices: grade 1 when varices were flattened by insufflation, grade 2 when they were not flattened but were separated by healthy mucosa, and grade 3 when varices were not flattened by insufflation and were confluent or pseudo-tumoral and obstructing the lumen (20); (2) red wale markings on the mucosal wall (21); (3) gastric varices along the cardia described as gastroesophageal varices 1 (GOV1) or gastroesophageal varices 2 (GOV2) and fundal varices (22) were recorded by retroflexion at each endoscopic examination; and (4) the presence of portal hypertensive gastropathy was also recorded. Each endoscopic procedure was performed or supervised by the same endoscopist (M.D.) and the criteria for recording the endoscopic signs remained unchanged throughout the study period. Based on previous experience both in adults and children (12,23–27) the endoscopic patterns carrying a high risk of bleeding [high-risk varices (HRV)] included grade 3 esophageal varices, grade 2 esophageal varices with red wale markings and/or gastric varices along the cardia, or gastric varices with and/or without esophageal varices.

Endoscopic Primary Prophylaxis Procedure

A total of 145 children with high-risk varices and who had not bled underwent sclerotherapy or band ligation as described previously (18). Each session was performed under general anesthesia and intubation, using a video endoscope, and under continuous intravenous octreotide therapy (2 µg/kg/h) (17); octreotide therapy was started 1 hour before the session and was tapered down to 1 µg/kg/h after 2 to 3 days. Sclerotherapy was primarily used for children whose weight was below 8 kg and in whom the 11 mm diameter of the ligature set precluded upper esophageal intubation. Sclerotherapy was performed using a single-use needle (Prince Medical, Ercuis, France) and injections of 1.2% polidocanol (Aethoxysclerol; Chemische Fabrik Kreussler and Co, GmbH, Wiesbaden, Germany). The mean volumes of sclerosant injected per session and per injection site were 10 mL (range, 5–15 mL) and 2.5 mL, respectively. Sclerotherapy sessions were repeated 3 times at weekly intervals and then monthly until varices were eradicated. Amoxicillin-clavulanic acid was given before each session of sclerotherapy. Variceal ligation was performed without an overtube, with a 6-shooter multiband ligator (Cook Medical, Limerick, Ireland). Each varix was ligated 1 to 2 cm above the gastroesophageal junction, with 1 or 2 rubber bands, and not more than 5 rubber bands per session. Ligation sessions were repeated every 4 weeks until eradication of the varices. For both sclerotherapy and banding, special care was taken, during the last session, to

treat the varices as low as possible in the esophagus and cardia. Eradication was defined as either the disappearance of all varices from the distal part of the esophagus or as the reduction of the varices to small grade 1 white columns, with no red wale markings and no gastric varices. The number of sessions was adjusted to the evolution of the endoscopic signs. Beta-blocking agents were not used. After eradication was obtained, endoscopic examination was carried out, as a rule, after 3 months, and then after 6 months, to detect and treat the emergence of varices at risk of bleeding. The intervals between the endoscopy sessions were progressively increased if eradication appeared stable. Parents were informed of the endoscopic findings, of the high risk of bleeding justifying prophylaxis, of the proposed treatment and of its potential adverse events. Informed consent from each child's parents was obtained in writing before each session.

The medical records of these 145 children were reviewed to analyze the following items: eradication of varices, time to and number of sessions for eradication, recurrence of varices after eradication, gastrointestinal bleeding during and after the endoscopic procedures, overall survival and bleeding-free survival. The following patient characteristics were recorded at the time of the first session of primary prophylaxis and were used as covariates for the statistical analysis of the results: age; weight; type of liver disease; total serum bilirubin concentration in children with cirrhosis; prothrombin ratio (in %); platelet count (per mm³); grade of esophageal varices; and the presence or absence of red wale markings, gastric varices along the cardia and portal hypertensive gastropathy, respectively. To assess the severity of the endoscopic pattern, we devised the HRV score, which is a composite score calculated as follows: one point for grade 1 esophageal varices, 2 points for grade 2 esophageal varices, three points for grade 3 esophageal varices, and 1 point each for the presence of red markings or gastric varices along the cardia. When esophageal varices of different grades were present, the highest grade was used for the calculation of the score.

According to French legislation, ethics committee agreement is not required for the retrospective collection of data corresponding to current practice. The data collection was carried out according to the recommendations of the French Data Protection Authority (Commission nationale de l'informatique et des libertés) and in accordance with the General Data Protection Regulation.

Statistical Analysis

Univariate analysis was performed using unpaired Student *t* test, 2-tailed Fisher exact test or log-rank test, where appropriate. Factors with *P* value ≤0.1 in the univariate analysis were entered into the multivariate analysis. Recurrence of gastroesophageal varices, overall survival and bleeding-free survival were analyzed using the Kaplan-Meier method. For emergence of recurring varices after eradication, the start of follow-up evaluation was the date of eradication of varices, and the end of follow-up evaluation was the date of recurrence of varices or, in children without recurrence, the date of liver transplantation, date of a surgical portosystemic shunt or Rex shunt, or date of the latest information. For overall survival the start of follow-up evaluation was the date of the first session of endoscopic treatment and the end of follow-up evaluation was the date of death or the date of the latest information. For bleeding-free survival, the start of follow-up evaluation was the date of the first session of endoscopic treatment and the end of follow-up evaluation was the date of bleeding or, in nonbleeders, the date of liver transplantation, date of a surgical portosystemic shunt or Rex shunt, or date of the latest information. The Cox model and other regression multivariate analysis were performed using R software (R core team 2019; <https://www.r-project.org/>).

RESULTS

Demographics

Table 1 and Table 1, Supplemental Digital Content, <http://links.lww.com/MPG/C858> show the main features of the 145 children at the time of the first session of endoscopic treatment; the platelet count was $\geq 150,000/\text{mm}^3$ in 36% of children. The endoscopic pattern was more severe and the proportion of children with a normal platelet count was higher in children under the age of 3 (Table 2). Gastric varices along the cardia were of the GOV1 type. The number of screening endoscopies performed before the one showing high-risk varices ranged from zero to 9 (mean, 1.3, median, 1). Banding was used in 114 children at a median age of 5 years (range, 6 months–17 years) and sclerotherapy was used in 31 children at a median age of 9 months (range, 3.5 months–7 years).

Table 3 and Figure 1, Supplemental Digital Content, <http://links.lww.com/MPG/C858> show the main results of the primary prophylaxis.

TABLE 1. Clinical, laboratory and endoscopic features at the time of the first session of treatment in 145 children with portal hypertension and high-risk gastroesophageal varices who underwent primary prophylaxis of bleeding by endoscopic sclerotherapy or banding

All children, n = 145	
Age	
Mean	5 y
Range	4 mo–17 y
Median	3.7 y
Weight, kg	
Mean	21
Range	4–78
Median	16
Cirrhosis/noncirrhotic, n	116/29
Biliary atresia/other causes, n	95/50
Bilirubin, $\mu\text{mol/L}$	
Mean	80
Range	4–523
Prothrombin ratio, %	
Mean	81
Range	36–100
Platelet count, $/\text{mm}^3$	
Mean	136,000
Range	12,000–522,000
Endoscopy	
Grade 2, n	66
Grade 3, n	79
Red markings, n	106
Gastric varices along the cardia, n	92
Gastropathy, n	87
HRV score,* mean	3.9

HRV = high-risk varices; n = number of children. *Defined as the sum of the grade of the esophageal varices (2 or 3 points) and of the presence (1 point) or absence (0 point) of red wale markings and gastric varices along the cardia, respectively.

Eradication of Varices

Eradication of the gastroesophageal varices was achieved in 135 (93%) of the 145 children. In 10 of the 145 children a failure of the endoscopic treatment was acknowledged: the varices persisted unchanged or increased after a transitory improvement (Table 2, Supplemental Digital Content, <http://links.lww.com/MPG/C858>). When comparing the 135 children with proven eradication of varices to the 10 children with acknowledged failure of primary prophylaxis, grade 3 esophageal varices, as opposed to grade 2, were associated with a worse probability of eradication ($P = 0.02$).

Mean time to eradication in the 135 children in whom eradication was achieved was 6 months. In the multivariate analysis, the presence of gastric varices along the cardia was associated with a longer time to eradication (Table 3, Supplemental Digital Content, <http://links.lww.com/MPG/C858>). The number of endoscopy sessions required for eradication ranged from 1 to 8 and was lower in children treated by band ligation than in children treated by sclerotherapy.

Recurrence of Varices

Recurrence of gastroesophageal varices was observed in 62 (45%) of the 135 children in whom eradication of esophageal and gastric varices was achieved. A first recurrence was recorded 2 months to 5 years after eradication including 7 (11%) in whom it was recorded between 2 and 4 months after eradication. The first recurrence was seen in children with all types of liver diseases and was found on the occasion of a bleeding episode in 3 children and on a scheduled endoscopy in the other 59 children. Management of the first recurrence included retreatment by banding or sclerotherapy and resulted in eradication in all but one child who presented with refractory bleeding from grade 3 esophageal varices and required a transjugular intrahepatic portosystemic shunt (TIPS) procedure. A second recurrence was recorded 7 months to 4 years and 10 months after the second eradication in 17 children, was treated endoscopically, and was complicated with refractory bleeding from junctional gastric varices in 2 children, which required liver transplantation or a TIPS procedure. A third recurrence was recorded in three children 12 to 36 months after the third eradication and was treated by band ligation without bleeding. A lower HRV score was associated with a lower risk of a first recurrence (Fig. 1A). There was no difference in the risk of a first recurrence between children with cirrhosis and children with noncirrhotic causes ($P = 0.97$, log-rank); in children with cirrhosis, there were no differences in the risk of a first recurrence depending on the pre-procedure total serum bilirubin concentration or prothrombin ratio ($P = 0.49$ and 0.23 , respectively, log-rank). The endoscopic pattern at the end of follow-up is shown in Table 4, Supplemental Digital Content, <http://links.lww.com/MPG/C858>.

Bleeding Episodes

Gastrointestinal bleeding occurred in 26 of 145 (17%) children in the course of the study. Children who bled could be sorted into 5 groups: (1) 6 children bled during a session or shortly thereafter; (2) 9 children bled from sloughing off of the esophageal mucosa with or without progression of the varices. In 8 of these 15 children who bled during the initial period of the procedure, an additional treatment was necessary because of the lack of efficiency of the endoscopic treatment and another child died while awaiting transplantation (Table 2, Supplemental Digital Content, <http://links.lww.com/MPG/C858>); (3) 7 children bled during or after a first or second recurrence and in 3 instances, an additional treatment was necessary to control bleeding; (4) 2 children bled from ectopic varices on the intestinal loop to the liver hilum or on the right colic flexure after eradication of the gastroesophageal varices; and (5) the fifth group consisted of one child

TABLE 2. Severity of endoscopic signs of portal hypertension and results of platelet counts depending on age in 145 children with portal hypertension and high-risk varices who underwent endoscopic primary prophylaxis of bleeding

	Age < 3 y (n = 64)	Age ≥ 3 y (n = 81)	P value
EV grade			
2	26	41	
3	38	40	0.18
Red markings			
+	56	50	
−	8	31	0.0006
Gastric varices along the cardia			
+	39	53	
−	25	28	0.60
Mean HRV score	4.09	3.76	0.013
Gastropathy			
+	44	43	
−	20	38	0.06
Platelet count/mm ³			
Mean	186,000*	96,000	<0.0001
Range	36,000–522,000	12,000–508,000	

Data were recorded at the time of the first session of treatment. EV = esophageal varices; HRV = high-risk varices; + = presence of sign; − = absence of sign. *A platelet count $\geq 150,000/\text{mm}^3$ was present in 2/3 of children under the age of 3.

who bled from a duodenal ulcer and of another, with obliterative portal venopathy, who presented with acute portal vein thrombosis and refractory bleeding from junctional gastric varices. One case of bleeding was recorded from portal hypertensive gastropathy, which was combined with bleeding from gastric varices.

Altogether, a failure of eradication of gastroesophageal varices by sclerotherapy or banding during the study period, either initially, after a recurrence, or on the occasion of acute portal vein thrombosis, was recorded in 14 of the 145 (9.6%) children.

A few children presented with nonbleeding adverse effects including fever in 2 children, an enclaved banding kit in one child, mucosal ulcers in 6 children (one of whom presented with esophageal stenosis) and transient pleural effusion with suspected esophageal perforation in one child.

Survival

Ten years after the first session of treatment, the probability of overall survival was 95% (Fig. 1B). Five of the 145 children died: a child with portal vein obstruction died because of severe combined lung and cardiac malformations and four children with cirrhosis died, including 3 children after liver transplantation. The probability of bleeding-free survival was 75% 10 years after the onset of treatment (Fig. 1B). In the multivariate analysis, a lower HRV score was associated with better bleeding-free survival. In the various analyses, the etiology of the liver condition was not found to affect the results of the endoscopic procedures (Table 5, Supplemental Digital Content, <http://links.lww.com/MPG/C858>).

In children with cirrhosis, a lower mean prothrombin ratio at the time of the first session of endoscopic treatment was associated with a higher risk of life-threatening bleeding [ie, resulting

TABLE 3. Eradication of gastroesophageal varices, recurrence of varices, and gastrointestinal bleeding in 145 children with portal hypertension and high-risk gastroesophageal varices who underwent primary prophylaxis of bleeding by sclerotherapy or band ligation

Outcome	
Eradication of varices, n	
Achieved	135
Failure	10
Time to eradication (135 children)	
Mean	6 mo
Range	2 wk–5 y
Median	2.5 mo
Number of sessions for eradication (135 children)	
Mean	2.8
Range	1–8
Recurrence after eradication (135 children), n	62
Interval eradication/recurrence, mean	16 mo
Range	2 mo–5 y
Median	12 mo
Bleeding after primary prophylaxis (145 children)	
All bleedings, n	26
Interval bleeding/first session, mean	12 mo
Range	7 d–6 y
Median	4 mo
Bleeding after initial session(s) n	15
Bleeding during a recurrence, n	7
Bleeding from ectopic sites, n	2
Others,* n	2

*Duodenal ulcer and junctional gastric varices following additional acute portal vein thrombosis, respectively.

in death or requiring urgent liver transplantation, see Duché et al (27)] after primary prophylaxis (mean prothrombin ratio: 65%, range: 36%–87% in children with life-threatening bleeding and 82%, range 48%–100% in children with no bleeding or no life-threatening bleeding, respectively; $P = 0.002$). This was confirmed in the multivariate analysis.

During the same 2006 to 2019 time period, 47 children who bled spontaneously from high-risk varices underwent endoscopic secondary prophylaxis of bleeding: eradication was recorded in 34 (72%) children, gastrointestinal bleeding in 20 (42%) children, recurrence of varices after eradication in 21 (61%) children, and 10-year overall and bleeding-free survivals were 91% and 43%, respectively.

DISCUSSION

There is no longer any doubt that, in children with portal hypertension, bleeding from gastroesophageal varices has very severe consequences. Results reported in the past 10 years, primarily in children managed after the year 2000, show the following: (1) a close to 9% risk of death in the 6 weeks following bleeding in a study of over 1900 children who bled at least once (28); (2) a 14%–15% risk of death or need for emergency liver transplantation

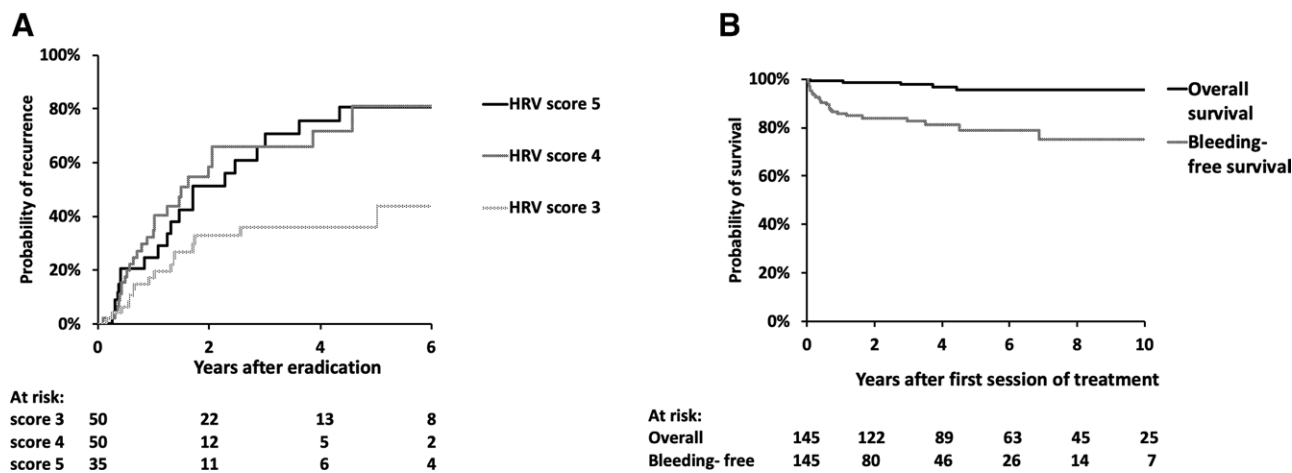


FIGURE 1. A, Cumulative incidence of recurrence of gastroesophageal varices after eradication by endoscopic sclerotherapy or band ligation in 135 children with portal hypertension and high-risk gastroesophageal varices in whom eradication was obtained, depending on the severity of the high-risk varices (HRV) score at onset of treatment ($P = 0.0051$, log-rank test). B, Probabilities of overall survival and of bleeding-free survival in 145 children with portal hypertension and high-risk varices who underwent primary prophylaxis of bleeding by endoscopic band ligation or sclerotherapy.

following bleeding in children with cirrhosis (25,27,29); (3) bleeding is the precipitant in 40% of cases of acute on chronic liver failure in children with biliary atresia (30); and (4) significant morbidity in over 50% of children who bleed (31). Death or significant morbidity are recorded in similar proportions following a first episode of bleeding and similarly in children with cirrhosis and noncirrhotic portal hypertension (28,31). Therefore, primary prophylaxis of bleeding deserves to be taken into serious consideration in children at risk. The risk of spontaneous variceal bleeding depends primarily on the endoscopic pattern of gastroesophageal varices, regardless of the cause of liver disease (12,24–27). This may result, in part, from the presence, in children with many cirrhotic as well as noncirrhotic causes of portal hypertension, of lesions and/or obstruction of the intrahepatic branches of the portal vein (32–36). These lesions create a presinusoidal block and could explain why the endoscopic patterns associated with a high risk of bleeding are similar in cirrhotic and noncirrhotic children. In children with extrahepatic portal vein obstruction, a surgical meso-Rex bypass should be attempted if the portal bifurcation and the recessus of Rex are patent. In all other children, primary prophylaxis with band ligation, or sclerotherapy in younger infants, can be considered a valid option. The overall impression emerging from the reports published so far suggests that this technique could be effective and safe. The results reported here assess the efficacy and safety in a large number of children of all ages, selected on strict endoscopic criteria and encompassing most causes of portal hypertension. Concerning the efficacy of the procedures, the main results are that an eradication of high-risk gastroesophageal varices could be obtained, after a mean period of 6 months, in over 90% of the children, at least one recurrence of varices was recorded in 45% of children in whom eradication had been achieved, and gastrointestinal bleeding of various origins occurred in 17% of all children during the period of study. The severity of the initial endoscopic pattern, be it grade 3 esophageal varices, gastric varices along the cardia or a high HRV score, was associated with worse outcomes. Conversely, the etiology of the liver condition was not found to have an impact on the outcomes. This underscores the need for early detection of clinical and ultrasonographic signs of portal hypertension in children at risk, even in the first months of life (5,27,37), and for early screening endoscopy to allow primary prophylaxis

to be performed before endoscopic signs are too advanced. One must also stress that the risk of recurrence of varices persists after endoscopic treatment unless liver transplantation or a surgical/TIPS procedure is performed and requires prolonged endoscopic surveillance to detect and treat emerging varices. Emergence of bleeding from ectopic varices cannot be prevented by endoscopic treatment and requires interventional radiology or surgical treatment.

In terms of safety, the 95% 10-year probability of overall survival after the first session is relatively acceptable, especially since four of the 5 recorded deaths were not directly related to the procedure. However, a word of caution is necessary: as seen in Table 2, Supplemental Digital Content, <http://links.lww.com/MPG/C858>, bleeding following the endoscopic treatment can have severe consequences in case of failure of the prophylaxis and requires a rapid alternative treatment which was not possible in one child who died while awaiting liver transplantation. In children with cirrhosis, a severe endoscopic pattern and a low prothrombin ratio, one should consider speeding up the time of liver transplantation rather than attempting primary prophylaxis.

CONCLUSIONS

Endoscopic primary prophylaxis of variceal bleeding is reasonably effective and safe in children with high-risk gastroesophageal varices. Worse results are observed in children with more advanced endoscopic features. This pleads for endoscopic screening in children with portal hypertension and early detection of varices warranting primary prophylaxis.

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