

The role of endoscopy in the diagnosis and treatment of inflammatory pancreatic fluid collections

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This is one of a series of statements discussing the use of GI endoscopy in common clinical situations. The Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE) prepared this text. In preparing this guideline, a search of the medical literature from January 1990 to February 2015 was performed by using PubMed. Additional references were obtained from the bibliographies of the identified articles and from recommendations of expert consultants. When limited or no data existed from well-designed prospective trials, emphasis was given to results from large series and reports from recognized experts. Guidelines for appropriate use of endoscopy are based on a critical review of the available data and expert consensus at the time the guidelines were drafted. Further controlled clinical studies may be needed to clarify aspects of this guideline. This guideline may be revised as necessary to account for changes in technology, new data, or other aspects of clinical practice. The recommendations were based on reviewed studies and were graded on the strength of the supporting evidence (Table 1).¹

This guideline is intended to be an educational device to provide information that may assist endoscopists in providing care to patients. This guideline is not a rule and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment. Clinical decisions in any particular case involve a complex analysis of the patient's condition and available courses of action. Therefore, clinical considerations may lead an endoscopist to take a course of action that varies from these

guidelines. This guideline supplements and replaces our previous document on the role of endoscopy in the diagnosis and management of cystic lesions and inflammatory fluid collections of the pancreas.²

Inflammatory pancreatic fluid collections (PFCs) arise as an adverse event of acute and chronic pancreatitis, pancreatic trauma, and pancreatic surgery. Due to similarities in their radiographic appearance, pancreatic cystic neoplasms frequently are misclassified as inflammatory PFCs.³⁻⁵ Although inflammatory PFCs were initially treated via surgical and percutaneous techniques, endoscopy is increasingly used to characterize and treat these fluid collections. This guideline will discuss the role of GI endoscopy in the evaluation, diagnosis, and treatment of inflammatory PFCs.

INFLAMMATORY PFCs

Definitions

The Atlanta classification of acute pancreatitis was revised in 2012, and inflammatory PFCs are currently categorized as acute peri-PFCs, pancreatic pseudocysts, acute necrotic collections, and walled-off necrosis (WON) (Table 2).⁶ Acute peri-PFCs occur early in pancreatitis, rarely become infected, and typically resolve spontaneously.⁷ On imaging, they appear homogenous, lack a defined wall, can be multiple, and conform to normal retroperitoneal fascial planes. Pseudocysts are fluid collections arising from the pancreas and peripancreatic tissues that typically result from acute peri-PFCs and persist for more than 4 weeks. They also may develop from necrotizing pancreatitis when necrosis of the neck and body isolates a still viable segment of pancreatic parenchyma in the tail, resulting in a “disconnected duct

TABLE 1. GRADE system for rating the quality of evidence for guidelines

Quality of evidence	Definition	Symbol
High quality	Further research is very unlikely to change our confidence in the estimate of effect.	⊕⊕⊕⊕
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	⊕⊕⊕○
Low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.	⊕⊕○○
Very low quality	Any estimate of effect is very uncertain.	⊕○○○

Adapted from Guyatt et al.¹**TABLE 2. Definitions of inflammatory pancreatic fluid collections**

Term	Definition	Contrast-enhanced CT findings
Acute peripancreatic fluid collection (peri-PFC)	Peripancreatic fluid associated with interstitial edematous pancreatitis with no associated peripancreatic necrosis. This term applies only to areas of peripancreatic fluid seen within the first 4 weeks after onset of interstitial edematous pancreatitis and without the features of a pseudocyst.	Homogeneous collection with fluid density Confined by normal peripancreatic fascial planes No definable wall encapsulating the collection Adjacent to the pancreas (no intrapancreatic extension)
Pancreatic pseudocyst	An encapsulated collection of fluid with a well-defined inflammatory wall usually outside the pancreas with minimal or no necrosis. This entity usually requires >4 weeks after onset of interstitial edematous pancreatitis to mature.	Well circumscribed, usually round or oval homogeneous fluid density No non-liquid component Well-defined wall (completely encapsulated) Maturation usually requires >4 weeks after onset of acute pancreatitis Occurs after interstitial edematous pancreatitis
Acute necrotic collection	A collection containing variable amounts of both fluid and necrosis associated with necrotizing pancreatitis; the necrosis can involve the pancreatic parenchyma and/or the peripancreatic tissues.	Occurs only in the setting of acute necrotizing pancreatitis Heterogeneous and non-liquid density of varying degrees in different locations (some appear homogeneous early in the course) No definable wall encapsulating the collection Can be intrapancreatic and/or extrapancreatic
Walled-off necrosis	A mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well-defined inflammatory wall. This usually occurs >4 weeks after the onset of necrotizing pancreatitis.	Heterogeneous with liquid and non-liquid density with varying degrees of loculations (some may appear homogeneous) Well-defined wall (completely encapsulated) Intrapancreatic and/or extrapancreatic location Maturation usually requires 4 weeks after onset of acute necrotizing pancreatitis

Adapted from Banks et al.⁶

syndrome.” Pseudocysts contain amylase-rich fluid, have essentially no solid debris, and possess a well-defined, non-epithelialized wall.

Approximately 20% of individuals with acute pancreatitis will develop necrosis, with secondary infection occurring in 30% of these patients.^{8,9} Acute necrotic collections (ANCs) develop during the initial 4 weeks of pancreatitis and contain variable amounts of fluid and necrotic pancreatic and peripancreatic tissue. On imaging, ANCs may be multiple, appear loculated, contain variable amounts of liquid and debris, and generally appear similar to acute peri-PFCs. However, ANCs contain necrotic tissue, often are associated with main pancreatic duct disruption, and are more likely to become infected. The distinction between ANCs and acute peri-PFCs typically

becomes clear after 1 week. WON is a collection of pancreatic and/or peripancreatic necrosis with a mature, encapsulated enhancing wall of reactive tissue. This typically occurs ≥ 4 weeks after the development of necrotizing pancreatitis. WON may be multiple, become infected, and be present some distance from the pancreas. Although contrast-enhanced CT often is used to assess the pancreas initially, magnetic resonance imaging (MRI) and MRCP may be superior to CT for detection of debris within fluid collections (to distinguish between pseudocysts and WON) and provide information concerning integrity of the main pancreatic duct.¹⁰ It may also more accurately predict the severity and prognosis of pancreatic inflammation.¹¹ EUS also may aid in characterization of these collections.¹²

Indications for treatment

The majority of acute PFCs will resolve spontaneously and do not require intervention. The indications for drainage of a PFC are treatment of corresponding symptoms or resolution of infected or enlarging cysts. Because of their recent onset (<4 weeks in duration) and lack of development of a mature wall, acute peri-PFCs and ANCs typically do not undergo endoscopic interventions.⁶ However, endoscopic drainage is increasingly used in lieu of surgical or percutaneous drainage for symptomatic sterile or infected pseudocysts and WON.¹³ Drainage of these lesions, if required, should be undertaken after 4 weeks to allow for encapsulation and better definition of the margins of the PFCs and potentially to reduce adverse events if drainage is performed. A study of 242 patients found that mortality was reduced as the time from hospital admission to intervention of the PFC was increased (0-14 days: 56%; 14-29 days: 26%; and >29 days: 15%; $P < .001$).⁹

Before drainage, contrast-enhanced CT, MRI/MRCP, or EUS should be considered to confirm that the fluid collection does not represent a cystic neoplasm, pseudoaneurysm, duplication cyst, or other noninflammatory fluid collection. Large pseudocyst size alone is not an indication for drainage, although pseudocysts larger than 6 cm tend to be symptomatic.^{14,15} ERCP may be considered before percutaneous, transmural, or surgical drainage of pseudocysts to further define anatomy and guide therapy, but it is not necessary in most patients, particularly when the aforementioned high-quality cross-sectional imaging is available.^{16,17} When performed preoperatively, ERCP should be done shortly before surgery to minimize the risk of infecting the PFC. ERCP is not typically used for assessing WON, because transmural drainage is the standard initial endoscopic treatment approach.

Drainage of sterile WON is indicated for gastric outlet or biliary obstruction because of the PFC, which may occur within 4 to 8 weeks after onset of pancreatitis. Additional indications include refractory abdominal pain, ongoing systemic illness, anorexia, or weight loss lasting more than 8 weeks after the onset of acute pancreatitis.¹³ The management option chosen should be based on local expertise and the severity of the patient's comorbidities. Infected PFCs often are drained but may be followed clinically when patients remain stable on antibiotics.¹³ Infected necrosis may not initially be distinguishable clinically from sterile necrosis. However, this distinction usually becomes clinically apparent 2 to 4 weeks after the onset of disease, when the incidence of infected necrosis peaks.⁸ Signs of infected necrosis include new-onset or persistent sepsis, clinical deterioration despite adequate support and no alternative source of infection, or gas bubbles within the PFC on radiologic imaging. EUS-FNA is generally not recommended to determine whether a PFC is infected. Furthermore, performing this diagnostic procedure is associated with a high false-negative rate and may contaminate

a previously sterile fluid collection.¹⁸ A study that intervened on patients solely based on a clinical suspicion of infected necrosis without using FNA was accurate in >90% of cases.¹⁹

Before-procedure preparation

Anticoagulant and antiplatelet medications (other than aspirin) should ideally be discontinued before endoscopy because endoscopic drainage and necrosectomy have been associated with acute and delayed bleeding.²⁰ Adequate interventional radiology and surgical support should be available in the event of severe bleeding or perforation during the procedure. Given the complexity of these procedures, deep sedation or anesthesia is typically used. To minimize the risk of gas embolism, carbon dioxide insufflation is recommended. Antibiotics are typically administered, especially for patients with suspected WON.

ENDOSCOPIC METHODS OF DRAINAGE

Pseudocysts

Available endoscopic approaches for drainage of pseudocysts are transmural,²¹ transpapillary,²¹⁻²³ or a combined transmural and transpapillary route.^{15,24} Factors influencing the decision to proceed with one approach over another include the following: (1) the anatomic relationship of the collection to the stomach or to the duodenum, (2) the presence of ductal communication with the pseudocyst, (3) cyst contents, and (4) the size of the collection.

Transmural technique

Transmural drainage of pseudocysts is achieved by accessing the cyst via the creation of a tract through the gastric or duodenal wall with subsequent balloon dilation and placement of 1 or more stents. The procedure typically has been performed by using 2 plastic double-pigtailed biliary stents. However, plastic stent diameter or number does not appear to be associated with the number of interventions required for cyst resolution for uncomplicated pseudocysts.²⁵ Recently, techniques using fully covered self-expandable metal stents or a novel lumen-apposing covered self-expandable metal stent (SEMS) specifically designed for pseudocyst drainage have been reported.²⁶⁻²⁸ One advantage of using SEMSs includes the need for a single stent, thus simplifying and shortening the procedure. Other possible benefits include a larger stent lumen diameter (≥ 10 mm), which may lead to more rapid drainage, a reduced risk of stent occlusion, and the potential to enter the collection repeatedly and more easily with a gastroscop to perform necrosectomy. However, there are no clear data to support the superiority of SEMSs over plastic stents for resolution of PFCs, and SEMS use adds to direct procedure costs.²⁹ One concern with using a transmural biliary SEMS is the risk of migration, prompting some to

place an anchoring plastic double pigtail stent within the covered SEMS.²⁶ Lumen-apposing metal stents possess broad anchoring flanges and a large inner diameter, which obviate the need to place an anchoring plastic stent and facilitate performance of through-the-stent endoscopic necrosectomy.^{28,30} A recent ASGE review provides an in-depth evaluation of new devices and techniques for the endoscopic management of PFCs.³¹

In addition to variations in the choice of drainage device, the technique of endoscopic transmural pseudocyst drainage has evolved. Initially, cyst puncture was done by using an endoscope or duodenoscope under direct endoscopic visualization with fluoroscopic assistance in the region of gastric or duodenal compression. The initial role of EUS in drainage of PFCs was to localize and mark the optimal puncture site. However many now perform EUS-guided cyst puncture and drainage solely with a therapeutic echoendoscope.^{32,33} Endoscopic and EUS-assisted transmural pseudocyst drainage have shown similar clinical efficacy and safety when direct endoscopic transmural drainage is feasible.³⁴⁻³⁶ However, the EUS-assisted approach has a clear advantage when luminal compression is absent.³⁶ A study limiting direct endoscopic transmural drainage to those with an endoscopically identifiable luminal indentation and no evidence of portal hypertension found the techniques to be equivalent.³⁵ Given these data, the EUS approach is preferred in the absence of an endoscopically defined area of extrinsic compression, an unusual location of the fluid collection,³⁷ documented intervening varices or portal hypertension,³⁸ or a prior failed direct endoscopic approach.³⁶

Transpapillary technique

Although transmural drainage has increasingly become the preferred approach for draining all pseudocysts, the placement of a pancreatic endoprosthesis with or without pancreatic sphincterotomy was used initially to treat pancreatic pseudocysts in communication with the main pancreatic duct.^{22,23} The proximal end of the stent (toward the pancreatic tail) may be placed directly into the collection for PFC drainage or may be placed across the area of duct disruption to divert additional pancreatic secretions from entering the PFC. Available data suggest that complete bridging of the leak is the best approach.^{39,40} Complete bridging of the leak appears to achieve higher resolution rates for collections in the pancreatic body and tail compared with the head.⁴¹ An advantage of the transpapillary approach over the transmural approach is decreased risk of bleeding or perforation that may occur with transmural drainage. In addition, this approach theoretically allows for identifying intraductal pancreatic stones and strictures that may be present and require treatment to achieve long-term cyst resolution. A retrospective single-center study found higher clinical success rates for transmural drainage in those also receiving

transpapillary stents to treat duct disruption.⁴² However, another single-center study found this incremental benefit to be limited to patients with partial duct disruptions, with no additional benefit seen in those with complete duct disruptions.⁴³ Potential disadvantages of transpapillary drainage include ERCP-related pancreatitis, stent-induced scarring of the main pancreatic duct, infection of the fluid collection, and the inability of this approach to adequately drain large cysts.^{44,45} Most recently, a large, multicenter study found comparable rates of PFC resolution when transmural drainage combined with transpapillary stenting was compared with transmural drainage alone.⁴⁶

WON

To drain WON endoscopically, a transmural approach similar to that described above is necessary to allow evacuation of solid material. However, the techniques used and the postprocedure management of the patient after initial drainage are more extensive than for uncomplicated pseudocysts and require highly skilled endoscopists and support staff.⁴⁷⁻⁴⁹ Traditionally, nasocystic drainage is performed in addition to the placement of 2 transmural plastic pigtail stents to facilitate the evacuation of necrotic debris and improve success rates. In patients who do not achieve clinical improvement within 48 to 72 hours with nasocystic lavage and transmural drainage, subsequent step-up to endoscopic transmural necrosectomy has been advocated by some authors.^{8,13,50} Multiple debridement sessions, typically performed every 48 to 72 hours, may be needed to achieve complete removal of all necrotic debris.⁵⁰ As mentioned above, the recent introduction of a lumen-apposing large-diameter metal stent facilitates the performance of necrosectomy and can potentially improve drainage of necrotic debris. Access to multiple transmural drainage sites also may aid in the clinical resolution of WON and avoid the need for necrosectomy.

Alternatively, dual endoscopic and radiologic drainage may be considered. Using this combined endoscopic and percutaneous approach, the investigators conducting 1 study with a median follow-up of 750 days found that surgical necrosectomy could be avoided in all 103 patients who completed treatment.⁵¹ The technique was associated with no pancreaticocutaneous fistulae or procedure-related deaths. It is plausible that transluminal drains may reduce the rates of pancreatic fistula formation compared with a solely percutaneous approach. Another method, described as the multiple transluminal gateway technique (MTGT), involves creating 2 to 3 unique transmural tracts, with 1 being used for nasocystic lavage, whereas multiple stents are placed in the other tracts to promote drainage of necrotic debris. A study of 60 patients with WON found that those receiving the MTGT approach had a higher rate of clinical success (91.7% vs 52.1%; $P = .01$) compared with those receiving conventional drainage via a single tract containing

2 plastic stents and a nasocystic drain.⁵² This benefit persisted even when figures were adjusted for PFC size and pancreatic duct stent placement. A recent study found that using a larger-diameter (18 mm), fully covered esophageal stent via a single tract may successfully treat WON in a single procedure without requiring necrosectomy.⁵³ Preliminary data from a single-center study suggest that performing direct endoscopic necrosectomy at the time of initial drainage and stent placement may achieve higher rates of resolution, reduce hospital length of stay, and lower overall health care utilization when compared with a step-up approach for WON.⁵⁴ Two small case series have reported endoscopic irrigation of the WON cavity with the use of hydrogen peroxide (100-500 mL of 3.0% H₂O₂ at 1:5-1:10 dilution) to irrigate the WON cavity to aid in dislodgement and extraction of necrotic debris while minimizing the need for endoscopic mechanical debridement during endoscopic necrosectomy.^{55,56} A discussion of the techniques and outcomes of endoscopic necrosectomy are beyond the scope of this document.

AFTER-PROCEDURE CARE

After uncomplicated endoscopic drainage of noninfected pancreatic pseudocysts, most patients do not require hospitalization.⁵⁷ Antibiotic prophylaxis usually is prescribed after drainage.⁵⁸ A follow-up CT scan typically is obtained 4 to 6 weeks after the drainage procedure to assess for PFC resolution. The internal stents are eventually removed endoscopically after radiographic resolution is documented. In patients with chronic pancreatitis who have undergone transmural drainage, endoscopic therapy of any related pancreatic duct obstruction should be performed to reduce the likelihood of PFC recurrence. Some authors have advocated delaying removal of transmural stents to promote resolution of any pancreatic duct disruptions.^{50,59} Long-term indwelling transmural stents may reduce rates of PFC recurrence. Two studies involving 33 and 30 patients assessing long-term transmural stent placement found that only 1 individual had PFC recurrence during a median and mean follow-up of 14 and 20 months, respectively.^{59,60} The lone recurrence developed in a patient who had a spontaneous stent migration. Of note, the smaller study was made up entirely of patients with WON and disconnected pancreatic duct syndrome.⁶⁰ In summary, long-term indwelling transmural stents may be indicated in patients with disconnected duct syndrome or duct disruption who may be at high risk of PFC recurrence.

ADVERSE EVENTS OF ENDOSCOPIC THERAPY OF PFCs

Serious adverse events may arise after endoscopic drainage of PFCs and include bleeding, perforation, infection, pancreatitis, aspiration, stent migration and/or

occlusion, pancreatic-duct damage, adverse events related to sedation, and death. Less common events include cardiac air embolism, development of an arterial pseudoaneurysm, and inadvertent gallbladder puncture.⁶¹⁻⁶³ One series of 148 patients undergoing EUS-guided transmural drainage of a mixture of pseudocysts, abscesses, and WON reported 8 adverse events (5.4%), including 2 perforations, 4 infections, 1 bleeding episode, and 1 stent migration.⁶⁴ Another series reported higher adverse event rates of 18% to 19%.³⁵ A systematic review of 17 studies (881 patients) found no significant difference in the rates of adverse events for PFCs drained with plastic (16%, 95% confidence interval [CI], 14%-39%) compared with metal (23%, 95% CI, 16%-33%) stents.⁶⁵ Adverse events appear to be increased during draining and debriding of necrosis.⁶⁶ It is recommended that endoscopic drainage of PFCs be performed only if surgical and interventional radiology support are available.⁵⁷ Infectious adverse events usually occur from inadequate drainage of fluid and/or removal of solid debris. If endoscopic drainage is performed solely by the transpapillary route, stent exchange, increasing the stent size, or conversion to a transmural approach may resolve the infection.

OUTCOMES OF ENDOSCOPIC THERAPY OF PFCs

Pseudocysts

Outcomes after attempted endoscopic therapy depend on the type of collection drained⁵⁷ and the experience of the endoscopist.⁶⁷ Pancreatic pseudocysts can be successfully drained in 82% to 100% of cases, with adverse events occurring in 5% to 16% and recurrence rates up to 18%.^{39,47,68,69} A randomized trial comparing 20 patients undergoing open surgical cystgastrostomy to 20 patients receiving endoscopic cystgastrostomy for pancreatic pseudocyst drainage found no recurrent pseudocysts in the endoscopy group over a 24-month follow-up period, compared with 1 recurrence in the surgically treated group.⁷⁰ There were no differences in adverse events between the groups, but the endoscopy group had a median hospitalization that was 4 days shorter, improved physical and mental health component scores during follow-up, and significantly lower mean costs (\$7011 vs \$15,052) compared with surgery.

Prospective studies comparing drainage devices (plastic stents vs covered metal stents vs nasocystic tubes, etc) have not been published to date. However, a retrospective study in debris-containing pseudocysts found improved short-term and long-term success rates when a nasocystic tube was placed in conjunction with transmural stents compared with transmural stenting alone.⁷¹ In addition, a recent systematic review of 17 studies totaling 881 patients compared the use of metal and plastic stents in the transmural drainage of PFCs (predominantly pseudocysts) and

found no differences in the rates of treatment success or recurrence.⁶⁵

WON

Experience with endoscopic drainage of WON is more limited than for pseudocysts, but it has achieved successful nonsurgical resolution in 70% to 80% of patients.^{69,72,73} Overall success rates for drainage of WON appear to be lower than for pseudocysts, with higher rates of adverse events.^{69,72,74} A recent systematic review of 14 studies (13 retrospective) totaling 455 patients found an 81% clinical success rate with adverse events observed in 36% and an overall mortality of 6%.⁷⁵ An average of 4 (range 1-23) endoscopic interventions were performed per patient. A randomized controlled trial of 22 patients with infected necrotizing pancreatitis found that patients treated with endoscopic necrosectomy had a much-reduced inflammatory response, a significantly reduced incidence of new-onset multiple-organ failure, and a significant reduction in the number of pancreatic fistulas compared with the surgically treated group.⁷⁶ In another study of 93 patients receiving endoscopic necrosectomy, 84% of patients with initial treatment success remained recurrence-free during a mean long-term follow-up of 43 months.⁷³ Pancreatitis recurred in 16%, with 10% requiring repeat endoscopic treatment and 4% undergoing surgery. A randomized comparison of the endoscopic transluminal and minimally invasive surgical step-up necrosectomy approaches is ongoing.⁷⁷

SUMMARY

1. We recommend that endoscopic drainage of PFCs be performed only after sufficient exclusion of alternative diagnoses, such as cystic pancreatic neoplasms and pseudoaneurysms. ⊕⊕⊕⊕
2. We recommend waiting for maturation of the cyst wall of PFCs before endoscopic intervention. ⊕⊕⊕⊕
3. We recommend drainage of symptomatic pancreatic pseudocysts. ⊕⊕⊕⊕
4. We suggest drainage of rapidly enlarging pancreatic pseudocysts. ⊕⊕⊕⊕
5. We recommend drainage of all infected PFCs in patients who fail to improve with conservative management alone. ⊕⊕⊕⊕
6. We recommend drainage of symptomatic sterile necrosis lasting more than 8 weeks after the onset of acute pancreatitis. ⊕⊕⊕⊕
7. We suggest that routine FNA of PFCs is not required to diagnose infected necrosis. ⊕⊕⊕⊕
8. We recommend that endoscopic drainage be considered for initial therapy before surgical drainage of pancreatic pseudocysts. ⊕⊕⊕⊕
9. We recommend using EUS for transmural drainage of PFCs in the absence of a luminal bulge or when portal hypertension is suspected. ⊕⊕⊕⊕

10. We recommend initial endoscopic transmural and/or percutaneous drainage of WON before consideration of endoscopic transmural necrosectomy or surgical drainage. ⊕⊕⊕⊕
11. We recommend that endoscopic drainage of PFCs be performed only with the availability of surgical and interventional radiology support. ⊕⊕⊕⊕
12. We suggest using CO₂ when performing transmural drainage procedures ⊕⊕⊕⊕

DISCLOSURES

V. Muthusamy is a consultant for Boston Scientific and Medtronic. K. Chathadi is a consultant for Boston Scientific. M. Khashab is a consultant for Boston Scientific and Xlumena.

Abbreviations: ANC, acute necrotic collection; ASGE, American Society for Gastrointestinal Endoscopy; MRI, magnetic resonance imaging; MTGT, multiple transluminal gateway technique; PFC, pancreatic fluid collection; SEMS, self-expandable metal stent; WON, walled-off pancreatic necrosis.

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