

# Prevention of Esophageal Strictures After Endoscopic Submucosal Dissection: A Promising Therapy Using Carboxymethyl Cellulose Sheets

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## Abstract

**Background** Esophageal stricture is one of the serious adverse events following endoscopic submucosal dissection (ESD). However, optimum preventive techniques are still lacking.

**Aims** Our primary objective was to evaluate the incidence of post-ESD esophageal stricture with the application of carboxymethyl cellulose (CMC) sheets. Secondary objectives were to determine the number of sessions of endoscopic balloon dilatation (EBD) required to resolve post-ESD strictures and the incidence rate of peri-operative adverse events.

**Methods** This was a pilot, single-center, prospective study. Seven patients who had high risks of developing post-ESD esophageal stricture were enrolled into our study. CMC sheets were applied to the mucosal defects

immediately after the completion of ESD. Patients were monitored and reviewed after ESD to detect any adverse events.

**Results** The incidence rate of post-operative stricture was 57 % (4/7 patients). Among patients who required EBD, the number of sessions performed was  $2.8 \pm 2.2$ . No serious post-operative adverse events were reported.

**Conclusion** The use of CMC sheets appears to be a safe and effective prophylactic treatment for esophageal stricture following extensive ESD.

**Keywords** Carboxymethyl cellulose · Esophagus · Endoscopy · Dissection

## Introduction

### ESD for Treatment of Early Esophageal Neoplasm

The application of endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) techniques in the treatment of early esophageal neoplasm are well known. ESD has an advantage over EMR for removing tumors en bloc, regardless of their size [1, 2]. ESD also permits a thorough histological assessment of the specimens removed in one piece with tumor-free lateral or basal margins. This will avoid any residual disease and local recurrence [2, 3].

### Complications of ESD

Several studies have reported multiple substantial risk of ESD-related complications, which includes potentially life-threatening perforation and post-procedural stenosis [4, 5]. The occurrence of stricture can cause dysphagia and may

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severely impair patients' quality of life (QOL). The exact incidence rate of post-ESD esophageal stricture remains obscure. However, reports show that cervical location, a tumor size greater than 3/4 of the esophageal circumference, and a longitudinal tumor diameter of more than 40 mm are associated with higher risk of post-procedural stricture [6]. In particular, the incidence rate of stricture is known to significantly increase in proportion to the overall size of the target lesion and the circumferential size of the post-ESD mucosal defect [7].

### Treatment and Prevention of Post-ESD Esophageal Stricture

Multiple strategies and methods had been proposed and investigated for prevention of post-ESD esophageal stricture [8]. Although endoscopic balloon dilatation (EBD) has been a treatment of choice in the setting of benign esophageal strictures, it still carries the risk of perforation [9]. Currently, multiple sessional EBD is recommended for prevention of post-ESD esophageal stricture [10]. However, this involves high cost with additional risk of perforations.

There is also a role of an anti-inflammatory approach to prevent post-ESD esophageal stricture. Some authors have advocated the use of endoscopic intralesional injections of steroids or systemic steroids. However, these carry the risks of delayed wound healing, ulcer formation and metabolic disturbance (hyperglycemia and osteoporosis) [11, 12].

Other agents includes *N*-acetylcysteine and mitomycin C with their antifibrotic effects but preliminary data showing their efficacy are still lacking [13–15]. Sakaguchi et al. [16] also reported a small pilot study demonstrating the efficacy of polyglycolic acid (PGA) sheets with fibrin glue to prevent post-ESD stricture.

In general, there is still a need to explore a better and efficient way to prevent post-ESD esophageal stricture.

### Material Used in the Trial and Its Rationale

Bioresorbable membrane consisting of hyaluronic acid and carboxymethyl cellulose (CMC) has gained regulatory approval for clinical use in both general and gynecological surgery following demonstration of efficacy and safety in reducing adhesions [17–19].

TiSTAT S-100 (CMC hemostatic sheet, 5 cm × 8 cm; by Beijing Textile Science Research Institute, Beijing; China food and drug administration number: 3640430) (Fig. 1a, b) is a biodegradable suture material and its potential as a method to reinforce the suture and minimize scar contracture in medical fields has been demonstrated [20–22]. The main mechanics for inhibition of scar

formation includes: (1) formation of a bio-physical barrier on the wound, (2) rapid clotting effect, via forming an adhesive plug compressing the vessels, activating clotting factors and accumulating platelets, (3) inhibition of fibroblast and human fibrinogen, (4) production of hyaluronic acid, and (5) promotion of epithelial cell growth [23].

TiSTAT S-100 achieved Food and Drug Administration (FDA) approval in 2007 and obtained the European CE mark in 2009. It consists of 100 % natural, plant-derived cellulose and can be completely absorbed via hydrolysis within 7–14 days. It has a high degree of biocompatibility with no known reports of rejection. However, there are no reports evaluating the efficacy of this material in preventing post-ESD stricture.

### Patients and Methods

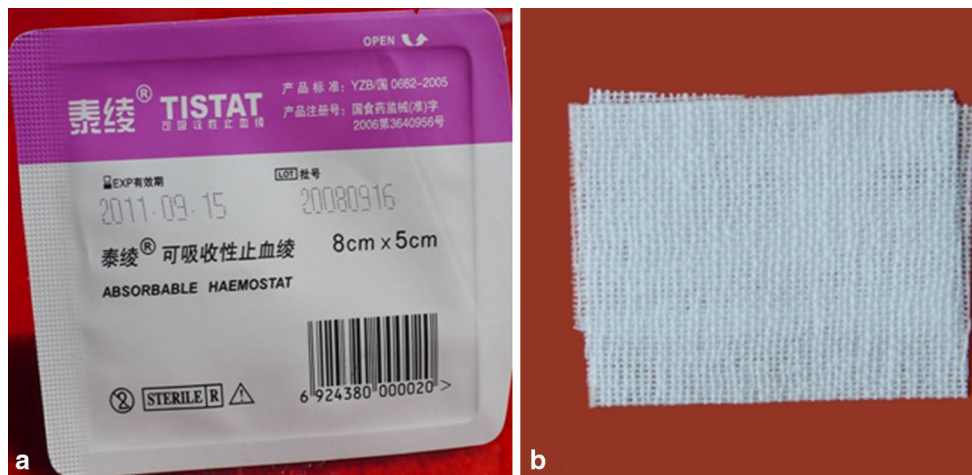
This was a pilot, single-center, prospective study. Application of CMC sheets after ESD was begun only after approval from the Research Ethics Committee of the Second Military University, Changhai Hospital.

Between April and September 2015, we enrolled subjects into our study who were referred for further treatment of superficial esophageal cancer. Only patients with an elevated baseline risk for developing post-ESD esophageal stricture were recruited. They were selected if they met one or more of the following criteria: cervical location (the area extending from the pharyngoesophageal junction to the suprasternal notch); a tumor size greater than 1/2 of the esophageal circumference (the size of mucosal defect greater than 3/4 of esophageal circumference); or a longitudinal tumor diameter of more than 40 mm (Fig. 2). Contraindications to the use of CMC sheets are almost non-existent. This includes patients who have anaphylaxis to components of CMC. We also excluded patients who had contraindications for ESD, such as: suspected invasion into or beyond the deep submucosal layer after diagnostic work-up ( $\geq$ T2sm carcinoma); uncooperative patients; patients who cannot provide informed consent; severe or uncontrollable coagulopathy; and patients with substantial comorbidity and limited life-expectancy.

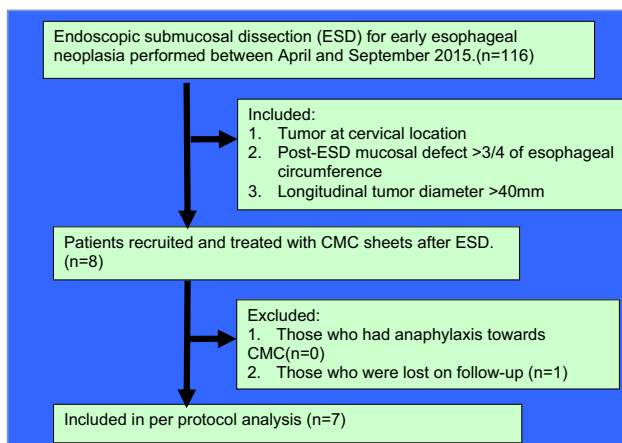
All subjects submitted written forms of informed consent for the application of CMC sheets in addition to giving consent for esophageal ESD according to normal clinical practice.

### Endoscopic Submucosal Dissection Procedure

A single-channel upper gastrointestinal endoscope (GIF Q260J; Olympus) with a transparent cap (D-201-10704; Olympus) attached to its tip and a high frequency generator



**Fig. 1** Carboxymethyl cellulose sheets used as a study material



**Fig. 2** Flow diagram of the recruited subjects

VIO 300D (ERBE; Elektromedizin, Tübingen, Germany) were used during ESD. All ESDs were performed at Changhai Hospital according to methods described in a previous study [24]. In brief, close observation of the targeted esophageal lesions was done using narrow band imaging (NBI) and chromoendoscopy with 2 % Lugol’s solution staining (Fig. 3a), followed by marking of the margin of the lesion using the Dual Knife (KD-630L; Olympus). The lesion was injected submucosally using a solution of 250 ml glycerin fructose/sodium chloride, 2 mg adrenaline, and 2 ml indigo carmine to elevate the lesion. The lesion was then incised and dissected using the Dual Knife/Insulated-tip Knife-2 (KD-611 L; Olympus) until ESD was completed (Fig. 3b).

**CMC Sheet Deployment**

Immediately after ESD had been completed, CMC sheets were prepared by cutting into multiple small pieces (each

measuring approximately 10 × 20 mm) (Fig. 3c) (Video). The transparent cap was switched to a cap with a longer distal tip (MH-463/MH-594; Olympus) in order to accommodate the sheet. After the CMC sheet had been grasped with endoscopic forceps, it was pulled into the cap (Fig. 3d) which was then inserted orally to the site of the post-ESD defect. The sheet was released onto the surface of post-ESD mucosal defect by releasing the forceps (Fig. 3e). The sheet adhered to the mucosal defect once it was exposed to the moist surface of the defect. This process was repeated until the defect was fully covered by the sheets (Fig. 3f).

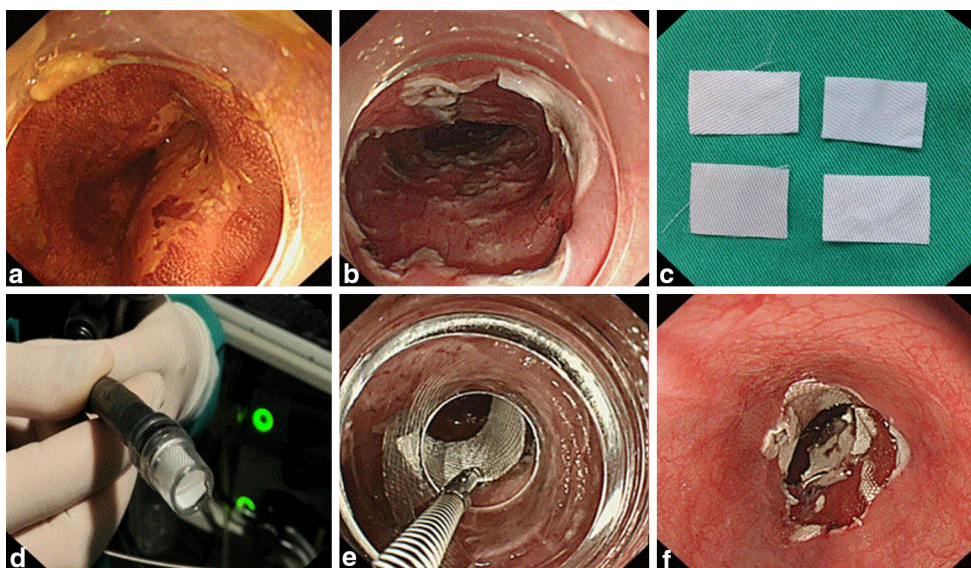
**Peri-operative Management**

On the day before ESD, patients were kept nil by mouth after their evening meal, and given intravenous fluid. Following ESD, Pantoprazole was given intravenously (40 mg twice a day) for the first 48 h. Oral pantoprazole (40 mg daily) was prescribed for 1 month after discharge. Routine laboratory investigations along with chest and abdominal radiographs were performed. Clear fluids and then soft diets were introduced in a gradual manner. Scheduled post-operative endoscopies were performed on days 7 and 28 after ESD, or at any time if patients developed dysphagia. If the patients did not show up for post-operative endoscopies, phone calls were made to evaluate patients’ symptoms.

**Definition of Post-operative Stricture**

Post-operative stricture was determined by the presence of stenosis of the esophageal lumen in which a 9.8-mm-diameter upper gastrointestinal endoscope (GIF Q240 or GIF H260; Olympus) was unable to pass through it or the

**Fig. 3** The management of a study subject. **a** An extensive early esophageal neoplasm viewed using chromoendoscopy and iodine staining. **b** A full circumferential mucosal defect immediately after endoscopic submucosal dissection (ESD). **c** Preparation of carboxymethyl cellulose (CMC) sheets. **d** CMC sheet pulled into the cap with a biopsy forcep. **e** Application of CMC sheets. **f** Defect appearance immediately after CMC sheets placement



presence of dysphagia. The day of stricture occurrence was defined as the day when the stricture was endoscopically confirmed.

### Endoscopic Balloon Dilation

In patients who developed an esophageal stricture, EBD was carried out using an esophageal balloon dilation catheter (Eclipse™ TTC wire-guided balloon dilator 12 mm/14 mm/16 mm; Cook Medical, USA) or Savary-Gilliard wire-guided polyvinyl dilators. EBD was repeated as required until the esophageal stenosis widened and it was possible to pass the endoscope through the esophageal lumen. Patients continued their endoscopic follow-up for a minimum of 4 weeks when the stricture had subsided.

### Follow-Up Endpoints

The primary objective of this study was to evaluate the incidence of post-ESD esophageal stricture with the application of CMC sheet. Secondary objectives were the number of sessions of EBD required to resolve any subsequent strictures. We also explored the feasibility and timing of deploying CMC sheet. Lastly, we evaluated the incidence rate of post-operative adverse events that were potentially attributable to the procedure and study material.

### Results

Seven patients fulfilled the inclusion criteria and were recruited into our study between April and September 2015. Patient baseline characteristics are summarized in Table 1.

All our patients presented with esophageal lesion(s) and left with a mucosal defect comprising 3/4 or more of esophageal circumference after ESD. En bloc esophageal ESD with tumor-free vertical and lateral margins were performed successfully in all subjects. There were no major intra-/post-operative adverse events, such as massive/delayed bleeding, signs of perforation, anaphylactic reaction, severe chest pain, cardiovascular events or death. Three patients developed low-grade fever while hospitalized after ESD. They were treated conservatively and discharged when well.

CMC sheets were all deployed successfully in all cases with a mean time of  $12.6 \pm 4.0$  min (Table 2). Each patient required only one CMC sheet, which was cut and divided into 8–10 smaller pieces to facilitate deployment. Three patients had an endoscopically visible residual CMC matrix after 1 week and they did not require any EBD sessions during follow-up. The overall incidence rate of post-operative stricture was 57 % (4/7 patients). Among patients who required EBD, the number of sessions performed was  $2.8 \pm 2.2$ . No post-operative adverse events were reported.

### Discussion

Post-ESD esophageal stricture is a major concern among patients who undergo near or full circumferential esophageal ESD. Beside prophylactic EBD sessions, current popular practice to prevent post-ESD esophageal stricture includes systemic and local injection of corticosteroids [8, 11, 12]. The incidence of esophageal stenosis following ESD is reported to be 75–92 % [13]. This incidence is reduced with prophylactic EBD sessions (59 %), intralesional injections

**Table 1** Baseline characteristics of seven subjects who underwent ESD for esophageal tumors in our study

Patient sex (men:women)	3:4
Patient age, mean $\pm$ SD (years)	62.4 $\pm$ 4.7
Tumor location (%)	
Cervical	0 (0)
Upper thoracic	2 (28.6)
Mid-thoracic	5 (71.4)
Lower thoracic	0 (0)
Tumor depth (%)	
Confined to the epithelium	0 (0)
Confined to the lamina propria mucosa	0 (0)
Confined to the muscularis mucosa	6 (85.7)
Sm1 (invading the submucosa $\leq$ 200 $\mu$ m)	1 (14.3)
Sm2 (invading the submucosa $>$ 200 $\mu$ m)	0 (0)
Tumor size, mean $\pm$ SD (mm)	44.7 $\pm$ 14.4 (7 patients)
Size of mucosal defect post-ESD (%)	
At least 3/4 esophageal circumference	5 (71.4)
Full esophageal circumference	2 (28.6)

*SD* standard deviation, *Sm* submucosa, *ESD* endoscopic submucosal dissection

**Table 2** Details of ESD and CMC sheet application procedures, adverse events, and their subsequent management

Procedure details	
Total ESD time, mean $\pm$ SD (min)	108.2 $\pm$ 47.3
Application time for CMC sheet, mean $\pm$ SD (min)	12.6 $\pm$ 4.0
Number of CMC sheet used for each patient, mean	1
Number of patients with visible CMC matrix after 1 week, <i>n</i> (%)	3 (42.9)
Adverse events	
Patients developing a stricture after ESD, <i>n</i> (%)	4 (57.1)
Time to stricture occurrence, mean $\pm$ SD (days)	28.0 $\pm$ 3.5
Sessions of EBD required, mean $\pm$ SD, <i>n</i>	2.8 $\pm$ 2.2
Major intra/post-operative adverse events, <i>n</i>	0

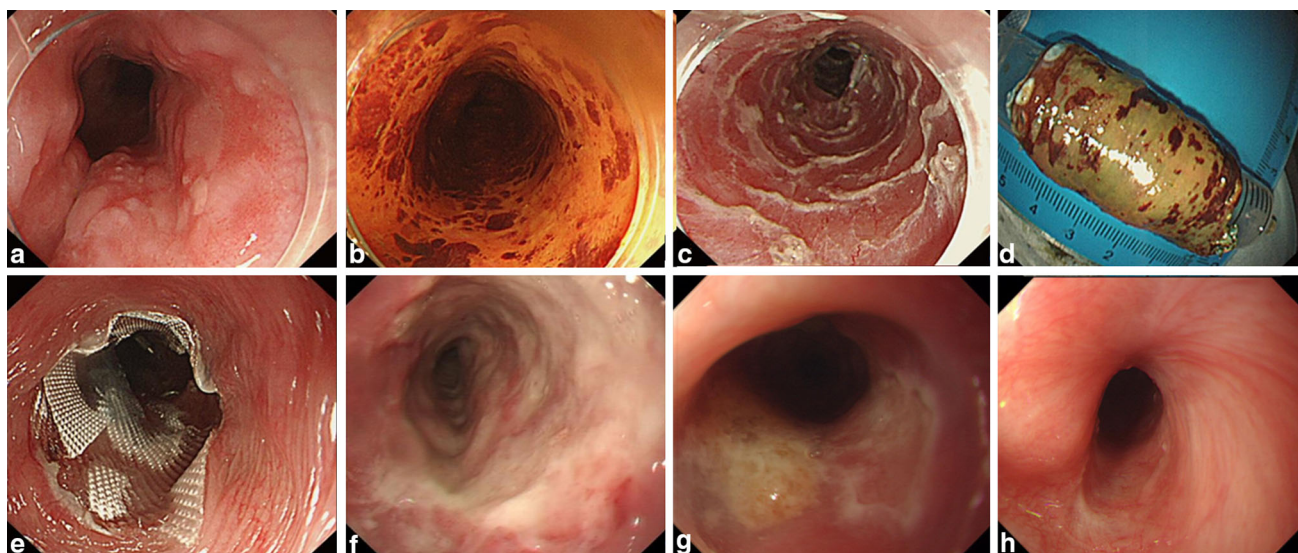
*SD* standard deviation, *ESD* endoscopic submucosal dissection, *CMC* carboxymethyl cellulose, *EBD* endoscopic balloon dilatation

of steroids (19 %) and systemic steroid (5.3 %) [11, 12, 14]. However, the use of steroids has been linked to certain morbidity such as systemic infection and post-operative perforation. There were also limited data showing the efficacy of anti-fibrotic agents such as N-acetylcysteine, mitomycin-C and PGA sheets [13–16]. Some clinical trials explored the potential of newer therapies such as scaffold-based and cell-based treatments, but their clinical evidence was still lacking [25–27]. Another recent clinical study also demonstrated the efficacy of viscous budesonide slurry in reducing post-esophageal stricture (37 % as compared to control group, 13.8 %,  $p < 0.05$ ) among patients undergoing complete endoscopic resection for dysplastic Barrett's esophagus and early esophageal adenocarcinoma [28].

Our study revealed that CMC sheet application was effective in reducing the incidence of post-ESD esophageal stricture. This was evidenced by the fact that the

total number of EBD required was reduced among patients who had high risks of developing a stricture. Our results (mean EBD post-esophageal ESD was 2.8) were fairly comparable with other studies using oral administration of corticosteroids (mean EBD post-ESD was reported to be 1.7) and focal triamcinolone injection (mean EBDs required were reported as 1.7 and 6.1) [12, 14, 29]. The best result thus far was the use of PGA sheet which reported a mean EBD of 0.8 [16]. However, all the clinical trials involved a small number of subjects, ranging from 8 to 40.

The application of CMC sheet is technically feasible and easy, requiring a single operator. The average amount of time to apply is fairly short, mean 12.6  $\pm$  4.0 min. This seemed acceptable in our clinical practice considering that multiple extra sessions of EBD would consume more time and cost (previous reports revealed mean EBD ranging



**Fig. 4** Evolution of mucosal defect post-ESD and CMC application from a study patient. **a** Suspicious mucosal erosions under bright light endoscopic view. **b** An extensive early esophageal neoplasm revealed after using chromoendoscopy and iodine staining. **c** Full circumferential esophageal mucosal defect immediately after ESD. **d** Esophageal neoplasm was removed en bloc. **e** Mucosal defect

immediately after the application of CMC sheets. **f** Mucosal defect 1 week post-ESD showing residual CMC matrix. **g** Mucosal defect 4 weeks post-ESD showing satisfactory wound healing with minimal scar tissue and stricture formation. **h** Mucosal defect was completely healed 2 months post-ESD with minimal narrowing

from 6 to 32 among cases without any medical intervention after ESD) [12, 14, 29].

CMC sheet demonstrated rapid dissolution and adherence onto the mucosal defect (within 1–2 min) after exposure to its moist surface, thus avoiding the need to use extra material (such as clips or fibrin glue) to secure sheet attachment. Once the sheet was dissolved, it formed a sturdy protective barrier which sealed the mucosal defect firmly even though the defect surface was uneven. Unlike the skin, the esophageal epithelial surface is constantly exposed to food, saliva and gastric juice, which may hinder further healing [8]. Thus, the barrier isolates the mucosal defect from those negative impacts for at least 1 week after ESD. However, not all of our patients had endoscopically visible CMC matrix after 1 week. In our opinion, the passage of food boluses and esophageal peristalsis would have certain detrimental effects on the sheet adherence. Another advantage was the transparency of matrix formation once the sheet was exposed to the mucosal defect. This did not obscure the view of the underlying mucosal defect if requiring further endoscopic intervention. It then takes approximately 7–14 days for complete absorption of the sheet via hydrolysis. As mentioned before, previous clinical trials have shown the superior capability of CMC sheet in wound healing and scar inhibition [19–23]. Our study was able to demonstrate the efficacy of the sheet by reviewing the scar formation of our patients in subsequent post-ESD endoscopies (Fig. 4a–h).

There were a few limitations in our study. First of all, the number of subjects may be too small to produce any significant result and it was not compared to a control group. Thus, a randomized controlled study involving a larger number of patients and the assignment of a control group will be desirable to demonstrate the efficacy of CMC sheet. Secondly, the effect and mechanism of CMC sheet in preventing post-ESD esophageal stricture are still not clear, although current data show the benefit of its application in other organs in reducing scar formation and enhancing the healing process [20–23]. Furthermore, the safety profile of CMC sheet for its use in ESD still requires thorough exploration, although no major adverse events were reported in our study.

## Conclusion

In summary, the use of CMC sheet shows great potential for reducing the incidence of esophageal stricture following ESD and also the number of sessions of EBD required post-ESD. Considering the safety profile relating to other previous methods of stricture prevention, this safe, cheap and simple technique may have great clinical value.

## Compliance with ethical standards

**Conflict of interest** All authors declare no financial relationships with a commercial entity producing health care-related products and/or services relevant to this article.

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