Summary of current experience with clinical use of BD Stent

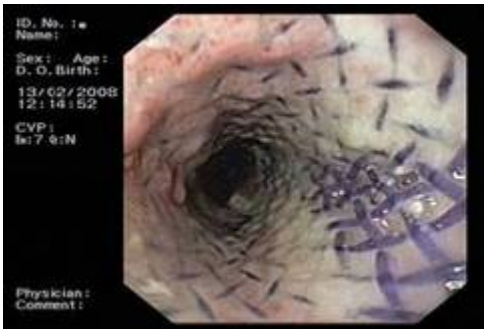
Biodegradable BD Stent manufactured by ELLA-CS obtained CE mark in December 2007.
344 sets of BD Stent have been manufactured and delivered since that time.
Majority of BD Stents were put on the market of 13 countries belonging to the European Union. The product was also marketed in 4 countries outside EU.
Unfortunately, ELLA-CS was not able to manage a full post-market surveillance of the product. The clinical feedback was sporadic and incomplete. Nevertheless we can use it for stipulating the principles of using BD Stent in order to avoid or reduce some complications and improve the therapeutic effect.

What lesson we have learnt from current experience?

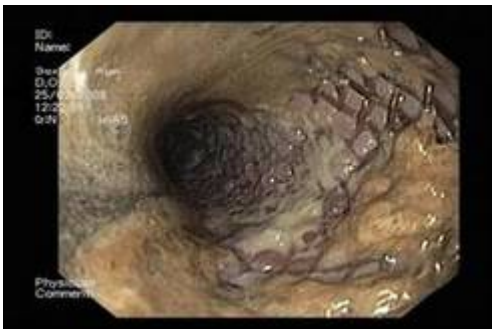
a) ***Majority of the patients implanted by BD Stent develop mucosal hyperplastic reaction of different intensity and clinical significance.***

The existence of the patients without any sign of hyperplastic reaction can be demonstrated by the case of the post-anastomotic stricture treated in January 2008 in Norway - Ulleval University Hospital in Oslo. See the pictures:

Stent and mucosa 2 weeks after implantation



4 weeks after the implantation



b) ***We have not observed an apparent link between type of benign esophageal strictures and frequency and intensity of the hyperplasia produced by BD Stent.***

However, we believe that the following factors increase the risk of hyperplastic reaction:
- Position of the stenosis at the upper third of the esophagus, particularly in patients with post-anastomotic stricture after laryngectomy;
- Decreased viability of the esophageal wall due to previous irradiation, multiple scars - e.g. those resulting from caustic injury or repeated dilations preceded the BD Stent implantation;
- Untreated gastroesophageal reflux. Gastric acid seems to enhance the hyperplastic reaction to mechanical irritation produced by BD Stent mesh.

c) ***The hyperplasia may occur along the whole length of stent, particularly around its ends. We have not observed obstruction of the stent lumen due to hyperplasia.***

d) ***The hyperplasia is usually without clinical significance.***

Till now ELLA has been reported about 8 patients who developed strong hyperplasia followed by dysphagia requiring a therapy (1 pt in Czech Republic; 3 pts in Spain – documented only 1 case; 3 patients in Mexico – poorly documented only 1 case; 1 pt in Poland – not documented). Those patients represent 2.3 % from 344 stented patients. However, the calculation is based exclusively on reported cases. The individual incidence in the countries was as follows:

- Czech Republic 1 pt among 47 pts (2.1 %)
- Spain 3 pts among 31 sold BD stents (9.7 %)
- Mexico 3 pts among 27 sold BD stents (11.1 %)
- Poland 1 pt among 14 sold BD stents (7.1 %).

The figures have to be considered as dubious because of low number of observed patients as well as poor follow up.

e) ***Dysphagia produced by mucosal hyperplasia could be successfully managed by pneumatic dilation. The frequency of the dilations was lower than that before BD Stent implantation.***
f) ***If the hyperplasia does not produce dysphagia, it should be left without treatment. It gradually diminishes till full recovery of the mucosa.***
g) ***Currently it is difficult to specify the long-term effect of BD Stent. However, it may reach 80 % after 22 weeks since the stent implantation.***
A. Repici IRCCS Instituto Clinic Humanitas (A.R.), Milan, **Italy**, in his unpublished study with 12 patients treated by BD Stent. The effect was measured by decrease of the initial dysphagia score.

Till now we have been reported on the patients developing intensive hyperplasia of esophageal mucosa as follows:

- **A case of 61-year old women with caustic stricture reported with the group of patients treated by custom made BD Stent within the period 2006 – 2007.**

Patient in the age of 18 months accidentally drank a lye. In the adulthood she developed 10-cm long stenosis in the middle esophagus which started to cause dysphagia treated by pneumatic dilations. Before the implantation of BD Stent the intervals between dilations were about 2 months and dilations got very painful. The patient refused the surgery.
The first BD Stent was implanted when the patient was 61 years old (04/2006). Two months after the implantation the hyperplastic stenosis developed at the upper end of the stent. It could be easily passed with the endoscope even without predilation.
Five months after the implantation of the first BD Stent the second biodegradable stent was implanted to manage the above mentioned stenosis (09/2006). The original caustic stenosis remained open even in the period of stent disappearance. After 3-month implantation period rests of the second stent dislocated. The caustic stenosis remained open (12/2006). Repeated dilations of the hyperplastic stenosis were performed.
In January 2007 the hyperplastic stenosis and the original caustic stenosis worsened. The third biodegradable stent was implanted. Three months later (04/2007) the hyperplastic stenosis recurred and had to be treated by repeated dilations. The stent was almost absorbed. In May 2007 a short hyperplastic stenosis relapsed. It was managed with fourth BD Stent.

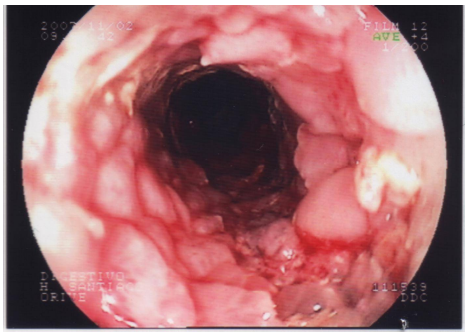
Comments made by ELLA:
This is a story of a patient with caustic stenosis which "matured" after years and began produce dysphagia. The patient was treated by repeated dilations for years. The dilations became frequent and painful. The patient refused the surgery and accepted the offer of treatment by custom made BD Stent. Without regard to the hyperplastic stenosis produced by BD Stent the patient insisted on repeated implantation of BD Stent. The hyperplastic stenosis was soft and could be easily dilated using repeated dilations. However, after some period the stenoses got worse and the patient asked for another BD Stent.
ELLA would like to note that the clinically significant hyperplasia occurred among 47 patients treated by custom made BD Stent in the period Dec 2005 – Dec 2007.

- **A case of patient with post-anastomotic stenosis in Spain reported by our distributor in February 2008**

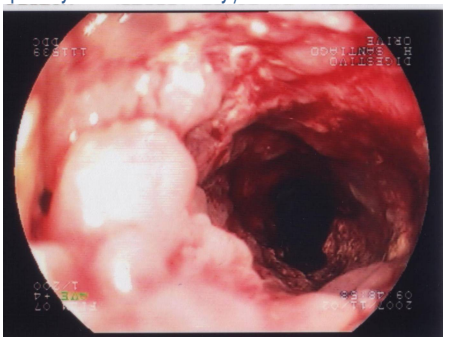
See the copy of the original information and our comments:

The stent has degraded after 4 months and, a membranous stenosis was formed which was easily dilated with pneumatic balloon. In the esophageal tract, where the stent was positioned, inflammatory pseudopolyp formations have formed (it is very common to see them where stents have been positioned). The post-surgery stenosis, refractory to endoscopic treatment, was treated implanted the stent. After 4 months, the stenosis is slightly dilated, although the condition of the patient has not been solved.
PHOTOS:
Prot biodegradable: pictures taken 1 month after stent implantation:

1 021- The mucosa is seen getting inside the mesh, this causes the pseudopolyp lesions.

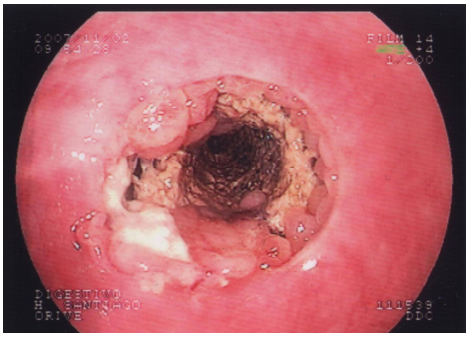


1 014- It is the area where the surgical anastomosis was. Pseudopolyp esophageal tissue can be seen introducing in the orificas of the mesh and closing gradually the lumen of the stent. (This is common with some uncovered stents, but it is not usual to occur son quickly and so strikinly)



1 013- Idem

1 009- Proximal end of the stent. It is seen how the esophageal tissue embraces the stent. After the stent disappears, a membranous stenosis will form.



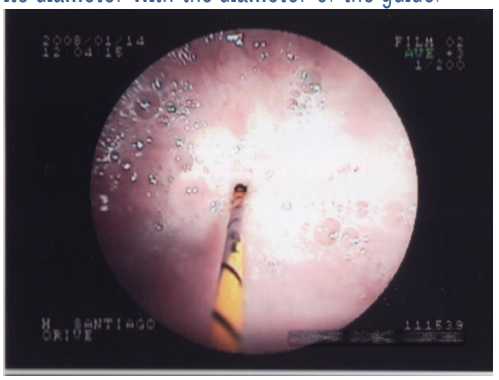
1 - Idem as 1 021 and 1 014.

Stenosis after biodegradable stent: pictures taken in month 4 of stent implantation:

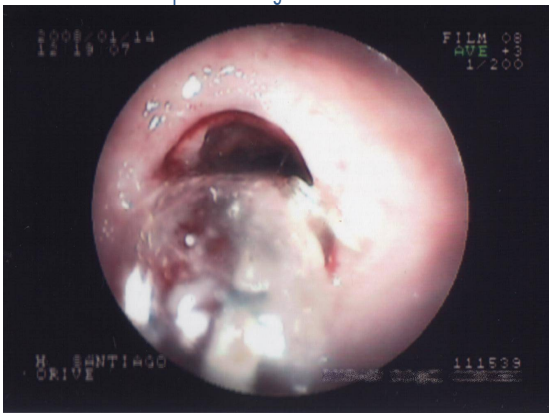
002- Where the proximal end of the stent was you can now see a small membranous point shaped stenosis.

The picture is missing.

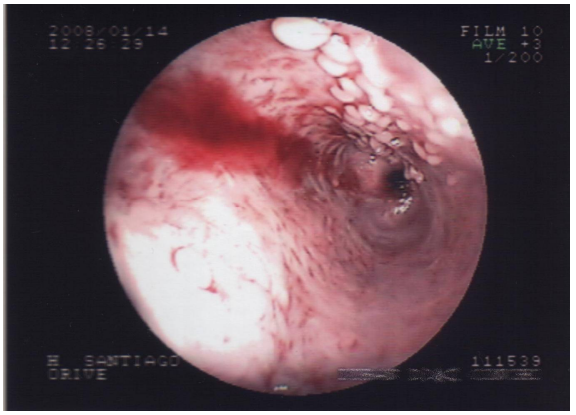
0- A 035 guide is passed through the stenosis so the small size of the stenosis can be seen when comparing its diameter with the diameter of the guide.



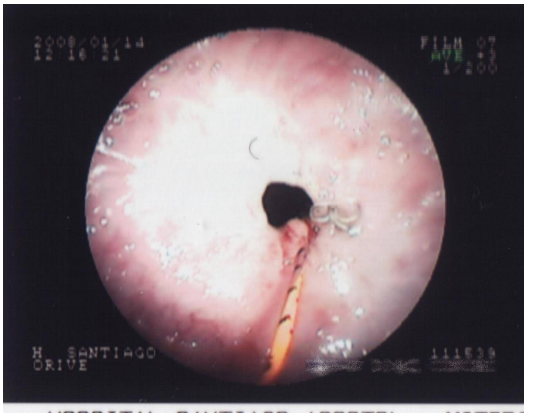
005- The membranous stenosis is satisfactorily dilated as it allows the tube to pass through.



010- After passing the membranous stenosis the esophageal mucosa has this appearance where the stent was placed.



007- Postsurgical stenosis (metallic sutures of the intervention can be seen), refractory to treatment with stent although its diameter (0.5cm) is now slightly bigger than before.



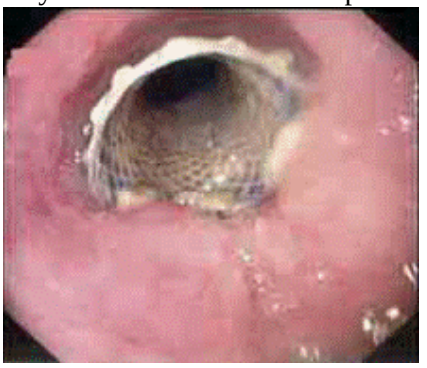
Comments made by ELLA:

The picture No. 1014 is presented to demonstrate formation of pseudopolyp esophageal tissue at the anastomotic area 1 month after the implantation. The hyperplastic mucosa was growing through the stent mesh and, gradually closing the stent lumen. However, the report does not mention a word about clinical impact of that closing, i.e. patient's complaint about dysphagia.

The picture No. 1021 demonstrates mucosal hyperplasia at the area underlying the stent mesh. It means that the endoscope easily passed the stent rim and its lumen. Where is a stent obstruction?

The picture No. 0(xx?) should demonstrate the tightness of point shape stenosis formed at the former proximal rim of the stent 4 months after the implantation. Nevertheless the picture No. 005 and 010 demonstrates free passage of the endoscope after easy dilation of the stenosis. In addition to it the picture No. 010 seems to demonstrate apparent reduction of mucosal irritation. The picture No. 007 demonstrates a limited effect of the BD Stent on the original post-anastomotic stricture 4 months after the implantation.

The stenosis resulting from irritation produced by proximal stent of BD Stent can be compared with that produced by non-degradable Polyflex 6 weeks after the implantation.



Repici A. et al. (Gastrointestinal Endoscopy 2004; 60:513-519)

The difference between the stenoses caused by stents lies in the need of Polyflex extraction whilst BD Stent is degraded. We expect gradual disappearance of the stenosis produced by BD Stent similarly to that observed with Polyflex.

If the BD Stent provided the patient with 3 months of free or slightly limited swallowing, it made a great work. It should be compared with the situation before the implantation, i.e. patient's history of repeated esophageal dilations.

The summary of ELLA comments:
BD Stent dilated the refractory post-anastomotic stricture for about 4 months and allowed the patient to swallow and improve his/her diet condition. BD Stent produced strong local inflammatory reaction resulting in the membranous stricture after 4-month implantation period. The stricture could be easily dilated. The post-anastomotic stricture recoiled about 1 month after the stent absorption. The patient's dysphagia recurred.
In our opinion the only alternative to the BD Stent can be plastic self-expandable stent Polyflex which is also recommended for management of benign esophageal strictures.
Let us mention a study with Polyflex recently published in Gastrointestinal Endoscopy in order to compare the described effect and complications of BD Stent with those potentially produced by Polyflex:

Holm AN. et al. Self-expanding plastic stents in treatment of benign esophageal conditions. GASTROINTESTINAL ENDOSCOPY Volume 67, No. 1: 2008 Rochester, Minnesota, USA
Background: *Recently, self-expanding plastic stents (SEPSs) have been proposed for the treatment of benign esophageal disease.*
Objectives: *Our purpose was to review our experience with SEPSs in patients with benign esophageal conditions.*
Design: *This was a retrospective case review of patients who underwent SEPS placement for benign esophageal disease, including (1) benign stricture, including reflux disease, ischemia, and idiopathic, (2) radiation-induced strictures, (3) anastomotic strictures, and (4) esophageal leak/fistulae.*
Patients: *Nineteen male and 11 female patients (average age 52.1 years, range 11-87 years) underwent SEPS placement.*
Interventions: *SEPS placement.*
Main Outcome Measurements: *Initial complications, stent migration, long-term complications, and treatment success according to clinical symptoms, follow-up endoscopy, or imaging.*
Results: *Eighty-three of 84 SEPS placements were successful. The most common complications were chest pain, dysphagia, nausea, and vomiting. No deaths were reported from stent placement. Stent migration was more frequent in proximal (30/44 stents, 68.1%) and distal (19/27 stents, 70.4%) compared with mid esophageal (3/10 stents, 30%).*
Migration was more frequent in stents placed for

- ***benign strictures (18/22 stents, 81.8%),***
- ***anastomotic strictures (18/24 stents, 75%), and***
- ***fistulae/leak (13/22 stents, 59.1%),***
- ***compared with radiation-induced strictures (4/14 stents, 28.6%).***

Only 5 of 83 interventions (6%) resulted in long-term improvement after stent removal.
Limitations: *This was a retrospective review, and patients were selected from a tertiary medical center.*
Conclusion: *Use of SEPSs for benign esophageal conditions resulted in frequent stent migration and few cases of long-term improvement. Further investigation is warranted to identify optimal patient populations and to guide future recommendations for the use of SEPSs. (Gastrointest Endosc 2008;67:20-5.)*

Finally, ELLA would like to note 31 pieces of BD stents put on the Spanish market till now. However, no report on complications does not mean, they do not exist at all.

- **A case of patient with post-anastomotic stricture after laryngectomy in Mexico reported by our distributor in September 2008**

The case was presented by Dr. Alfredo Guitrón Cantu - Chief of Departamento de Endoscopia Digestiva, Hospital de Especialidades No. 71, Instituto Mexicano del Seguro Social, Torreón, Coahuila, during National Live Gastroenterology Congress held within September 3rd – 7th in Ixtapa, Zihuatanejo, Mexico.
See the copy of the original information (in Spanish) and our comments:

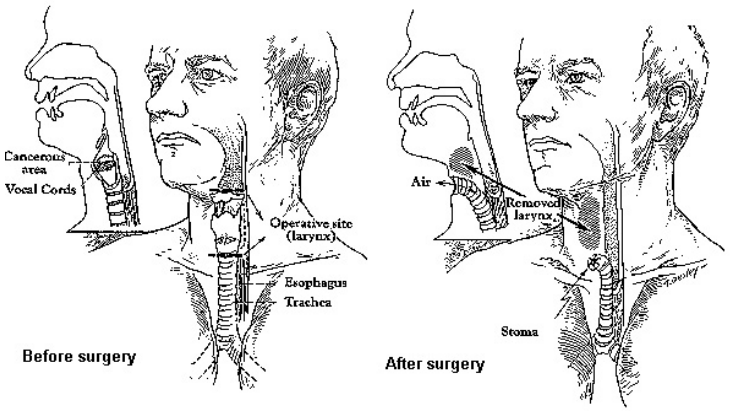
"Nombre: AAR

Edad: 54
Antecedentes personales patológicos:
-Diagnostico de CA de laringe en mayo del 2006 con laringectomia total con reconstrucción mediante colgajo de pectoral con desarrollo de estenosis de hipofaringe posterior a dicha reconstrucción.

-Múltiples endoscopias superiores (13) para dilatación con balón y Savary + aplicación de esteroides inyectados sin respuesta.
Se propone colocación de prótesis biodegradable en 24 de Junio 2008 (colocación exitosa) posteriormente 2 episodios de impacto alimentario y aplicación de argón plasma (27 Julio y 19 agosto), se cita el 29 de agosto para tercer aplicación de argón., actualmente en vigilancia".

The medical history can be read as follows:

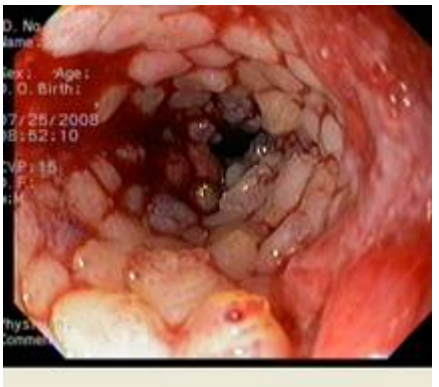
The patient suffered from laryngeal carcinoma that was totally resected in 2006. The surgery was performed by Dr. Alfredo Guitrón Cantu – see above (aguitron@prodigy.net.mx).
The patient started to suffer from the stricture that developed in the reconstructed hypopharynx.
During this operation, the surgeon removes the larynx through an incision in the neck and performs also a tracheotomy. He/she makes an artificial opening called a stoma in the front of the neck. The upper portion of the trachea is brought to the stoma and secured, making a permanent alternate way for air to get to the lungs. Several reconstructive procedures can be used to rebuild the pharynx and improve your ability to swallow after the operation.

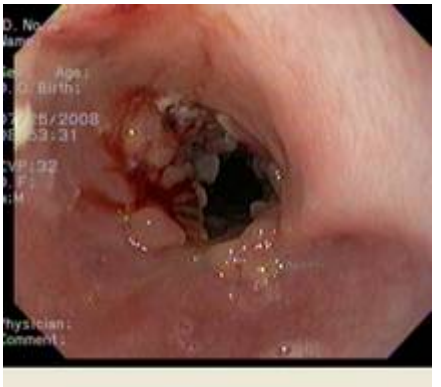


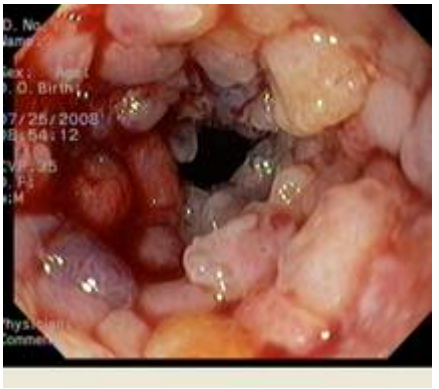
Basing on the text of the patient's history I think suturing his esophagus to the medial part of the pharynx. The pectoralis major flap was used for the throat reconstruction.

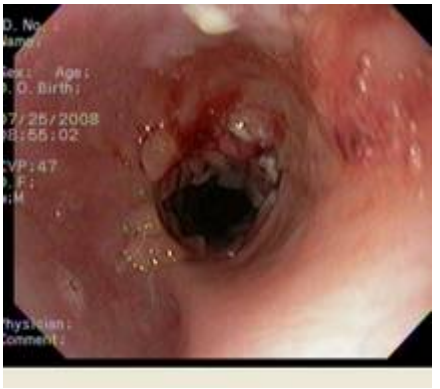
In June 2008, after failure of multiple balloon dilation Dr. Guitron and his colleagues decided to implant biodegradable BD Stent.
Since that time the patient faced two episodes of food impact in the stent. *(It was said due to the esophageal hyperplasia.)* The first obstruction happened about one month, the second two months after the implantation. Both obstructions were managed by using argon plasma coagulation. The third plasma coagulation was done in the end of August 2008. The patient is currently under follow up observation.

ELLA also obtained some endoscopic pictures made by Dr. Guitron in some patients treated by BD Stent. Unfortunately they are not precisely identified and interpreted. However, some of them demonstrate strong mucosal hyperplasia which is apparent even without interpreting of examining endoscopist:









Comments made by ELLA:
The pharyngeal reconstruction increases much the risk of mechanical irritation produced by the BD Stent. The upper part of the stent has to be placed in the pharynx through the preserved upper esophageal sphincter. Consequently, the pharyngeal muscles repeatedly constrict and elevate the stent during the oropharyngeal phase of the swallowing. ELLA thinks this movement to be much more intensive than that produced by esophageal peristalsis if BD Stent is placed at the indicated position in the esophagus - see the following text. This results in excessive mechanical irritation and mucosal hyperplasia.

Placing the stent in the upper third of the esophagus is prohibited by current IfU of BD Stent see the following citation from the IfU no. SX-BD-10-AJ-01/08/I/REV-0-01/2008:
"Indications:
The SX-ELLA Stent Esophageal Degradable BD (BD Stent) is designed for dilation of benign esophageal lesions, namely:

- *stenosis (peptic, anastomotic or caustic) refractory to standard therapy,*
- *achalasia refractory to standard therapy.*

Contraindications:
Inability to pass the 9.4-mm (28-F) delivery system through the stricture;
Benign strictures in the upper part of the esophagus too close to the cricopharyngeal muscle."

There were 2 patients suffering from strong hyperplastic reaction after BD Stent implantation in Mexico (one described by Dr. Guitron, one case non-documented).

During the National Live Gastroenterology Congress in Mexico was also presented a case of successful BD Stent implantation in 78-year old patient with refractory peptic esophageal stricture (*"un paciente masculino de 78 anos con una estenosis péptica refractaria a tratamiento con dilataciones*"). The implantation was performed by Dr. Clara Luz Martínez García, Jefa del Servicio de Endoscopia Digestiva, Hospital Regional No 1 in Mexico City. However, in December 2008, i.e. about 3 months after the implantation, ELLA-CS was reported that the patient developed esophageal hyperplasia. Unfortunately the information was presented as personal communication without any details. That is why ELLA-CS is not able to take a lesson from that case.

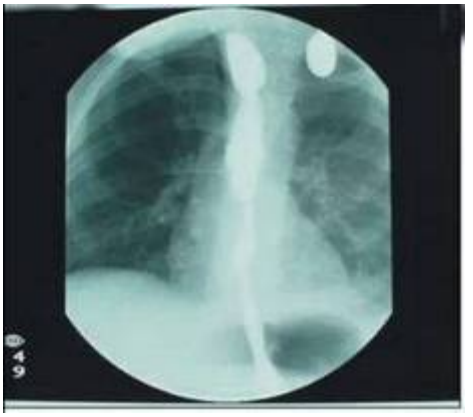
- **Case of a 5-year old boy with caustis stricture reported by the attending physician within the post-implantation period (Minsk, Byelorussia)**

Adapted excerpt from the unpublished article produced by the attending physician – Dr. Oksana Bychkova from Centre of Children Surgery (Minsk, Belarus):

In November 2005 4 years old boy accidentally swallowed caustic liquid containing high concentration of sodium hydroxide. He was admitted into Centre of Children Surgery (Minsk, Belarus). Endoscopic examination revealed a severe caustic lesion within full length of the esophagus and gastric lesion. After stricture formations repeated dilations were performed every 2 – 3 days for the first month. Later the interval between dilations reached 14 days. That situation lasted for one year. The patient passed 64 dilations in general anesthesia. He experienced esophageal perforation, severe mediastinitis and pleuritis. The high amount of anesthetic agent caused toxic damage of the liver and,

consequently, iron deficiency anemia. The child was considered the candidate for esophagocoloplasty but his parents did not give consent for the surgery.

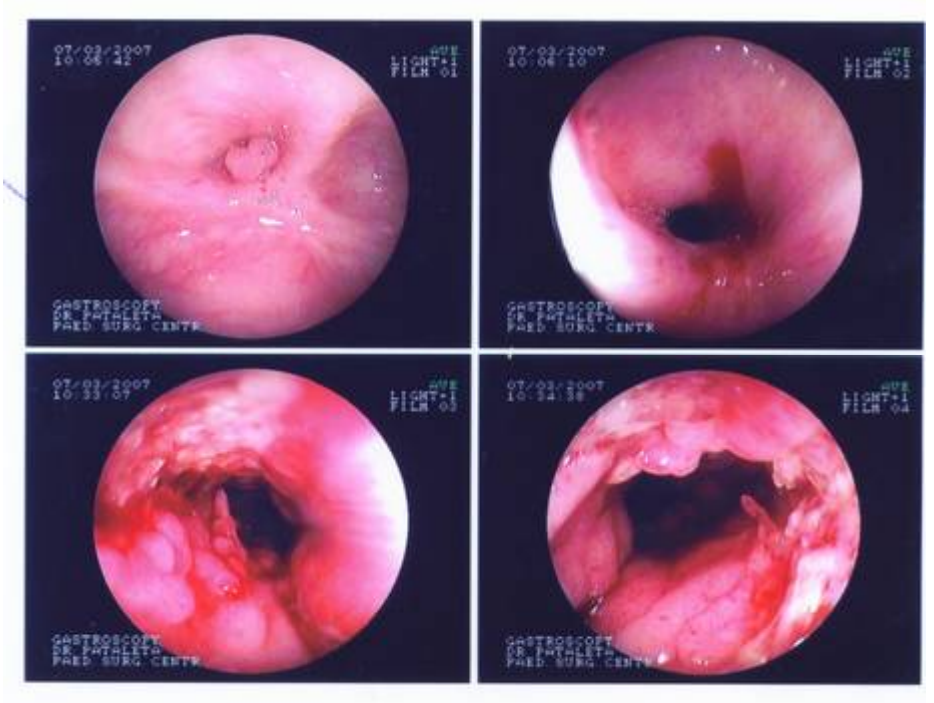
In November 2006 the custom-made BD Stent was implanted. At that time the patient had 2 esophageal strictures – a less distinctive in upper third and distinctive one at the level Th6 – Th8. Development of the stricture lead to esophageal shortening an axial hernia.



It was decided to place the stent into the tight stricture in the lower part of esophagus. The stent was successfully placed. The fluoroscopic swallow examination was regularly performed during the implantation period. Stent remained in place and allowed free swallowing solid food.

Endoscopic examination performed 2 months after the implantation (January 2007) revealed extensive mucosal hyperplasia at place of the stent location, especially around its proximal part. Without any reference to the fact that the patient did not complain about dysphagia, the endoscopist resected the hyperplastic mucosa above the upper end of the stent.

12 weeks after the implantation (beginning of March 2007) the patient started to complain of difficulties with swallowing the solid food. The hyperplastic granulations and stenosis at the former position of the upper end of the stent were demonstrated with endoscopy:



The stenosis required repeated dilation within 14-day interval for 4 months (until May 2007).

In May 2007 patient started to be treated by proton pump inhibitor (Nexium). The medication prolonged the interval between dilations to 4 weeks. The patient's health condition, including biochemical parameters, significantly improved. This built confidence of the boy's parents in the therapeutic approach.
The patient developed a stricture at the level Th5 – Th6 one year after the implantation of the first stent (December 2007). The second BD Stent was implanted. The hyperplastic stenosis occurred above the proximal stent end 12 weeks after the implantation. It was treated by repeated dilations within one-month intervals. The patient could eat solid food within the complaint-free intervals.
Fluoroscopic examination in June 2008 demonstrated disappearance of the axial hernia and reflux of gastric content into the esophagus. The therapy with Nexium was finished.
In August 2008 the patient developed 2 – 3-mm stenosis in the middle esophagus that was managed by balloon dilation. Restarted administration of Nexium resulted in prolongation of the dilation intervals to 3 weeks.
Now the boy is 7 years old what correspond to the middle of childhood. Without regard to his serious illness he experienced a growth spurts within the last two years. He grew 10 cm and gained 20 kg of weight. The therapy with BD Stent allowed him to lead almost normal life, visit a school. He gained self-confidence and believes in his recovery.
The therapeutic plan supposes repeated implantation of customized BD Stent in the future, at least till the early adulthood.

Comments made by ELLA:
This medical history of the child patient demonstrates the benefit brought by BD Stent even if it produces mucosal hyperplasia and stenosis. Those complications are acceptable in comparison with mutilating surgery which is an alternative to BD Stent.
The worsening of dysphagia due to discontinuance of PPI administration seems to demonstrate the clinical significance of that medication.
The effectiveness of BD Stent in child patients with caustic esophageal strictures is supported by experience of Vandenplas Y. et al. from Unit of Pediatric Gastroenterology and Department of Gastroenterology, Universitair Ziekenhuis Brussel Kinderen, Brussels, Belgium. The authors successfully implanted a 10-year old boy with a corrosive esophageal stenosis. More than 5 months after complete degradation of the stent, the stenosis did not re-develop and the patient remains asymptomatic. The patient was administered by oral omeprazole (20 mg/day) all the time.

- **A case of patient with achalasia in Poland reported by our distributor in November 2008**

ELLA has been reported about a patient with recurrent achalasia treated by BD Stent implantation. The case was presented by Dr. P. Nowakowski from Clinical Hospital No 7 in Katovice, Poland during „Endoscopy Day" in Katowice organized by Polish Society of Gastroenterology in November 2008. The patient was said to develop strong hyperplastic reaction. ELLA had contacted the physician asking him for details, pictures etc. but unfortunately without any response.
The case of the hyperplastic stenosis followed BD Stent implantation does not correspond to the positive results reported by Dr. Tersip who implanted first custom-made BD Stents in patients with achalasia.

Last note made by ELLA-CS with respect to the complications produced by implanted BD Stent, particularly hyperplastic reaction – stenosis:
The only way how to obtain exact and reliable information in that field is to organize small but well defined clinical studies.
For that reason ELLA-CS has established the cooperation with Professor P. Fockens and co-workers from Department of Gastroenterology and Hepatology, and Department of Surgery of Academic Medical Center in Amsterdam, Netherlands. The investigators are conducting the study called ESBIO – Endoscopic treatment of benign anastomotic esophageal strictures with biodegradable stent.
The other cooperation has been established with a specialist from UK. The study should be designed as a "proof of concept" pilot study. Because of early stage of the project ELLA is obliged not to disclose the details of the study.

ELLA also tried to establish cooperation with Assoc. Prof. Blaszczuk from Clinical Hospital No. 1 in Wroclaw, Poland, and organize the study of BD Stent implantation in patients with refractory

achalasia. Although the proposal of the study was submitted in November 2008, ELLA-CS has not received any answer.

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Date: 2008-12-30