Carol Rees Parrish, M.S., R.D., Series Editor

Pragmatic Management of Nutrition in Severe Acute Pancreatitis

Dushant Uppal

Severe acute pancreatitis (SAP) is a form of acute pancreatitis (AP) with significant morbidity and mortality. Nutrition is critical to supportive management, with appropriate route and timing of nutritional support paramount to optimal outcomes. Previous paradigms of maintaining patients (NPO) while utilizing parenteral nutrition (PN) have evolved. Enteral nutrition (EN) is now generally preferred, with PN being utilized only in select situations. Additionally, data support the use of early initiation of EN, within 48 hours of admission, to reduce gut barrier dysfunction and infectious complications. While limited data suggest that gastric EN may be pragmatic and non-inferior to jejunal EN, caution is recommended if using gastric EN. Finally, while it is reasonable to trial oral nutrition in patients experiencing a less protracted course with improved pain and hunger, long term EN is recommended in those patients expected to have a prolonged need for nutrition support.

INTRODUCTION

Acute pancreatitis (AP) is an inflammatory condition of the pancreas ranging in severity from mild to severe and contributing to significant burden/cost to the healthcare system. In 2012, AP accounted for approximately 280,000 hospital admissions in the USA, with a median length of stay (LOS) of 4 days and a total cost to the healthcare system of $2.6 billion.[1] Management predominantly involves supportive care with IV fluids and pain control in the acute setting. The severity of AP, as defined by the revised Atlanta criteria, may be classified as mild, moderate, and severe. Severe acute pancreatitis (SAP) occurs in approximately 15-20% of patients with AP and is defined by the presence of persistent organ failure (>48 hours).[2] A further 20% of patients with SAP may have necrotizing pancreatitis, defined as focal areas of non-viable pancreatic parenchyma >3cm in size or >30% of the pancreas.[2] Predicting the severity of AP is critical to optimizing management strategies including timing and type of nutrition. While scoring systems may be cumbersome, simple clinical and lab parameters may provide ample distinction between predicted mild AP and SAP at the time of presentation. In particular, persistent (>48 hours) systemic inflammatory response syndrome (SIRS), defined by two or more of the following four criteria: (1) temperature < 36 °C (96.8 °F) or >38°C (100.4 °F), (2) heart rate >90/min, (3) respiratory rate >20/min, and (4) white blood cells (<4 × 109/L (<4 K/mm3), >12 × 109(>12 K/mm3) or 10% bands, is predictive

Dushant Uppal, MD, MSc, Assistant Professor of Medicine, Division of Gastroenterology & Hepatology, University of Virginia, Charlottesville, VA

of SAP.[3] This distinction permits optimization of management and support in SAP including the delivery of nutrition support. Nutrition is a critical element of supportive care as it is thought to diminish:

1. damage to gut barrier with resultant increasing intestinal permeability and initiation of SIRS, sepsis and associated infected necrosis
2. translocation of bacteria/toxins which is considered the main cause for superinfection/ SIRS
3. pancreatic inflammation predisposing to gastric stasis/abdominal distension[2]

Certainly, keeping a patient with SAP 'nil per os' (NPO) may be appropriate at presentation if they are intolerant or incapable of eating. However, fear of worsening inflammation and/or infection in SAP with eating based on the physiologic understanding that gastric accommodation and delivery of partially digested proteins and fats lead to pancreatic stimulation, has pervaded nutrition management in AP. This led to the long-held belief that keeping patients NPO for prolonged periods, while providing parenteral nutrition (PN), was optimal. The paradigm has evolved with literature now demonstrating improved outcomes in patients with SAP being trialed on oral nutrition or receiving enteral nutrition (EN) compared with PN. Furthermore, recent data and critical assessments of the literature have shed more light on the optimal route and timing of EN in patients with SAP. Certainly, the merits of each nutrition modality should be considered in specific clinical scenarios to optimize patient outcomes (Table 1).

Parenteral Nutrition (PN) vs Enteral Nutrition (EN)

The belief that keeping a patient NPO and utilizing PN would lead to optimal outcomes was germane to management of AP for years. However, data from a number of studies have refuted this notion, demonstrating that outcomes with PN tend to be worse.[4-9] In particular, patients with AP who are placed on PN may experience more hyperglycemia and suffer increased line related infections or other infectious complications.[2]

Additionally, it has been demonstrated that gut mass and barrier function may be improved in patients with SAP who are enterally fed compared with those patients kept NPO and/or placed on PN.[2,10] This altered physiology has been postulated to be responsible for increased systemic infections, organ dysfunction, increased need for surgical intervention, hospital LOS and mortality.[4-9]

A Cochrane review of 8 trials with a total of 348 patients with AP demonstrated a reduction in death, MOF, systemic infection, need for operative intervention and hospital LOS for patients receiving EN compared to those receiving PN.[9] Furthermore, a subgroup analysis of patients with SAP receiving EN had a lower risk of death and MOF compared with those patients on PN. This improvement in major complications and death was corroborated in a subsequent meta-analysis of 8 RCTs including 381 patients comparing PN to EN in patients with SAP.[8] Thus the data to date support the notion that EN should be favored over PN as it leads to improved outcomes in patients with SAP.

Although PN use in patients with AP, including SAP, is not advised as the initial form of nutrition support, there are certain conditions where it may be indicated. For instance, in the rare instances of mechanical bowel obstruction or bowel perforation, EN would be ill advised and PN preferred, or when adequate nutrition intake cannot be met by EN and/or po intake. Additionally, in patients with lymphatic disruption and chylous ascites not responding to a fat free or fat restricted diet or elemental EN, transient PN may be indicated.[11,12]

EN vs Oral Nutrition

While the data demonstrating the benefit of EN over PN is robust, data regarding EN vs oral nutrition in SAP is somewhat limited and incongruent. Although some studies have demonstrated improved gut mass and barrier function in patients receiving EN over PN, another study by Powell et al.,[13] demonstrated no difference in inflammatory markers, interleukin 6, soluble tumor necrosis factor receptor[1] and C-reactive protein between patients with SAP who were fed by mouth and those receiving EN. Several additional studies comparing oral nutrition vs EN in patients with AP found no statistical significance in complications between the two groups.[14,15] The study by Stimac et al.,[15]

Table 1. Pros and Cons of Nutrition Routes in SAP

Nutrition Route	Pros	Cons
Oral	• No procedures or devices required • Easier to adjust nutrition regimen/caloric intake • Easier to transition to home regimen	• Increased risk of worsening pancreatitis • Increased risk of morbidity/mortality • Wider range of variation in caloric intake day to day • Difficult to ensure adequate intake at home
Nasogastric (NG)	• Easy bedside access • No need for enteral pump • Permits higher feeding rates and bolus feeds	• Possible increased risk of pancreatic stimulation and worsening pancreatitis • Nasal necrosis or sinusitis • Not suitable in patients with gastric outlet obstruction and/or need for gastric venting
Nasojejunal (NJ)	• Potential reduced risk of aspiration • Permits enteral access beyond points of duodenal compression from inflamed pancreas • Possible reduced risk of pancreatic stimulation	• Post pyloric placement may be difficult • Requires pump for feeding • Bolus feeding not possible • Increased risk of tube clogging/ dislodgement • Nasal necrosis or sinusitis • May migrate back into stomach
Percutaneous Gastrostomy with Jejunal Extension (PEG-J)	• Durable enteral access • No risk of nasopharyngeal injury • Permits gastric venting in outlet obstruction • May be placed endoscopically, radiologically, surgically	• Risk associated with tube placement (bleeding, infection, perforation) • Peristomal tube leak, bleeding, infection • Relatively contra-indicated in patients with ascites, bleeding diatheses or poor window for PEG placement • J-arm may migrate back into stomach
Parenteral Nutrition (PN)	• Direct nutrition that bypasses need for luminal absorption • Can be used for patients with bowel obstruction or perforation • Can be used for patients with intractable nausea and vomiting	• Requires central venous access (TPN) • Increased risk for line related infections and DVT • Increased risk of mucosal barrier dysfunction with resultant bacterial translocation/infection • Increased morbidity/mortality compared with EN

demonstrated a RR reduction in death and MOF in pts on EN vs 'nil by mouth' (NBM), but these did not meet statistical significance. However, the NBM group received more IVF early and during the remaining hospital course and oral nutrition was introduced to both groups variably, but as early as 3 days. It is thus unclear if longer duration of EN could have resulted in statistically significant reductions in risk of mortality, MOF, and infectious complications. Furthermore, all patients received prophylactic antibiotics for 10 days, a practice that is no longer recommended and could have contributed to similar outcomes between both groups.

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The Python trial,[14] compared early EN within 24 hours of admission with oral diet after 72 hours in patients with AP at high risk for complications. Two hundred eight patients at 19 centers were randomized with a primary composite end point of major infection or death. The primary end-point occurred in 30% of the early EN group vs 27% of the on demand group leading the authors to conclude that there was no superiority of early nasoenteric feeding compared with oral feeding after 72 hours. However, caution is advised in extrapolating the results of this study to clinical practice for those patients with proven SAP due to several limitations. A substantial proportion (one third) of patients did not meet initial criteria for SAP at the time of enrollment into the trial, nor did the study identify differences in outcomes among those patients with true SAP following initial resuscitation. Additionally, the transition to oral nutrition occurred for both groups during their hospital course (full oral tolerance at 9 days for EN group vs 6 days for on demand group), yet the primary outcome compared 6-month mortality and major infections without additional assessment of symptoms and oral feeding tolerance in the interim. Further, the results from the intention to treat (ITT) analysis, as it pertains to those patients with true SAP, may be misleading as a large proportion of the on-demand group received EN (31%), yet were included in the analysis as patients in the on-demand arm instead of the early EN arm. Thus, it remains possible that longer duration EN, through and beyond the primary hospitalization, may result in improved morbidity and mortality in patients with SAP.

The paucity of data and these disparate data should lead practitioners to act cautiously when introducing oral diet for patients with SAP. Nevertheless, in those patients with a more benign clinical course who improve rapidly, a trial of po intake is appropriate. At our institution, EN is often used preferentially in those patients with severe necrotizing pancreatitis and infection, or at the first signs of intolerance in those patients with SAP cautiously initiated on oral nutrition.

Type of EN

With respect to types of enteral formulations, elemental or polymeric products may be used as there are no data to support the superiority of one over the other.[16,17] Alhough some studies have demonstrated pancreatic exocrine insufficiency, based on fecal elastase and quantitative fecal fat

Table 2. Indications/Contraindications for NJ and PEG-J in SAP

Type of Jejunal Access	Indications	Contra-indications
Nasojejunal (NJ) tube	• Early access for EN to assess tolerance • Patient preference to avoid PEG tube • Expected improvement in SAP with likely po tolerance within 4-6 weeks • PEG tube contra-indicated	• Nasopharyngeal disorders (epistaxis, sinusitis, altered anatomy) • Increased aspiration risk • Gastric outlet obstruction (need for gastric venting) • Likelihood of transition to oral diet prolonged (>4-6 weeks)
Percutaneous gastrostomy tube with jejunal extension (PEG-J)	• Expected need for EN >4-6 weeks • Significant necrotizing pancreatitis • Gastric outlet obstruction (need for gastric venting) • Patient preference to avoid NJ placement for cosmetic reasons • Nasopharyngeal disorder precluding NJ placement	• Expected transition to oral diet during hospitalization • Poor window for PEG tube placement • Ascites • Bleeding diatheses

testing, to be a variably common occurrence (13%-87%) following SAP, paricularly alcohol related and/or necrotizing pancreatitis,[18-21] other studies have demonstrated likely recovery of exocrine function, particularly in those patients not requiring pancreatic debridement or drainage.[22-24] Our institutional practice is to first employ polymeric EN as it has been well tolerated and less costly. If steatorrhea develops or persists, and there does not appear to be sufficient pancreatic damage suspected, we then undertake an evaluation for clostridium difficile infection. In our experience, if infective colitis is ruled out, patients generally will accommodate well to polymeric feeds as the acute decrement in exocrine function experienced with SAP resolves. However, should steatorrhea or weight loss persist to suggest more semi-acute or chronic exocrine insufficiency, or there is significant pancreatic necrosis on imaging, then transition to semi-elemental or full elemental EN, or the addition of pancreatic enzymes, may be considered. In these scenarios, fecal elastase may help to guide changes in EN formulation in those patients suspected as having pancreatic insufficiency, so long as the patient is not experiencing diarrheal stools, which could dilute fecal elastase, leading to a false positive result.

Timing of EN

The benefit of EN on morbidity and mortality in SAP is supported by the literature with additional data demonstrating improved outcomes with early initiation of EN.

A retrospective review of 197 patients with predicted SAP compared patients receiving early EN, within 48 hours of admission to those receiving delayed EN, after 48 hours and demonstrated reduced mortality, development of infected necrosis, respiratory failure, and need for ICU admission in the early EN group.[25] However, the study results must be considered carefully, given the study's retrospective nature, as bias may have existed with respect to the allotment of each type of therapy for the included patients. For instance, the delayed group had a trend towards greater use of PN. Taken together, the increased need for ICU admission and PN use in the delayed group may be reflective of a more critical course that resulted in delayed initiation of EN and resultant increased morbidity/mortality.

Nevertheless, subsequent studies have demonstrated improved outcomes with early initiation of EN.[7,13,25-31] A Cochrane review of 11 RCTs by Petrov et al.,[32] demonstrated improved outcomes with respect to MOF, pancreatic infectious complications, and mortality in those patients with AP receiving EN within 48 hours of admission compared with those receiving PN. The improved outcomes are postulated to be due to improved immune function with early initiation of nutrition support. This improvement in immune function was evidenced by Sun et al.,[29] who showed that compared with delayed EN, those patients receiving early EN experienced lower levels of cytotoxic CD4+ T lymphocytes and CRP in addition to reduced MOF, SIRS, pancreatic infection, and ICU LOS. Thus, the available data support the initiation of EN in patients with SAP within 48 hours, if clinically feasible.

Gastric Nutrition vs Jejunal Nutrition

While EN in SAP is clearly of benefit, literature regarding route of enteral support is somewhat disparate. As discussed earlier, studies comparing PN with EN demonstrate reduced mortality and morbidity in patients with SAP receiving EN. Most of these early studies utilized jejunal feeding. However, given the sometimes cumbersome nature of jejunal feeding tube placement, more recent studies have attempted to elucidate the difference in outcomes between patients with SAP receiving nasogastric tube (NGT) vs nasojejunal tube (NJT) feedings. In a clinical feasibility study conducted by Eatock et al.,[33] 22 out of 26 patients with SAP receiving NGT feeds within 48 hours of admission tolerated the feedings well without evidence of clinical or biochemical deterioration. A subsequent RCT of early NGT vs NJT feeding in SAP, conducted by the same group, found no statistically significant difference in inflammatory markers or pain scores between the groups.[34] However, they did not objectively evaluate long-term outcomes or differences among patients with necrosis. Subsequently, a RCT by Kumar et al.,[35] comparing NJT to NGT feedings in patients with SAP found no difference in LOS, need for surgical intervention, or death. However, time to initiate EN was up to one month after presentation with SAP,

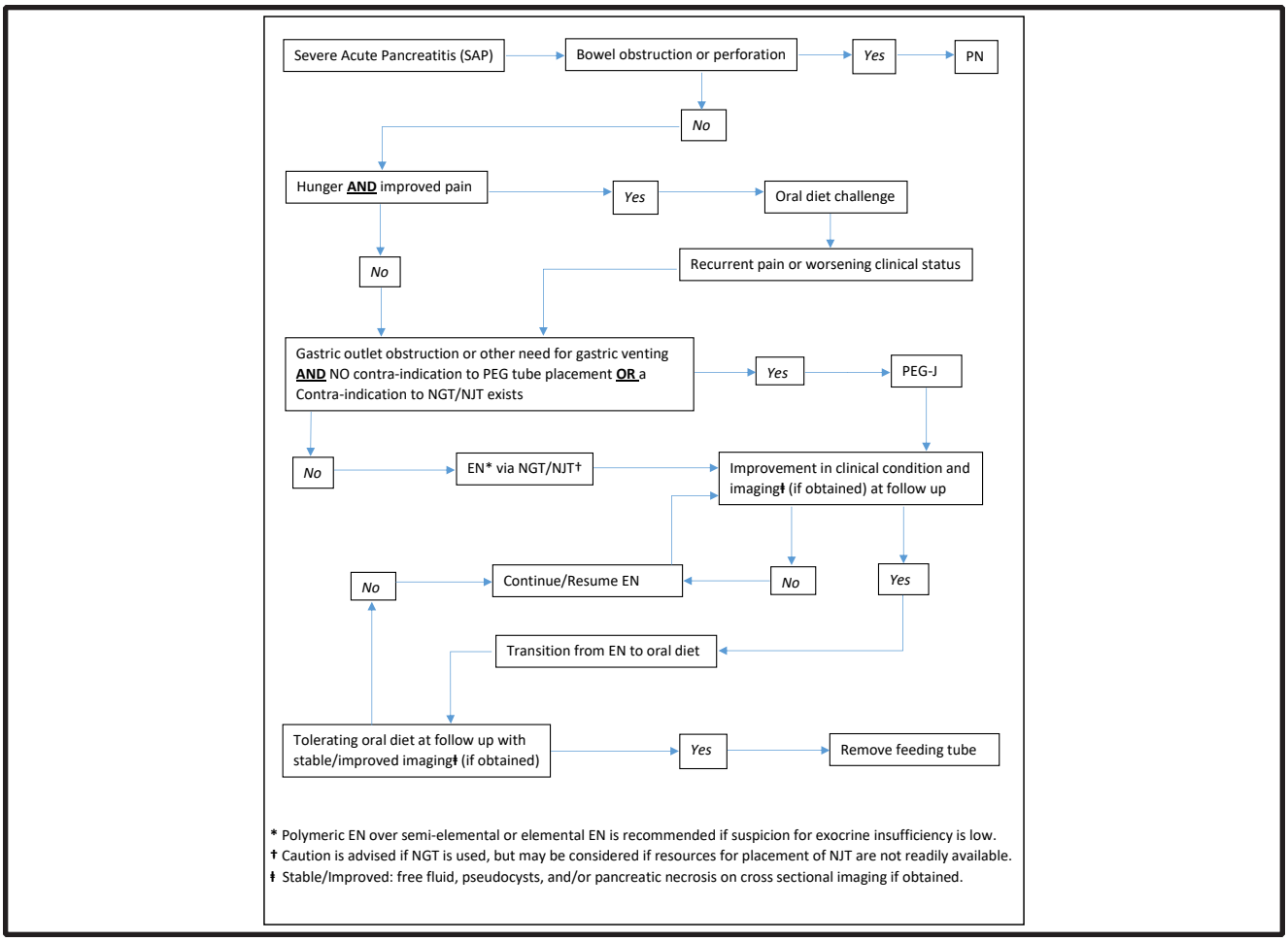

Figure 1. Suggested Algorithm for Nutrition in Severe Acute Pancreatitis (SAP)

and both groups only received low EN infusion rates. Furthermore, long-term outcomes were not compared. Additionally, the authors concluded that EN was tolerated in both groups. However, if the EN rate had been optimized to meet true nutritional requirements and volumes, a difference in tolerance may have been appreciated. These two studies and a third RCT, comprising a total of 157 patients, comparing NGT vs NJT feeding in SAP were used to conduct a meta-analysis.[36] The authors of the study reported no significant differences between groups receiving NGT feeds vs NJT feeds in their RR of mortality, diarrhea, exacerbation of pain, and meeting energy balance, leading them to conclude that NGT feeding was not inferior to NJT feeding in patients with predicted SAP. However, the authors also cautioned that the results of the study would require larger RCTs as their evaluation was not adequately powered. Moreover, the meta-analysis was limited by the small and heterogeneous trials included, non-blinding, delay in patients being initiated on EN in the two studies from India, and the lack of confirmation of NJT positioning.

Although the available data suggest that NGT feeding may be non-inferior and that NGT placement may be more pragmatic given the potential difficulties in NJT placement, the data are not robust. Furthermore, jejunal feeding in SAP may be physiologically sensible. Data demonstrate higher secretions of trypsin and lipase in subjects who have formula delivered to the duodenum compared with those receiving jejunal feedings at least 40cm beyond the ligament of Treitz and this may potentiate further pancreatitis.[37] Nevertheless, if NGT feedings are pursued in SAP caution is advised and reassessment of the patient's clinical condition and tolerance of feeding is recommended.

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NJT or Percutaneous Endoscopic Gastrostomy Tube with Jejunal Extension (PEG-J)

When the decision is made to utilize EN, an empiric decision to place a NJT or transition to PEG-J must be made. In rare circumstances NJT placement may not be possible due to altered nasopharyngeal anatomy or issues with nasopharyngeal bleeding or infection. If the tube can be placed easily, NJT is generally appropriate for patients initially if transition to oral diet during the hospitalization is likely. Additionally, NJT placement may be appropriate in the setting of necrotizing pancreatitis without gastric outlet obstruction or in patients with significant malnutrition where it remains unclear if they will be able to meet oral caloric targets early, but are likely to transition to full oral diet shortly following hospitalization. However, in the setting of necrotizing pancreatitis with outlet obstruction, which may necessitate gastric venting, PEG-J placement may be more ideal. Long term NJT use out of the hospital may also not be palatable due to cosmetic concerns if the patient is planning on returning to work and cannot otherwise advance to oral diet. Finally, PEG-J may be of benefit in the setting of SAP with significant necrotizing pancreatitis necessitating repeat debridement, as the need for enteral support may be greater than 6 weeks in these circumstances. Relative contraindications to PEG-J placement may include poor window for endoscopic or radiographic placement, ascites, or bleeding diatheses (Table 2).

When to Transition to Oral Nutrition

As mentioned previously, the data regarding oral vs early EN in patients with SAP is limited and caution is advised in early re-introduction of oral diet in these patients. However, in a large majority of patients with SAP, a trial of oral nutrition tolerance prior to discharge may be reasonable, particularly as hunger returns. In a study by Zhao et al.,[38] no difference in adverse events or complications were identified in patients with moderate or SAP who received early oral re-feeding based on return of hunger vs those patients who received conventional oral refeeding when clinical symptoms and laboratory parameters had resolved. Of course, if oral tolerance fails due to worsening pain, infection, or inability to meet caloric needs, then EN should be introduced/resumed until clinical re-assessment with or without interval imaging can be undertaken. If the patient is well at that point, re-introduction of oral diet is reasonable. Additionally, though empiric, our institutional practice tends to favor continued EN at the time of discharge in the subgroup of SAP patients with necrotizing pancreatitis with infection or gastric outlet obstruction. In these patients, our pragmatic approach is to maintain EN until clinical reassessment is completed following hospital discharge or debridement/drainage if necessary (Figure 1). If the patient is clinically better and necrosis, if present, is stable/improved and no further intervention is anticipated, oral diet is resumed. Of course, if signs of intolerance occur earlier, interval imaging is obtained more urgently and oral diet is either transitioned back to EN or maintained based on imaging and patient parameters. When the durable tolerance of oral nutrition is demonstrated and imaging, if obtained, is encouraging, feeding tube removal is undertaken. Although this approach may be difficult, owing to the need for close patient follow up and interval imaging, it is undertaken in an effort to limit worsening clinical status of the patient and prevent premature removal of enteral access.

CONCLUSION

SAP is a clinically debilitating condition with significant morbidity and mortality that requires attention to optimal supportive management, including nutrition, for improved outcomes. The classic paradigm of maintaining a patient NPO while providing parenteral support has evolved, with PN now being recommended only in very select situations. Literature supports the early introduction of EN in SAP within 48 hours, if po challenge fails, and while the literature appears to demonstrate clinical equipoise with respect to gastric vs jejunal feeding, it is not robust and clinical management must be approached cautiously. As with other interventions, close reassessment of clinical, laboratory, and radiographic parameters once any nutritional support is initiated is paramount to improved patient outcomes. In an effort to limit cost and simplify management, ongoing assessment of oral diet tolerance is reasonable in those patients with hunger and improved pain prior to discharge. However, pragmatically, the use of

long term EN in SAP patients is recommended in those with demonstrated intolerance of oral diet either due to pain, early satiety, or inability to meet caloric requirements. This may be via NJT in those patients expected to transition to oral diet within 4-6 weeks. Alternatively, patients with gastric outlet obstruction, severe necrotizing pancreatitis necessitating debridement, and those patients requiring enteral access, but unable to tolerate NJT placement, a PEG-J may be more appropriate. Ultimately, optimal patient outcomes with respect to nutrition in SAP are realized when attention to literature is married to diligent observation of the individual patient and reorienting therapy based on clinical, biochemical, and radiographic response to implemented strategies. ■

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