New developments in endoscopic ultrasound-guided therapies

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ABSTRACT
Endoscopic ultrasound (EUS) has opened new horizons in minimally invasive therapies for diverse gastrointestinal pathologies. Digestive Disease Weak 2015 held in Washington, DC., USA featured exciting research articles on EUS-guided therapeutic procedures. EUS-guided biliary drainage has been attempted and described for many years. There seems to be a lot of interest among various international groups to compare this technique with other alternatives in terms of efficacy and safety. Similarly, EUS-guided pancreatic drainage of cysts and fluid collections continues to evolve with new stents and devices being developed specifically for deployment under endosonographic guidance. EUS-guided ablation of cystic pancreatic tumors is innovative but not always effective. Combining alcohol ablation with injecting chemotherapeutic agents may improve long-term results regarding efficacy. Similarly, for solid pancreatic tumors there appears to be ongoing interest and continuing efforts in injecting different chemotherapeutic or ablative agents, delivering fiducials for radiation guidance and even attempting ablation with radiofrequency. Gastric variceal treatment and EUS-guided anastomoses also continue to be investigated. This review article is focused on the recent developments in EUS-guided therapies presented at Digestive Disease Week (DDW) 2015.

Key words: Ablation, biliary drainage, chemoablation, cystic pancreatic tumors, Digestive Disease Week (DDW), endoscopic ultrasound (EUS), EUS-guided biliary drainage, fiducials, gastric varices (GVs), pancreatitis, pancreatic adenocarcinoma, pancreatic cysts, pancreatic neuroendocrine tumor (PNET), pancreatic pseudocyst, pancreatic tumors, pseudocyst, radiofrequency, walled-off necrosis

INTRODUCTION
Endoscopic ultrasound (EUS) has opened new horizons in minimally invasive therapies for diverse gastrointestinal pathologies. digestive disease week 2015 held in Washington, DC., USA featured exciting research articles on EUS-guided therapeutic procedures. This review article is focused on the recent developments in EUS-guided therapies presented at Digestive Disease Week (DDW) 2015. This is an open access article distributed under the terms of the creative commons attribution-noncommercial-sharealike 3.0 license, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

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**ENDOSCOPIC ULTRASOUND-GUIDED BILIARY DRAINAGE**

EUS-guided biliary drainage (EUS-BD) has emerged as an alternative therapy for biliary duct decompression in cases of endoscopic retrograde cholangiopancreatography (ERCP) failure. DDW 2015 featured impressive progress in the research on EUS-BD in all the known approaches including the antegrade transpapillary (AT), EUS rendezvous procedure (RV), and direct transluminal hepaticogastrostomy (HG) and choledochoduodenostomy (CD). These research presentations were focused on assessing the efficacy and safety of EUS-BD and comparing it with the traditional percutaneous transhepatic biliary drainage (PTBD). Authors reported results in terms of the success and complication rates. Technical success was defined as endoscopic evidence of biliary drainage across the stent and clinical success was defined as a >50% reduction in serum bilirubin in 2-4 weeks of the treatment. The results of these studies are summarized in Table 1.[2-12]

In these studies [Table 1], common indications for EUS-BD were: Obscured ampulla by invasive cancer or enteral stent, surgically altered anatomy, and failed deep biliary cannulation. The most commonly reported adverse events during EUS-BD included postprocedure bile leak, subcapsular hematoma formation, peritonitis, cholangitis, and cholecystitis. In a prospective multicenter study by Nakai et al,[5] the most common complications within 48 h of the procedure included pain (9%), cholecystitis (3%), and cholangitis (3%). Late (>48 h) complications included cholangitis (18%) and cholecystitis (6%). Khashab et al[4] reported median stent patency duration of 536 days (95% CI 383-689), which was significantly more as compared to 8.9 months (median time to stent dysfunction) as reported by Nakai et al[5].

In a retrospective analysis on EUS-BD with antegrade transpapillary (AT) technique, Dhir et al[8] reported that the rate of postprocedure pancreatitis was equivalent to those reported to ERCP and could be due to papillary manipulation during ante-grade stent placement.

In a multicenter randomized phase II study, Giovannini et al[10] divided the patients into two arms. Arm A patients underwent PTBD and arm B patients

### Table 1. Results of studies performed on EUS-BD at DDW2015

| Reference | Single center/Multicenter | Study design | Number of patients (n) | Technical success (%) | Clinical success (%) | Adverse events (%) |
|-----------|---------------------------|--------------|------------------------|-----------------------|---------------------|-------------------|
| Weillert[2] | Single | Prospective observational | n=25 [AT (8), HG (10), CD (1), RV (5)] | 96 | 92 | 12 |
| Khashab et al.[3] | Single | Prospective observational | n=46 [AT (3), CD(24), HG (12), HJ (1), RV (6)] | 86.90 | 94.40 | 23.90 |
| Khashab et al.[4] | Multi | Prospective observational | n=95 [AT (12), HG (15), CD (53), HD (4), RV (11)] | 95.70 | 95 | 10.50 |
| Nakai et al.[5] | Multi | Prospective observational | n=34 [CD (34)] | 97 | 100 | Early-3-9 Late- 6-18 |
| Iwashita et al.[6] | Multi | Prospective Observational | n=20 [RV (20)] | 80 | 100 | 15 |
| Banerjee et al.[7] | Single | Retrospective | n=26 [HG (5), CD (14), RV (7)] | 88.40 | 94.40 | 15.30 |
| Dhir et al.[8] | Multi | Retrospective | n=56 [AT (56)] | 96.64 | — | 14.28 |
| Senturk et al.[9] | Single | Retrospective | n=34 [HG (19), CD (6), RV (9)] | 76.50 | — | 44.10 |
| Studies comparing EUS-BD vs. PTBD | | | | | | |
| Giovannini et al.[10] | Multi | Prospective trial | EUS-BD (20) | 95 | — | 35 |
| Teoh et al.[11] | Multi | Retrospective | RV (64) | 94 | — | 17.20 |
| Bill et al.[12] | Single | Retrospective | RV (25) | 86 | — | 23.40 |
| | | | PTBD (25) | 76 | — | Early: 16, Delayed: 12 |
| | | | | 100 | — | Early: 12, Delayed: 25 |

AT: Antegrade transpapillary, CD: Choledochoduodenostomy, EUS-BD: Endoscopic ultrasound-guided biliary drainage, HG: Hepaticogastrostomy, PTBD: Percutaneous transhepatic biliary drainage, RV: Rendezvous procedure, HJ: Hepatojejunostomy, HD: hepatoduodenostomy
underwent EUS-BD. Hospitalization time was significantly less in EUS-BD arm (6 days, range: 3-30 days) compared to PTBD arm (12 days, range: 2-2 days), \( P = 0.02 \). They reported that complication rate was higher in PTBD arm (60%) \( \text{vs.} \) the EUS-BD arm (35%); so the authors decided to stop randomization and continue to include patients only in the EUS-BD arm further in the study.

While retrospectively comparing the results of patients undergoing PTBD versus EUS-BD using RV technique, Bill et al.\(^{[15]}\) reported significantly more requirement of repeat biliary interventions (15/25 \( \text{vs.} \) 4/25, \( P = 0.001 \)) and hospital stay (median 5 days \( \text{vs.} \) 1 day, \( P = 0.02 \)) in the PTBD arm \( \text{vs.} \) EUS-BD arm.

Park et al.\(^{[13]}\) reported the results of a trial using a 7F stent introducer and a modified hybrid metal stent, which functioned as a dedicated device for one-step EUS-guided biliary drainage (DEUS group), and compared the results with the other group which used fully covered metal stents with antimigration properties (FC group). The technical and clinical success were identical in both the groups (DEUS vs. FC). However, the procedural time (10 ± 4.8 min \( \text{vs.} \) 16.8 ± 10.8 min, \( P = 0.035 \)), the rate of additional fistula dilatation (13% \( \text{vs.} \) 100%, \( P < 0.001 \)) and adverse effects rate (0% \( \text{vs.} \) 33%, \( P = 0.024 \)) were significantly more in the FC group. Thus, authors concluded that EUS-BD using this dedicated device has less risk of procedure adverse effects.

Dollhopf et al.\(^{[14]}\) performed a retrospective analysis of EUS-BD procedure using a novel lumen-apposing, self-expanding metallic stent incorporated in an electrocautery enhanced delivery system that allowed direct puncture of the target, and insertion and release in a one-step-fashion. Results of using one-step fluoroless EUS-BD and gallbladder drainage using Hot-Axis\(^{\text{TM}}\) were impressive (technical success in 94.7% and clinical success in 88.9% of the cases).

Nakai et al.\(^{[15]}\) reported the results of a retrospective analysis on EUS-BD using a temporary nasobiliary (NB) tube in patients with prior trans papillary or transbilioenteric anastomosis (BEA) biliary stenting. They performed this procedure in 16 patients and none developed peritonitis. The authors concluded that temporary biliary drainage reduces bacterial load in bile as well as facilitates bile duct puncture by contrast injection and thus, reduces the risk of peritonitis.

Luna et al.\(^{[16]}\) performed a retrospective review on patients who underwent EUS-BD and divided them into two groups. Group 1 had coexisting ascites whereas the group 2 did not. They reported that the risk of infection was the same in both the groups and therefore, suggested that presence of ascites was not a contraindication in patients undergoing EUS-BD.

The data reported so far indicate that EUS-BD was required in 5-10% of the patients with failed ERCP; however, Holt et al.\(^{[17]}\) questioned this number by performing an interesting analysis in a tertiary center where both standard and advanced cannulation techniques were used in ERCP. At their center, physicians performing ERCPs failed to cannulate only 0.6% of the patients with native papilla and these cases were managed by EUS-BD or PTBD. They also reported that the cost of successful outpatient ERCP was significantly less than patient admission for EUS-BD (\( \$4170 \text{ vs.} \$17,469, \ P < 0.00001 \)) or PTBD (\( \$4170 \text{ vs.} \$37,129, \ P < 0.00001 \)). From their experience, the authors implied that EUS-BD was required in less than 1% patients with native papilla.

Khan et al.\(^{[18]}\) performed a meta-analysis comparing the safety and efficacy of EUS-BD \( \text{vs.} \) PTBD and included three prior studies for their analysis. They reported that both techniques were equally efficacious (risk difference (RD)-0.17\([-0.43, \ 0.10]\), \( P = 0.22, \ I^2 = 90\% \)); however, EUS-BD has a better safety profile compared to PTBD [odds ratio (OR) 0.17(0.05, 0.62), \( P = 0.007, \ I^2 = 39\% \)].

ENDOSCOPIC ULTRASOUND-GUIDED DRAINAGE OF Pancreatic fluid collections and pancreatic pseudocysts

Recent data have shown that EUS-guided drainage of pancreatic fluid collections (PFCs), pancreatic pseudocysts (PPs), walled-off necrosis (WON), and pancreatic abscess are a safe and efficacious alternative to surgical debridement and necrosectomy.\(^{[19]}\) Table 2 summarizes the results of the studies performed on EUS-guided pancreatic fluid drainage featured at DDW 15.\(^{[20-23]}\) In these studies, technical and clinical successes were defined by successful placement of the draining stents and complete resolution of the PFC or PP, respectively. The commonly reported adverse effects were stent maldeployment, bleeding, pneumoperitoneum, and access site infection. Results of these studies have been summarized in Table 2.
Dhir et al.\cite{20} prospectively evaluated the efficacy and safety of EUS-guided pseudocyst drainage with the early removal of fully covered self-expandable metal stents with pancreatic duct stenting in selected patients. They performed magnetic resonance cholangiopancreatography (MRCP) at 3 weeks of follow-up and reported clinical success in 95% of the patients but ductal leak in 7.1% and duct disconnection in 4.7% of the patients. ERCP with stenting was successfully performed in patients who had ductal leak. They performed multivariate analysis, which showed that pancreatic ductal leak or disconnection was an independent factor affecting pseudocyst resolution at 1 month (\(P = 0.0001\)). Overall, the technique of pancreatic stenting with short-term placement of metallic stents is safe and efficacious for the management of PP.

In a retrospective single center review of patients undergoing EUS-guided pseudocyst drainage, El Zein et al.\cite{23} reported a mean procedural time of 61 (12-145) min. Among the patients in whom transgastric stents were used, successful removal was reported 42 (20-90) days after the index procedure.

In a comparative retrospective study, Ardengh et al.\cite{24} reported that EUS-guided necrosectomy for WON was associated with significantly less acute adverse effects (37% vs. 71%, \(P < 0.01\)) compared to surgical necrosectomy. The rates of late adverse effects (bowel and biliary obstructions) and requirement of repeat procedure were also significantly less in cases of EUS-guided necrosectomy compared to surgical necrosectomy (0% vs. 21%, \(P = 0.04\); 0% vs. 27%, \(P = 0.01\) and 8% vs. 36%, \(P = 0.02\)). The mean follow-up period in this study was 493 days and there was no statistically significant difference in patients of both arms in terms of long-term sequelae including pseudocyst formation, cases of diabetes onset, and the need for pancreatic enzymes.

These results indicate that EUS-guided drainage is a safe and efficacious technique for the drainage of pancreatic fluid collections, pancreatic pseudocysts, WON, and pancreatic abscess.

**ENDOSCOPIC ULTRASOUND-GUIDED ABLATION OF CYSTIC AND SOLID PANCREATIC TUMORS**

**Chemoablation**

EUS-guided chemoablation using alcohol and taxols has been proposed as a therapy for mucinous pancreatic cysts. In a prospective single arm trial, Atar et al.\cite{25} performed EUS-guided injection of albumin-bound paclitaxel in five patients of mucinous cystic neoplasms and intraductal papillary neoplasms (IPMNs). Cyst size reduction was reported in three patients on the 6 month of follow-up of the CT scan; the cyst size increased in one patient and there was no change in the fifth patient. Authors suggested that albumin-bound paclitaxel is an efficacious agent because of its low viscosity and long duration of action. Studies with more patients may be needed in the future to determine its effectiveness.

In a prospective double-blinded randomized controlled trial, Moyer et al.\cite{26} divided the patients receiving EUS-guided chemotherapy (3 mg/mL paclitaxel and 19 mg/mL gemcitabine) into two arms. The alcohol arm (EA) patients underwent lavage with 80% ethanol, whereas patients in the alcohol-free arm (FA) underwent lavage with normal saline. Statistical analysis performed at 3 months and 6 months showed no significant difference in the cyst size reduction between patients belonging to the two groups (EA vs. FA; 74% vs. 81%; 91% vs. 90%). No complications were reported in patients of FA arm, however one patient in EA developed pancreatitis. Authors from their initial experience suggested that alcohol was not required for cyst ablation when chemotherapy specifically designed for pancreatic tumors was used.

**Table 2. Results of studies performed on EUS-guided PFCs drainage**

| Reference         | Single-center/ Multicenter | Study design   | Type of collection | (n) | Technical success (%) | Clinical success (%) | Adverse events (%) |
|-------------------|-----------------------------|----------------|-------------------|-----|-----------------------|---------------------|-------------------|
| Dhir et al.\cite{20} | Single                     | Prospective observational | PP               | 47  | 91.48                 | 95.34               | 4.60               |
| Siddiqui et al.\cite{21} | Multi                      | Retrospective  | PP (12), WON (68) | 80  | 99                    | 91                  | 11                |
| Larghi et al.\cite{22}  | Multi                      | Retrospective  | APFC (4), PP (18), PA (19), WON (52) | 93  | 100                   | 92.50               | 5.30               |
| El Zein et al.\cite{23}   | Single                     | Retrospective  | PP                | 18  | 100                   | 100                 | 0                 |

PP: Pancreatic pseudocyst, WON: Walled-off necrosis, APFC: Acute peripancreatic fluid collection, PA: Pancreatic abscess
Kandula et al.\textsuperscript{[27]} reported the results of a systematic review and meta-analysis to evaluate the efficacy and safety of EUS-guided ethanol ablation of pancreatic cysts. Complete cyst resolution was reported in 53.19% [95% confidence interval (CI) = 44.76 to 61.56] and partial cyst resolution was reported in 27.12% (95% CI = 19.96 to 34.94) patients. The reported complications were abdominal pain in 7.17% (95% CI = 3.43 to 12.12) and pancreatitis in 4.15% (95% CI = 1.45-8.17) patients. Authors concluded that EUS-guided ethanol ablation of pancreatic cysts may be a safe alternative to the standard surgical management; however, prospective randomized control studies with long follow-up are required to determine the efficacy and safety of this therapy.

Park et al.\textsuperscript{[28]} prospectively evaluated the safety and efficacy of EUS-guided ethanol-lipiodol mixture for the ablation of pancreatic neuroendocrine tumors (<2 cm). Complete resolution was seen in 3-month follow-up CT scan in 22 of the 40 tumors. Seven patients needed a repeat procedure for complete resolution, making the primary technique effectiveness rate 72.5% (29/40). It was also noted that the technique was more effective in capsulated tumors as compared to noncapsulated tumors. Authors, therefore, suggested that this technique was effective for ablation of <2 cm pancreatic neuroendocrine tumors.

Desmoplastic reaction is a known cause of chemotherapeutic resistance in pancreatic cancer patients. Mohamadnejad et al.\textsuperscript{[29]} evaluated the safety and survival outcome of EUS-guided fine-needle injection (FNI) of gemcitabine in patients with locally advanced nonmetastatic pancreatic cancer. No adverse effects were reported in the treatment group. The 6-month survival rate was significantly more in the gemcitabine group (92% vs. 48%, \( P = 0.01 \)) as compared to the control group. However, there was no statistically significant difference in the 1-year survival rates between the two groups, suggesting only short-term benefit of EUS-FNI of gemcitabine.

Results of an interesting pilot study to inhibit pancreatic tumor progression at the molecular level was presented by Nishimura et al.\textsuperscript{[30]} Chondroitin sulfate is a glycosaminoglycan, which is upregulated in pancreatic cancer cells and is known to promote tumor invasion. Synthesis of this molecule is mediated by an enzyme, carbohydrate sulfotransferase 15 (CHST15). Results of this study showed that synthesized CHST 15 dsRNA inhibits the expression of the enzyme CHST 15. Patients with unresectable CHST 15-positive pancreatic cancer were injected CHST 15 dsRNA under EUS guidance. One month follow-up showed a decrease in tumor size from a mean size of 32.2 mm to 30 mm and a reduced CHST 15 staining. Studies with more number of patients and longer follow-up using this technique may open new dimensions in treating unresectable pancreatic cancer with minimally invasive techniques.

Endoscopic ultrasound-guided fiducial delivery

Fiducial markers are useful for controlling image-guided radiation therapy in various tumors. Nieto et al.\textsuperscript{[31]} prospectively evaluated the performance characteristics of dedicated EUS-guided multifiducial delivery system in 13 patients with documented gastrointestinal (GI) malignancies. The procedure was technically successful (deployment of at least three fiducials) in 92% (12/13) patients. The accuracy of fiducial placement was verified by a CT scan after the procedure. No complications were reported in any of these procedures. Impressive results and excellent CT visualization suggest that EUS-guided fiducial deployment is a safe and efficacious radiation delivery method for GI malignancies.

Radiofrequency ablation

EUS guided radiofrequency ablation (RFA) has been shown to be feasible in the pancreas in animal studies. Song et al.\textsuperscript{[32]} presented the initial experience of using EUS-guided RFA in six patients with unresectable pancreatic cancer. They used an 18-gauge endoscopic RFA electrode and a VIVA RF generator for the procedure. This treatment did not have any major side effects such as bleeding or pancreatitis in these patients; however, two patients had mild abdominal pain, indicating that EUS-RFA can be a technically feasible and safe treatment in patients with unresectable pancreatic cancer. While this is interesting, clearly more work is needed before one can make a dent in the poor prognosis of unresectable pancreatic adenocarcinoma.

However, EUS-guided RFA may be an interesting approach in tumors with a clear and measurable outcome such as in neuroendocrine tumors. Surgery is the standard of treatment for insulinomas. EUS-guided-RFA may be used for patients who are not fit for surgery. Lakhtakia et al.\textsuperscript{[33]} reported rapid relief of symptoms and normalization of serum glucose, C-peptide levels, and fasting insulin up to 6 months in three patients treated with EUS-RFA.
**Celiac plexus/ganglia neurolysis**

EUS-guided celiac plexus neurolysis (CPN) is a routine practice for pain management for patients of pancreatic cancer.[34] In a prospective study, Hasan et al.[35] investigated correlation of intraprocedural vital sign changes (heart rate change of >15 beats/min) with pain relief and quality of life after the procedure using indices such as visual analog scale (VAS) and brief pain inventory. Twenty-six of the 51 patients who had significant VAS score showed better pain control and less interference at work, relationships, body image, and financial status at 8 weeks of follow-up. Based on the results, the authors suggested that their observation should be further explored for improving the outcomes of EUS-CPN.

**Gastric variceal obliteration**

Endoscopic therapy of gastric varices (GVs) with 2-octyl cyanoacrylate can be performed by direct endoscopic injection (DEI) or by fine-needle injection (FNI) under EUS guidance. Bang et al.[36] retrospectively compared the incidence of rebleeding and the adverse effects of the two techniques. There was no difference in the overall incidence of GV rebleeding; however, recurrent all-cause rebleeding was higher in the DEI group (57.9% vs. 22.6%, P = 0.004). No coils were used in the EUS group in this study. Based on the mixed results, the authors suggested that further prospective studies might be required to compare the two techniques in the treatment of GVs.

Bhat et al.[37] retrospectively evaluated safety and long-term outcomes in patients receiving EUS-guided treatment for gastric fundal varices using coil embolization and cyanoacrylate glue injection. The treatment was technically successful in 99% of the cases and hemostasis was achieved in all cases of acute hemorrhage. Procedure-related adverse effects were reported in 5% of the cases, which included self-limiting pain and signs of embolization. The median follow-up period was 348 days. Rebleeding from GVs were reported in 7% of the cases. The authors concluded that EUS-guided combined coil and CYA injection was a safe and efficacious treatment for GVs obliteration and prevention of rebleeding. It also reduces the risk of embolization. In their experience, this is an effective modality for primary prophylaxis for large GVs.

**Anastomosis formation**

Surgical management may not be possible in all cases presenting with complete gastric outlet obstruction (GOO). For such patients, Kumbhari et al.[38] presented a video case demonstrating EUS-guided gastrojejunostomy (GJ) using lumen apposing fully covered metallic stents. They performed the procedure in an 86-year-old female presenting with GOO secondary to locally advanced pancreatic cancer. Upper gastrointestinal (UGI) series following the day of procedure revealed a patent GJ stent and upper endoscopy on day 7 showed no gastric residue and the standard gastroscope was able to pass through the stent into the jejunum. The successful and functional placement of the stent by EUS-GJ technique suggests that this may be a suitable alternative to surgery in patients who have failed with regard to enteral stent placement.

Bile duct injury following cholecystectomy may be managed by additional surgery for anastomosing the transected bile duct with small intestine. Cho et al.[39] presented a video case for managing a case of transected bile duct by EUS-guided hepaticoduodenostomy using a fully covered metal stent in a patient who was not fit for surgical treatment. The authors concluded that EUS-guided hepaticoduodenostomy might be an alternative to surgery in patients with transected bile duct post cholecystectomy.

**CONCLUSION**

DDW 2015 showed significant progress in the research on EUS from its use as a diagnostic tool to a minimally invasive therapeutic modality for diverse gastrointestinal and pancreaticobiliary pathologies. Results of the studies performed on EUS-guided biliary drainage were impressive and safer than the traditional percutaneous biliary drainage in patients with failed ERCP. For drainage of pancreatic fluid collections, pancreatic pseudocysts, pancreatic pseudocysts, pancreatic abscess and WON, EUS-guided techniques have shown better results than surgical drainage and necrosectomy. EUS-guided therapies have opened new dimensions in ablation of cystic and solid pancreatic tumors using chemotherapy and radiotherapy. The results of these studies are promising and prospective randomized control trials are required to further determine the outcomes of these procedures. Further research also needs to focus on technical details and variables affecting the outcomes of EUS-guided pain management in pancreatic pathologies. EUS-guided coiling and glue injection have shown successful results...
in management and primary prophylaxis of GVs. EUS-guided GJ and hepaticocholedocojejunostomy may be minimally invasive alternatives to surgery in unfit patients for management of GOO and bile duct transection injury, respectively.

Overall, tremendous progress has been achieved in research on EUS-guided therapies and future studies will help us better understand the dynamics and outcomes of these techniques.

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There are no conflicts of interest.

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