

ORIGINAL PAPERS

Management of refractory esophageal stenosis in the pediatric age

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ABSTRACT

Introduction: Refractory esophageal stenosis (RES) is a major health problem in the pediatric population. Several techniques such as stent placement or C-mitomycin (CM) have been described as alternative treatments. We present our experience with both techniques, in our case with biodegradable stents (BS) and sometimes the association with stents and CM.

Material and methods: Six patients have been included: 2 post-operative fistulas in patients with type I esophageal atresia; 1 operated atresia without fistula; and 3 caustic strictures. 5 BS were placed in 4 children: 3 of them in cases of atresia (2 prosthesis in one case) and the other one in a case of stricture. CM was used in 5 cases: in 2 of them from the beginning, and in the other 3 cases after failure of the stent.

Results: When placed in fistulas, BS were fully covered. One of them successfully treated the fistula, but the other one was not effective. One stenosis was successfully treated with SB (in the case of persistent fistula), but recurrence was observed in the other 2 cases. One of these was solved with CM, and the other one needed a second stent. In the remaining 2 cases (one atresia and one caustic stricture) CM was effective after 1 and 2 sessions respectively. Overall, 5 out of 6 stenosis have been successfully treated (83.3%), and 1 out of 2 fistulas (50%).

Conclusions: Association of BS and CM has been effective in the management of RES in children.

Key words: Esophageal stenosis. Pediatrics. Biodegradable stent. Mitomycin.

INTRODUCTION

Dilation is the reference technique in the management of esophageal stenosis in the pediatric age. There are moderately sized randomized studies analyzing therapeutic alternatives and the different techniques used in clinical practice are based on published cases or descriptive studies of case series, mainly in adult populations. Moreover there are certain ethical problems when developing

new therapies and these patients are usually managed conservatively.

The concept of stricture refractory to dilation has not been absolutely defined, but a number of 3 non-effective dilations are usually used (1). The differences between caustic and postoperative stenosis remain unclear as well.

Metallic stents have been used (steel and nitinol) (2), as well as biliary (3) and tracheobronchial (4) prosthesis and silicone (5), plastic (Polyflex) (1), polytetrafluoroethylene (6) or biodegradable (polydioxanone) (7) stents in cases of post-operative stenosis and caustic strictures in children, with variable results and high rates of stent migration.

The advantage of BS in the pediatric population is that there is no need for their removal, although in a study including 8 children with metallic stents, no difficulties for their removal were reported (2).

When using stents, an important fact is that these can be customized (5) and compared to dilation they provide maintained radial expansive force with time, so stenosis can be treated more easily or decrease the frequency of dilations (8).

Only one case of BS in the pediatric age has been published (7).

Several authors have reported the effectiveness of CM injected (9) or extended (10) over the stenotic area in pediatric cases of RES. CM is an anthracycline with antineoplastic and anti-proliferative properties due to its capacity to inhibit the activity of fibroblasts, suppressing the formation of fibrosis and scars due to apoptosis. It has been used for the treatment of stenosis in ophthalmology and otolaryngology (9,11,12).

We present 6 cases of RES treated with BS and/or CM which may provide a new approach in this population so often treated with interventional procedures.

METHODS

Six patients have been included (February 2010-December 2013). All the procedures took place in an operating room under general

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anesthesia, and with endoscopic support. We normally used pediatric endoscopes (Pentax EG-1580K and 5.9 mm Olympus GIF-XP160), but in children over 15 kg we used larger diameter endoscopes (9.2 mm Olympus GIF-165) as this makes the technique easier (there is no need for guide wire exchange) and this also shortens the anesthesia times.

In 4 children, an endoscopic gastrostomy was also placed. In one of them, this was used as a lower access point for stenosis cannulation and introduction of a BS.

Stent placement procedure

In 3 cases, customized BS (“SX ELLA-BD” by ELLA-CS, Hradec Kralove, Czech Republic) were placed after measuring the stenosis length, the portion of healthy esophagus over and above the stricture and the diameter of the esophagus, especially at the proximal end. We ordered BS according to these measurements, with a smaller introducer system in an 8 month-old child, as the standards (28F) were too big for this patient. In this case we used a straight stent with no cups because there was not enough room in the introducer. In the other 2 cases, as the esophagus was dilated, standard BS were used.

In all the cases soft and low radial force dilation was performed initially (HERCULES balloon by COOK-WINSTON, Salem, USA), so the introducer system could be placed. All the patients were under proton-pump inhibitors for the treatment of gastroesophageal reflux and anti-reflux surgery had been previously done in 2 patients.

C-mitomycin procedure (Fig. 1)

We prefer the use of endoscopes with a working channel greater than 2.8 mm as the procedure can be done in just one step. The stenotic area needs to be dilated (10-12 mm balloons) (1a, 2a) prior to CM administration. The technique will be different depending on the stenosis length (Fig. 1): in short strictures (< 1 cm) 0.4 ml of CM (0.4 mg/ml) is injected in every quadrant (1b) (13); in long strictures (> 1 cm) we perform an adaptation of the technique described by Broto (14):

- After placement of the guide wire the endoscope is removed.
- As a technical innovation a 15mm biliary extraction balloon is placed distal to the stenosis (this prevents CM migration and damage of healthy tissue) (2b).
- Using a double lumen biliary brush, CM (0.4 mg/ml) is carefully distributed over the stenosis (2c). The total amount of CM depends on the child’s weight: in children < 12.5 kg, 2.5 ml of CM are used; in patients > 12.5 kg, 5 ml are administered.
- Then a 8 mm balloon is inflated for 5 minutes in order to provide a closer adherence of CM to the esophageal wall (2d).
- Finally the esophagus is cleaned up with water and all the liquid is removed using the endoscope (2e).

In children younger than 2 years old (or under 10 kg) it is not possible to use a biliary brush if the stenosis is long. In this situation we only apply CM over the stenosis and extend it with a smaller brush.

The decision about the initial use of BS or CM was based on the previous evolution of the stenosis and its length. In short, for stenosis with no previous complications we started with CM. In patients with

an associated fistula, previous complications or long stenosis, we decided to use BS first.

RESULTS

We present the descriptive analysis of a prospective case series of RES in children who have been treated with alternative techniques such as BS and CM.

Case 1

A 6 year-old girl with severe esophagitis and gastritis after caustic ingestion. After one month the patient underwent dilation due to esophageal stricture, presenting a mild perforation which was treated conservatively. After 4 months the patient was sent again for esophageal and antral dilation. The gastric stricture was resolved (6 dilations), but the esophageal remained (9 dilations). After 10 months a “ELLA” BS (16 x 60 mm - customized) was placed.

The child reported intermittent thoracic pain for 4 months, with a good response to medical treatment. Moreover, she presented stenosis due to proximal hyperplasia (resolved after 3 dilations). Distal stenosis recurred after 4 months (as long as the stent was absorbed) with the need for more dilations. After 9 months we decided to use CM injection in this patient (2 sessions) with a good response. Eighteen months later this child still has a good oral intake.

Case 2

A 3 year-old boy presented with a VACTERL syndrome (esophageal and anorectal atresia) requiring multiple surgical reconstructions and a gastrostomy.

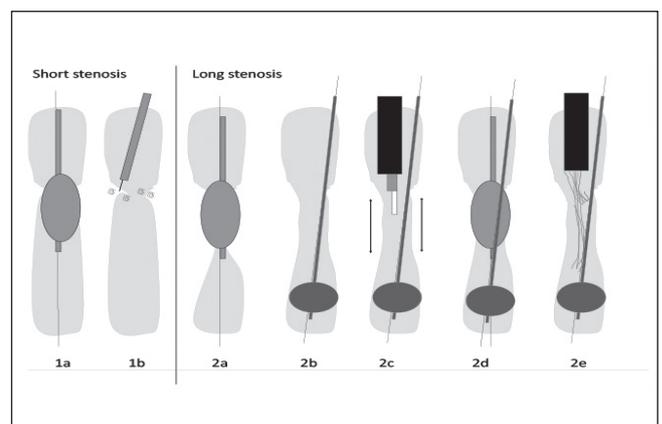


Fig. 1. Application technique of C-mitomycin.

There was a need for dilations due to stenosis of the esophageal-ileo-coloplasty, but these were discontinued as he presented with a cervicothoracic abscess. After one year, as dilations were unsatisfactory and the fistula remained, a “ELLA” BS (fully covered stent, 18 x 60 mm - customized) was placed. We faced great technical difficulties as the anatomy of proximal esophagus was severely altered, so we used the gastrostomy orifice to pull out the wire-guide. During follow-up the patient presented with a new cervical abscess (because the stent moved distally) and this was treated with replacement of the BS and antibiotics. After 8 months he presented with re-stenosis and CM was then used, with the placement of a second stent (uncovered). Finally, after absorption of this stent the fistula was resolved, but a complete esophageal stenosis occurred.

The time for complete stent absorption was 5 and 4 months respectively.

Case 3

An 8 month-old girl with type I long-gap esophageal atresia who required surgery when she was 2 months old. She presented with anastomotic stenosis and came for dilation on 3 occasions (every 4 weeks). During the third dilation, the wire passed to the mediastinum and the child remained in the intensive care unit as she developed mediastinitis.

At 7 months the patient was suffering recurrent aspiration pneumonia and a broncho-esophageal fistula was observed. After discussion in a multidisciplinary committee, at 8 months a partially covered “ELLA” BS (60 x 150 x 40 mm) was placed. A straight stent, with no cups, was customized so an appropriate introducer could be used as the patient was a small child of 5 kg.

Oral intake was restarted, but she went onto have respiratory complications again after 7 months. At this time the stent was totally absorbed and the stenosis was resolved, but a fistula was observed again, with the need for surgical repair: cervical esophagostomy and further esofagogastroplasty. After surgery she had a fair evolution from her respiratory and gastrointestinal symptoms.

Case 4

A 2 year-old girl with caustic stenosis required dilations every 4 weeks as she presented frequent restenosis. The stricture was 1 cm long and the lumen only 2 mm. After 7 dilations we decided to initiate CM. She received 2 sessions (the second one 40 days after the first) of 1.6 ml of CM injection followed by progressive dilations, complete resolution was observed. Caustic ingestion occurred 2.5 years ago, and the patient has not required any more dilations in the last 19 months.

Case 5

A 13 year-old boy with an operated type 1 atresia (*Sharli* esophagogastroplasty) presenting with chronic dysphagia due to fibrotic proximal esophagus and stricture of the anastomosis. After 2 unsatisfactory dilations (2 months between dilations), a standard uncovered “ELLA” BS (23 x 8 mm) was placed just under Kilian’s area as the proximal esophagus was very tortuous. Two weeks later he presented with severe throat pain, and an ulcer was observed under the proximal end of the stent. Perforation was discarded in a computed tomography and medical treatment with pain killers and enteral nutrition were started with a good evolution and wound healing after 2 weeks. The patient needed more dilations, with a higher frequency than previously, and after 6 of them CM was associated with no response. Finally definitive surgical treatment was decided one year after the placement of the BS.

In this patient reabsorption of the stent was observed at 5 months, with presence of a great amount of hyperplastic residual tissue and a need for a higher number of dilations.

Case 6

A 2 year-old girl was operated on when she was 2 months old due to a type 1 esophageal long-gap atresia. Two months later she presented with stenosis of the anastomosis and required dilations (14 sessions every 4-8 weeks as restenosis was observed). Moreover this patient was born with a severe tracheomalacia and this caused significant problems with nasotracheal intubation and extubation difficulties during all the dilation procedures.

The use of CM was decided after 14 dilations and the patient has shown a great response after only one session as no new stenosis and no symptoms have been observed after 19 months.

Series analysis

We present the results of 5 stent placements in 4 patients (2 stents were needed in one case). The stenosis was solved in 2 cases, we observed partial or temporary response in 3 cases, and there was clinical worsening in one patient (secondary to esophageal ulceration). Three stents were customized and the other 2 were the standard commercialized ones (with the smallest lumen: 23 x 8 x 23 mm). In 3 cases, uncovered stents were used, fully covered in one patient, and partially covered in the other one. In those patients with a fistula (2 cases), fully covered stents were effective but not the partially covered.

The observed complications with BS were: chest pain (2/5, 40%), severe hyperplasia (2/5, 40%), mild hyperplasia with no need for dilation (2/5, 40%), migration with

further replacement of the stent (1/5, 20%) and ulcer (1/5, 20%). All these complications were managed conservatively.

In the case of CM, 5 therapies were applied to 6 patients (2 sessions in 4 patients, and 1 session in the other one). Stenosis was permanently resolved in 3 cases (60%) and CM injection was not effective in the other 2 cases (40%). No adverse effects were registered. The average time spent during CM sessions was 28.7 minutes (16-75 minutes).

Globally, and considering both techniques, 4 out of 6 stenosis were resolved (66.6%), as well as 1 out of 2 fistula (50%). The fistula in which our technique was unsatisfactory required surgical treatment. The 2 cases of stenosis with no response were also sent for surgery. One of them presented complete esophageal closure and reparative surgery was necessary.

The follow-up of the patients after BS or CM was between 8 months and 2 years.

DISCUSSION

The concept of refractoriness has not been well defined because there are doubts over whether the limit to define it should be established at three to five dilations (1,15). A recurrent or refractory stenosis is defined as an anatomic restriction secondary to luminal scarring or fibrosis which conditions dysphagia with no endoscopic evidence of inflammatory process. This may happen if a diameter of 14 mm is not achieved in 5 sessions every 2 weeks (refractory) or if a satisfactory diameter is not maintained in 4 weeks after 14 mm were achieved (recurrent) (16). These criteria are not easy to apply in children so clinical, endoscopic and radiologic criteria should be considered in this population as we have done.

Dilations are aggressive procedures performed under deep sedation, with a high risk of complications (micro breaks of the esophageal wall that lead to scarring and fibrosis) and also with high rate of recurrences.

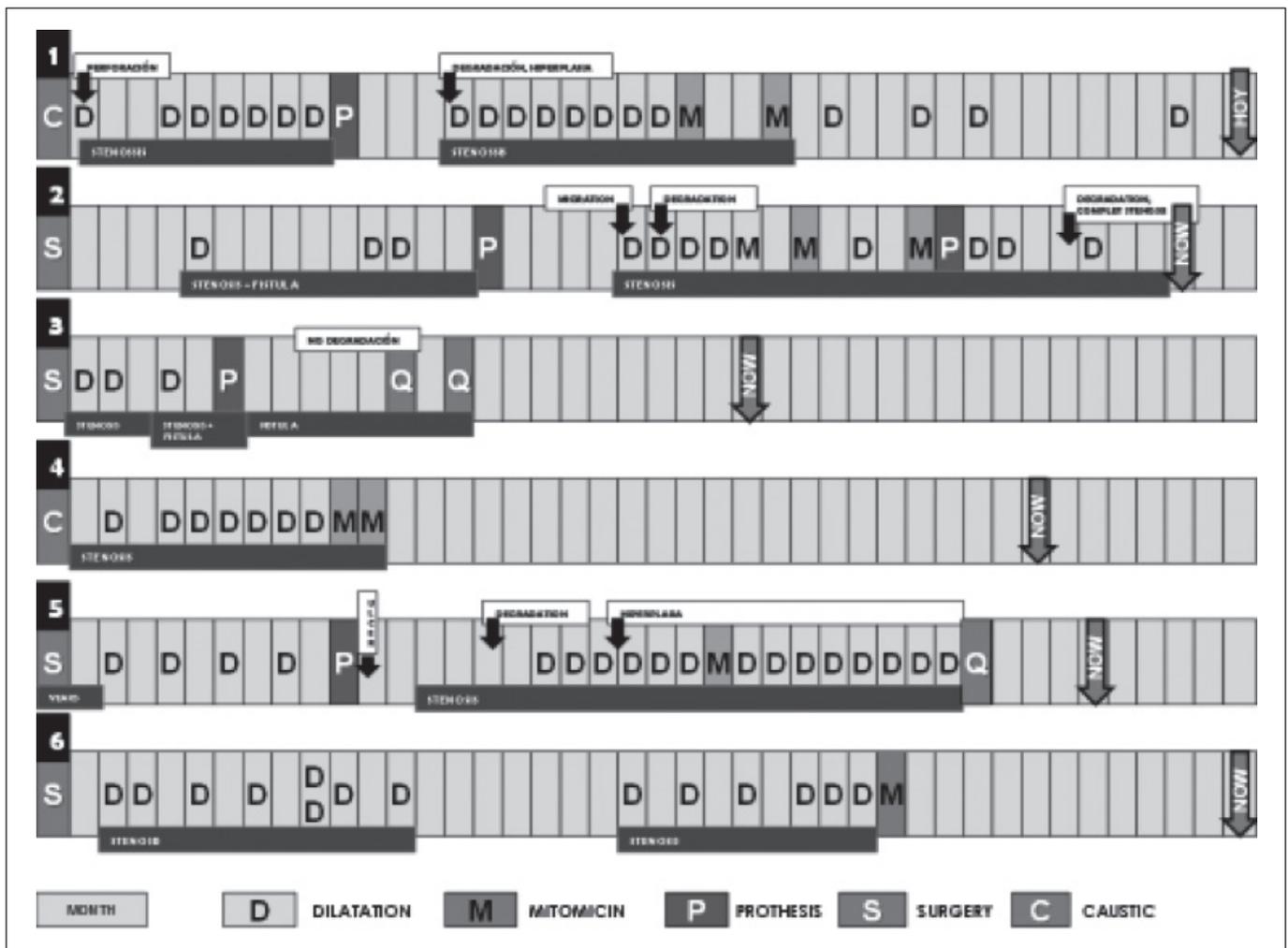


Fig. 2. Case series refractory esophageal stenosis.

One additional problem in our population was that two of the children had perforations, one of them after dilation, and the other one due to postoperative leaks which made any further management complicated as inner and outer fibrosis was produced. The covered stent resolved the fistula, even after a short migration time, but the stenosis remained, and this patient was also not a good candidate for reparative surgery. In case number 3, there was not enough contact between the dilated esophagus and the stent because this had no cups (the introducer was extremely small) and food was deposited between them. This could be the reason why the fistula was not resolved. We consider the presence of cups in the stents essential (especially if the esophagus is dilated due to long-time evolution stenosis) so these will remain placed and the risk of migration will be lower. In case number 5 there was not a good response probably because we used a standard and longer stent which produced an excavated and painful ulcer on the proximal esophagus.

BS have shown to be as safe and effective as in benign esophageal stenosis in adults (17). The main advantage of BS is that there is no need for removal. In adults, fully or partially covered stents are usually used in benign diseases, but these need to be removed after some time and in some circumstances more stents are needed after removal (18). Severe complications have been described when removing esophageal stents, such as perforations, bleeding, and problems related to sedation and the need for further endoscopic procedures. This is why we have worked with BS as our aim was to avoid the removal of the stents. Higher migration rate have not been reported with BS compared with other types of prosthesis. In one of our cases, the BS migrated but it was successfully replaced. In a German case series including 12 children the rate of migration was higher when using plastic stents than with silicone or nitinol stents (19).

One disadvantage of BS is early degradation promoted by acid. Moreover this degradation is more evident at high pressure points such as stenosis. We have observed degradations from 4 to 7 months, with no relation with the presence of anti-reflux surgery (the case of 7 months degradation had anti-reflux associated with anti-secretory agents).

One hundred and thirty-two cases of BS have been reported in esophageal benign and malignant disease (Table I), but there is only one case in a pediatric patient and this stent was ineffective because it caused excessive reflux and presented distal migration (7). There are two more cases of BS placed in children in Minsk, but these have not been published (information obtained from the manufacturer and also referred by Vandenplas) (7). In a Belgian series (abstract) including 24 BS in 20 patients, with no data with regard to esophageal stents or the ages of the patients, the authors report that after 6 months, in 52% of the cases there is a need for further procedures and 60% of the patients reported pain (31).

Higher rates of hyperplasia, including severe cases, have been reported when using these stents (24,32). We have ob-

Table I. Series analysis

| | Age of onset | Dilations prior to any procedure | Kind of stent | Effectiveness in stenosis | Effectiveness in fistula | Pain | Hyperplasia | Anti-reflux | Degradation | MC | Effectiveness MC | Follow |
|--------|--------------|----------------------------------|------------------------------|---------------------------|--------------------------|-----------|-------------|-------------|-------------|-----|------------------|--------|
| Case 1 | 6 | 7 | 6 x 14 NC | + | NA | ++ | ++ | No | 1-4 m | 2/C | +++ | 18 m |
| Case 2 | 3 | 3 | 6 x 18 CC 7 x 23/18/23 NC | + | +++ NA | - - | + + | Yes | 5 m 4 m | 2/I | - | 20 m |
| Case 3 | 0.5 | 3 | 6 x 15 PC | ++ | +/- | - | + | Yes | 7 m | NA | NA | 3 m |
| Case 4 | 2 | 7 | NA | - | NA | - | NA | No | NA | 2/I | +++ | 19 m |
| Case 5 | 12 | 4 | 8 x 23/18/23 NC | Worsening | NA | +++ Ulcer | ++ | Yes | 5 m | 2 | - | 21 m |
| Case 6 | 1 | 14 | NA | - | NA | - | NA | Yes | NA | 1/I | +++ | 24 m |

Table II. References on biodegradable stents

| <i>Author</i> | <i>Year</i> | <i>Journal</i> | <i>Stent</i> | <i>Number</i> | <i>Esophageal diseases</i> |
|--------------------|-------------|--------------------------|---------------------------|---------------|------------------------------|
| Goldin (20) | 1996 | GIE | Instent | 5 | Bening stenosis |
| Fry (21) | 1997 | GIE | Prototipo AB-Esophacoil | 1 | Bening stenosis |
| Tanaka (22) | 2006 | Digestion | Ultraflex ac. poliláctico | 2 | Bening stenosis |
| Saito (23) | 2007 | World J Gastroenterol | PPLA | 13 | Bening stenosis |
| Dhar (24) | 2009 | GIE | BD-SX-ELLA | 4 | Refractarial bening stenosis |
| Vandenplas (7) | 2009 | J Paediatr Gastr Nutr | BD-SX-ELLA | 1 | Caustic stenosis |
| Orive-Calzada (25) | 2009 | Endoscopy | BX-SX-ELLA | 1 | |
| Stivaros (26) | 2010 | Eur Radiol | BD-SX-ELLA | 2 | Bening/malignant stenosis |
| Repici (17) | 2010 | GIE | BD-SX-ELLA | 21 | Refractarial bening stenosis |
| Hirdes (18) | 2011 | Am J Gastr | BD-SX-ELLA | 26 | Refractarial bening stenosis |
| Van Boekel (27) | 2011 | Clin Gastroent Hepatol | BD-SX-ELLA | 18 | Refractarial bening stenosis |
| Cerna (28) | 2011 | Cardiovasc Interv Radiol | BD-SX-ELLA CC | 5 | Leaks and perforations |
| Van Hooft (29) | 2011 | GIE | BD-SX-ELLA | 10 | Anastomotic stenosis |
| Griffths (30) | 2012 | Surg Endosc | BD-SX-ELLA | 24 | Bening/malignant stenosis |

Table III. Comparative on mitomycin

| <i>Author</i> | <i>Journal</i> | <i>Year</i> | <i>Number of patients</i> | <i>Number of children</i> | <i>Data</i> | <i>Results</i> |
|----------------|---------------------------------|-------------|---------------------------|---------------------------|---|---|
| Rahbar (9) | Arch Otolaryngol Head Neck Surg | 2002 | 15 (1 esophageal) | 0 | Prospective | 67% mayor improvement 27% less improvement 7% no improvement |
| Afzal (10) | Lancet | 2002 | 2 | 2 | | 100% success |
| Kumar (40) | Indian Assoc Pediatr Surg | 2005 | 10 | 10 | Prospective | 100% success |
| Uhlen (42) | Endoscopy | 2006 | 4 | 4 | | 100% success |
| Olutoye (43) | J Pediatr Surg | 2006 | 1 | 1 | | 100% success |
| Gillespie (44) | Head Neck | 2007 | 20 | 0 | Adults with HNC and esophageal stenosis | 100% success |
| Zur (45) | Int J Pediatr Otorhinolaryngol | 2007 | 1 | 1 | | 100% success |
| Rosseneu (41) | J Pediatr Gastroenterol Nutr | 2007 | 16 | 16 | Multicenter | 62.5% mayor improvement 19% less improvement 19% no improvement |
| Fröhlich (46) | Z Gastroenterol | 2007 | 1 | 1 | | 100% success |
| Broto (14) | Cir Pediatr | 2007 | 3 | 2 | | 100% less success |
| Daher (47) | J Pediatr Surg | 2007 | 1 | 1 | | 100% success |
| Heran (39) | J Pediatr Surg | 2008 | 2 | 2 | Catheter by PEG | 50% success |
| Spier (13) | Gastrointest Endosc | 2009 | 1 | 0 | By injection | 100% success |
| Chung (48) | J Vasc Interv Radiol | 2010 | 1 | 0 | By endoscope | 100% success |
| Machida (49) | Endoscopy | 2012 | 5 | 0 | Adults, post-DES esophageal | 100% success |

mainly a surgical pathology. If there is no fistula, decisions will depend on the length of the stenosis: in long (< 1 cm) and fibrotic stenosis (as caustic) the use of covered stents will be the procedure of choice; in short stenosis the op-

tion will be CM sessions (up to 5 sessions). If there is no response, the alternative technique should be considered. Failure of both techniques means need for surgery, different stents, stricturotomies, etc. One more possibility is

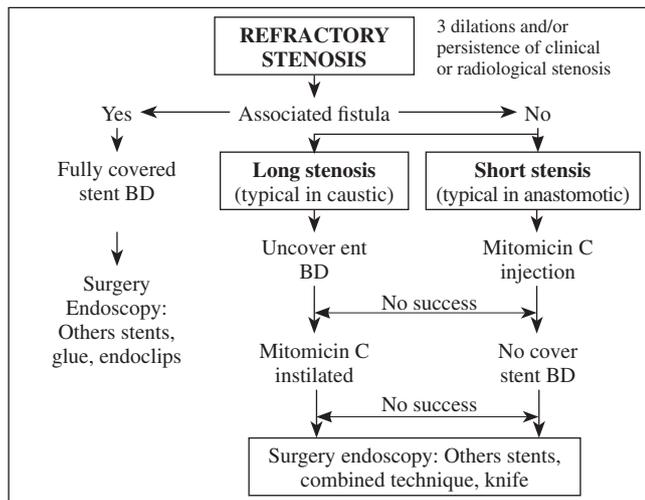


Fig. 3. Management of refractory esophageal stenosis in the pediatric age.

association of several techniques as stenting could help to maintain the effects of CM.

CONCLUSIONS

We think that the possibly of developing customized BS allows the design of appropriate stents for each individual case. BS do not need to be removed but side effects can be significant and a limiting factor. These stents have been effective when treating fistula, but this effectiveness has been more limited to the management of esophageal stenosis, which have presented recurrences but on the other hand have also needed dilations for longer time periods. Anti-reflux treatment must be intensified as this leads to longer stent maintenance and lower rates of side effects.

CM is an alternative for stenosis with no response to dilations and its use is associated with low rates of side effects.

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