EXPERT REVIEWS

The oral refeeding trilemma of acute pancreatitis: what, when and who?

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Melody G Bevan, Varsha Asrani and Maxim S Petrov*

Department of Surgery, University of Auckland, Auckland, New Zealand
**Author for Correspondence:*
Tel.: +64 99 232 776
Fax: +64 93 779 656
max.petrov@gmail.com

Tolerance of oral refeeding is an essential goal of nutritional management of acute pancreatitis. However, oral feeding intolerance remains one of the most common complications in patients with this disease. It often results in longer periods of hospitalization, increased treatment costs, increased risk of readmission, and reduced quality of life. The traditional practice involves keeping patients nil by mouth followed by gradual stepwise reintroduction of food. However, it does not have a solid evidence base and, hence, there is increasing interest in determining alternative strategies that may be beneficial in reducing the occurrence of oral feeding intolerance. This review focuses on the randomized controlled trials that investigated the key questions informing the nutritional management of acute pancreatitis: when to feed, what to feed and who is in charge of the decision-making.

Keywords: acute pancreatitis • gut rousing • nutritional management • oral feeding intolerance • oral refeeding • patient-centered care

Oral refeeding is a key component of management in the convalescence period of acute pancreatitis (AP), and its tolerance is an important criterion for hospital discharge. Unfortunately, a relapse of symptoms following reintroduction of oral diet is common, with oral feeding intolerance (OFI) reported in up to 50% of patients [1]. These patients are often hospitalized for longer, have increased treatment costs and increased risk of readmission, particularly those who are discharged with gastrointestinal symptoms or without tolerating a full diet [2]. Further, a recent large prospective cohort study showed that OFI has a significant impact on patient's quality of life (QoL) [3]. In this study, OFI was found to impair five of the six QoL domains in AP patients: physical limitations, pain, sleep, psychological function and visceral function.

Growing awareness of the burden of OFI over the past decade has resulted in an increase in the number of interventional studies aiming to improve oral refeeding practices and reduce the unacceptably high occurrence of OFI. A systematic literature review published in 2007 identified only one interventional study [4], while a similar search of the literature now identifies more than a dozen interventional studies. These studies included nearly 1500 patients and investigated a variety of alternative refeeding strategies. From these studies, the approaches to reduce OFI can be broadly categorized into three areas: what to feed, when to feed and who governs these feeding decisions (Figure 1).

What to feed

The initial meal given to patients with AP is considered to be important in determining whether reintroduction of oral intake is tolerated. Patients following the conventional stepwise refeeding protocol are traditionally started on a hypocaloric clear liquid diet (CLD), and if this first meal is well tolerated, light diet (modified either in texture or in fat content) and full diet (solid, with calorie and fat content of a normal diet) are introduced in a stepwise manner until the patient can tolerate a full oral diet [5].

Light diet

A randomized controlled trial by Jacobson *et al.* compared outcomes in 121 patients with mild AP (defined as the absence of pancreatic necrosis or organ dysfunction) who received either the conventional stepwise refeeding or a

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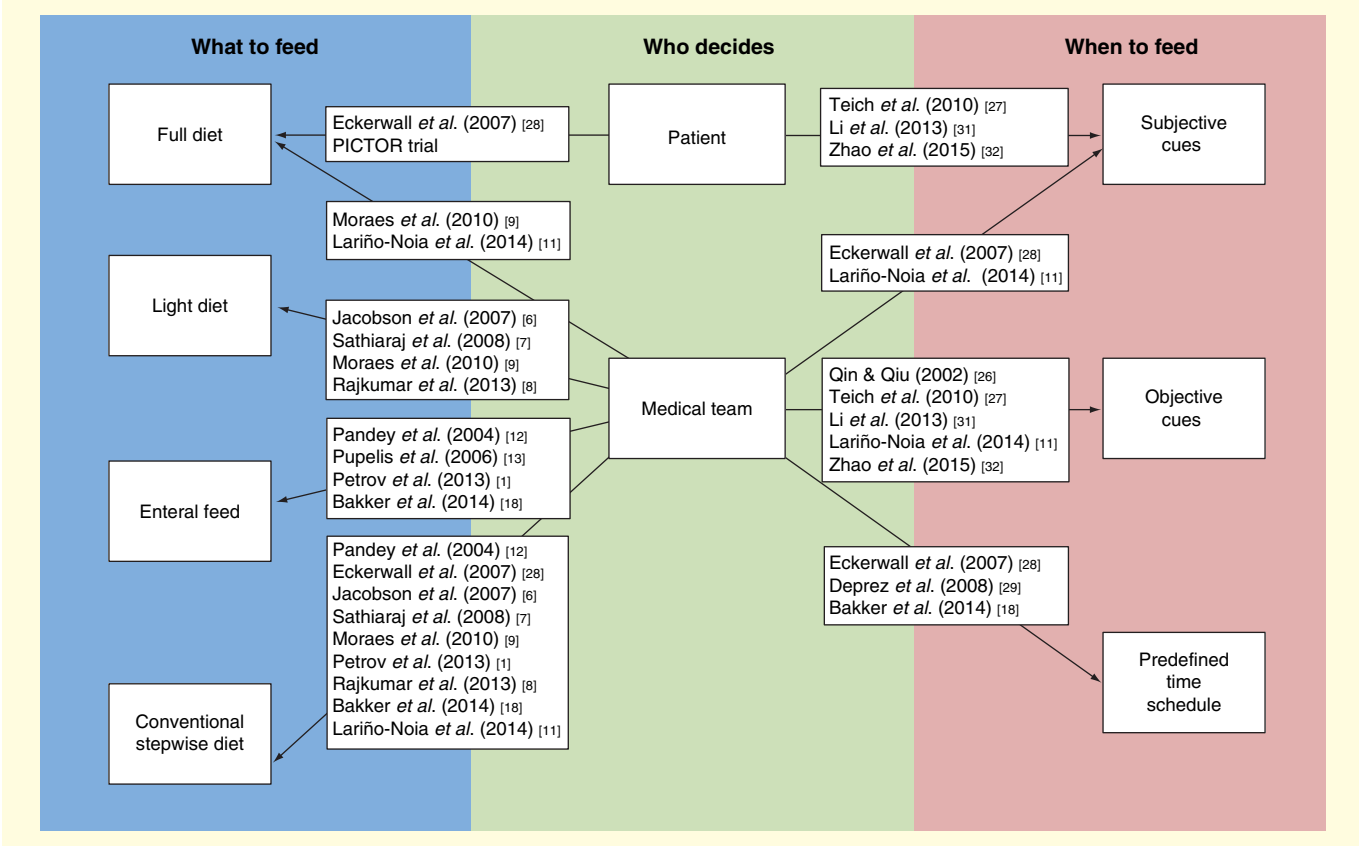

Figure 1. Summary of trial arms investigating the oral refeeding trilemma in acute pancreatitis.

light diet as the first meal [6]. All patients were monitored daily by a study nurse who recorded dietary information, food tolerance and pain levels. Similar rates of OFI were reported in patients who received the light diet, compared to the conventional group. While a light diet was well tolerated by the majority of patients and made no statistically significant difference in the hospital length of stay or rate of readmission between the two groups, it is worth noting that the combination of an open-label design and poorly defined discharge criteria could have led to the possibility of patients in the intervention group being kept longer for observation.

The safety of refeeding with a light diet was also investigated in later studies conducted by Sathiaraj *et al.* [7] and Rajkumar *et al.* [8] in which 101 and 60 patients, respectively, were randomized to receive either a light diet or conventional refeeding beginning with a CLD. All patients in the study by Sathiaraj *et al.* had confirmed mild AP (no pancreatic necrosis, abscess, pseudocyst, organ dysfunction, hypotension or hypoxemia) and were monitored daily for evidence of OFI. Patients included by Rajkumar *et al.* had predicted mild AP (Balthazar scores ≤ D), and there was no information regarding the frequency of monitoring OFI. No difference in tolerance was found between the two arms in either study, suggesting that a light diet is as safe as the current conventional protocol. In contrast to the study by Jacobson *et al.*, both studies found that patients starting on a light diet had a significantly reduced length of hospitalization (an average difference of 2 days in both studies) [7,8]. It is interesting to note that, although discharge was ultimately at the discretion of the treating team, both these studies had pre-defined discharge criteria included in their protocol, following the tolerance of a full diet. This may rationalize the difference in the length of hospitalization that was observed in these studies.

Also, none of the patients receiving light diet in the study by Rajkumar *et al.* were readmitted in the 30 days following discharge [8]. However, the generalizability of the data from this study is questionable, given that 90% of AP cases were of alcoholic etiology and the study population had an 11:1 male to female ratio, which is clearly not representative of the general population.

Full diet

Going one step further, Moraes *et al.* randomized 210 patients with mild AP (no organ dysfunction and <30% pancreatic necrosis) to begin oral refeeding with either a CLD, a light diet or a full solid diet [9]. Similar rates of OFI were reported in each group, and no difference in the length of hospitalization was seen between the three groups. However, a sub-group analysis revealed that patients who began oral refeeding on a solid diet and tolerated it had a significantly shorter length of hospitalization compared to those who began on a CLD or light diet (median 1.5 days shorter). In this case, discharge bias is

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highly unlikely to explain the lack of a difference observed in the main analysis, as the authors used objective and pre-defined patient discharge criteria following full oral tolerance. The authors also mentioned that a double-blind study design was used. However, the feasibility of blinding both patients and physicians to the difference between a CLD and a solid diet is questionable. Also, the authors chose to report only the per-protocol statistical analysis, rather than the intention-to-treat analysis, which raises the risk of bias. However, the authors addressed this concern in their response to a subsequent letter to the editor, and reported that there were no statistically significant differences between the outcomes from the two analyses [10]. A further limitation of this study is that the authors failed to report any measures taken to conceal the allocation of patients during randomization.

A subsequent study by Lariño-Noia *et al*. compared patients with mild and severe AP (defined according to the 1992 Atlanta classification) randomized to receive either a diet increasing in calories in a stepwise manner or a full caloric diet [11]. All patients were assessed prospectively (frequency has not been stated), and pre-defined discharge criteria were in place for all participating patients. No significant difference was found in terms of either the length of hospitalization or the frequency of OFI between the two groups. However, the conclusions drawn by this study may not be widely applicable as all meals in both groups were solid foods from first introduction, rather than the conventional CLD stepwise procedure. Also, the authors noted that the number of patients with severe AP was not large enough to confirm the applicability of the findings to severe cases. Interestingly, sub-group analysis revealed that an initial full caloric diet was beneficial in reducing the length of hospital stay (median 2 days shorter than the study's stepwise diet), but only when refeeding was started earlier than the conventional practice.

Enteral feed

An alternative approach is to minimize the period of gut disuse by timely introduction of low rates of enteral feed. An early study by Pandey *et al*. compared outcomes in 28 AP patients who were randomized to receive either oral or jejunal refeeding, with both groups undergoing a progressive increase in calories [12]. Patients were interviewed for abdominal pain on a daily basis during the refeeding period. The authors noted that although there was no statistically significant difference in abdominal pain from refeeding between the two groups, this may be attributed to type II error. Consequently, the lack of observed benefit in this study should not be interpreted as early enteral feeding not being beneficial.

A small feasibility study by Pupelis *et al*. adopted a strategy of starting oral feeding with small oral boluses of standard enteral formula in patients who did not have severely impaired intestinal motility [13]. Feeding was commenced predominantly within 48–72 h of admission. After 2 days of tolerance, the enteral formula was supplemented with light food, which was gradually advanced to a full diet. The volume and frequency of enteral feed boluses were increased according to each individual's tolerance. This protocol, while clinically practical, makes it difficult to accurately gauge the occurrence of OFI in the study population. However, it does appear that most patients tolerated this enteral to oral transition, including those with necrotizing AP. The authors noted that the aim of this process was to speed the recovery of gut function, rather than to achieve caloric goals. This is in line with their supposition that it is the supply of nutrients to the gut which is important in recovery, rather than the amount of food or nutritional status. However, the resulting reduction of OFI and earlier tolerance of refeeding is also likely to contribute to the maintenance of an adequate nutritional status.

In the MIMOSA trial, 35 patients with mild-to-moderate AP (defined according to the determinant-based classification [14,15]) were allocated to either receive nasogastric feeding within 24 h (starting at 0.4 ml/min) or be kept nil per os until oral refeeding, according to the conventional protocol [1]. All patients were monitored daily using a patient diary, and followed a pre-defined discharge plan after successful oral tolerance. This study found that patients who received early enteral tube feeding had a significantly reduced risk of OFI, reduced need for opiates and reduced abdominal pain. Further, the use of tube feeding did not impair the overall QoL or the individual QoL domains during hospitalization [16]. The exact mechanism of benefit from tube feeding remains to be investigated in further studies, but it may be due to reasons other than improvement of the upper gastrointestinal motility, as the analysis of motility endpoints in the MIMOSA trial showed that the use of nasogastric tube feeding did not significantly affect the Gastroparesis Cardinal Symptoms Index [17].

A multicenter study conducted by Bakker *et al*. sought to investigate the effect of early (within 24 h of hospital admission) enteral feeding compared with late (at 72 h or later after hospital admission) oral feeding and enteral feeding if required [18]. The study did not find a statistically significant difference between the two groups and the authors chose to interpret this as favoring feeding at 72 h after admission as the preferred nutritional strategy. Several aspects need to be taken into account to interpret the findings impartially. First, the study has been widely touted as the trial of early versus late enteral tube feeding. However, less than one-third of patients in the control group received tube feeding. Hence, the results of this study do not invalidate the supremacy of early tube feeding, which is based on a large body of evidence comprising an indirect meta-analysis of randomized controlled trials [19], retrospective cohort studies [20–22] and direct head-to-head randomized comparison of early versus late tube feeding [23]. Second, the authors attempted to include patients with severe AP by using predictive criteria such as Acute Physiology and Chronic Health Evaluation-II score ≥8, modified Glasgow score ≥3 or C-reactive protein >150 mg/l [18]. However, they clearly failed to do so as only 9% of patients had multiple organ failure. Hence, the overwhelming majority of patients in the study did not pose to benefit from tube feeding in terms of

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the composite primary endpoint (mortality and infectious complications), and the composite endpoint had not been validated [24]. Third, the trial may have been useful in determining the best refeeding practice, but despite outlining the criteria for reintroduction and response to intolerance of oral intake in a separately published protocol [25], no data were provided regarding the number of patients in the early tube feeding group experiencing OFI or pain relapse following feeding. It is unfortunate that a proper comparison between the studied strategies cannot be made with regard to feeding tolerance [18].

When to feed

Another important aspect of oral refeeding is the timing of food reintroduction. The traditional approach is to start oral feeding when abdominal pain is controlled and pancreatic enzymes have normalized [5]. The emerging alternative approaches are based on objective or subjective cues interpreted by treating teams, or on pre-defined time schedules.

Objective cues

It is common practice in many hospitals to await the objective parameters such as pancreatic enzyme levels and CT scans to normalize before commencing oral refeeding. A study conducted by Qin and Qiu aimed to determine the objective cues for reintroducing oral diet [26]. A total of 204 patients with AP began oral refeeding with a light fluid meal, based on the routine protocol of their treatment center (normalization of amylase, gastrointestinal function, symptoms and signs). Patients who successfully tolerated this first meal were randomized to advance their diet in a stepwise manner, based either on routine protocol or the improvement of the pancreas (as determined by ultrasound or CT imaging). This study reported a greater relapse in abdominal pain and an increased relapse of AP in the routine group; however, the methodological data for this were not provided. Further, the authors did not provide any indication of the length of time patients relying on pancreatic imaging took to progress to normal solid food, or how symptoms of intolerance were assessed. Given that the patients in the routine group began eating light solid food a minimum of 6 days after initial oral refeeding, and the imaging group took even longer to progress, the practicality of applying this study's findings to clinical practice is debatable.

A large multicenter study by Teich *et al.* randomized 143 patients with mild AP (no respiratory support, catecholamine therapy, renal support therapy, enteral or parenteral nutrition, alcohol withdrawal) to either lipase-directed refeeding (when lipase had normalized to <2× the upper limit of normal) or patient-directed refeeding (when opioid analgesics were no longer required) [27]. Even though the study protocol had no pre-defined discharge criteria, length of hospitalization and pain levels were similar in both groups. However, the use of a twice-daily visual analog scale rather than more objective outcomes means that the rates of intolerance cannot be reliably determined from these data. Also, the use of subjective visual analog scale scores means that the results of this study are sensitive to cultural and regional influences on pain perception, as noted by the authors. Recruitment for this study was prematurely terminated due to a poor accrual rate, and this may also have influenced the study results. Although the hypothesized pain improvement and reduced hospital stay could not be established, this study did show that lipase-directed reintroduction may not be necessary for safe refeeding. The high number of dropouts due to protocol deviation in the lipase-directed group also brings into question the external validity of this study.

Subjective cues

The study by Lariño-Noia *et al.* investigated more subjective signals to begin refeeding, specifically the resolution of bowel symptoms [11]. In this trial, patients were allocated to receive either oral nutrition according to the standard procedure (presence of bowel sounds, cessation of abdominal pain, absence of fever, and decreasing lipase and blood leukocyte levels) or early refeeding (presence of bowel sounds). The authors found that early refeeding based on symptom improvement was safe, as patients who began refeeding earlier (after the bowel sounds resumed) tolerated oral intake and experienced the same amount of gastrointestinal symptoms as patients who waited for traditional objective cues to normalize. Also, when earlier-fed patients were given a full caloric diet immediately, they had a significantly reduced length of hospitalization (median 2 days reduction), suggesting there is clinical benefit to early refeeding.

Pre-defined time schedule

Several studies have investigated the effect of reintroducing oral intake at specific time points during hospitalization. A study conducted by Eckerwall *et al.* in patients with predicted mild AP (Acute Physiology and Chronic Health Evaluation-II score <8) compared outcomes of patients who followed a standard fasting and refeeding protocol with the outcomes of patients who were allowed to begin eating on the day of admission [28]. Patients were monitored daily for nutritional and clinical outcomes. The study found that patients who were allowed to eat from admission started on solid food significantly earlier than the fasting group and showed no significant difference in tolerance or other complications, but had a significantly shorter length of stay (average 2 days shorter). There were no pre-defined discharge criteria set in this study, and patient discharge was entirely at the discretion of the medical team.

Similar findings were reported by Deprez *et al.*, who allocated 25 patients with predicted mild-to-moderate AP (Ranson score <3, computed tomography severity index <5, <30% necrosis and C-reactive protein <12 mg/dl) to be fed either within 24 h of pain resolution or 72 h after admission [29]. This study was only published in abstract form, and therefore, no data were available regarding discharge criteria or post-refeeding monitoring. Patients in the early feeding group tolerated the reintroduction of oral diet as well as those who did not receive food for 72 h, and had a significantly shorter length of hospitalization (average reduction of 2.6 days). However, the

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Table 1. Comparisons made by published randomized trials investigating the type of refeeding diet in patients with acute pancreatitis.

	Enteral feed	Conventional stepwise diet	Light diet	Full diet
Full diet	–	Moraes *et al.* (2010) [9] Larino-Noia *et al.* (2014) [11]	Moraes *et al.* (2010) [9]	
Light diet	–	Jacobson *et al.* (2007) [6] Sathiaraj *et al.* (2008) [7] Rajkumar *et al.* (2013) [8]		
Conventional stepwise diet	Pandey *et al.* (2004) [13] Petrov *et al.* (2013) [1] Bakker *et al.* (2014) [23]			
Enteral feed				

difference between the initiation times of refeeding in the two groups is unclear, and no data were available to clarify this.

Who decides

The third question in the oral refeeding trilemma is who makes the decisions on when, what and how to refeed. These kinds of decisions are typically at the discretion of the treating teams, and it is only recently that patient-directed approaches have been considered. A recent review argued that shifting from a physician-centered approach to one that incorporates patient goals is necessary for the provision of quality healthcare, and provides advantages to both patients and treating teams alike [30].

In a study conducted by Li *et al.*, 149 patients with predicted mild AP (Ranson score <3) were randomly allocated to receive either routine or early oral refeeding [31]. Those in the routine group were kept fasting until pancreatic enzymes had normalized, bowel sounds returned, abdominal discomfort was absent and patient hunger had returned. In the early refeeding group, it was up to the patients to decide when to resume oral intake, based on their subjective feelings of hunger. Patients were assessed daily for symptoms of OFI, and pre-defined discharge criteria were established for all patients. The authors demonstrated that patient-directed refeeding time resulted in significantly shorter hospital stays (an average reduction of 3.6 days) with no increased risk of adverse events in the presence of abnormal serum markers.

A later study by Zhao *et al.* showed that these findings are also applicable to patients with moderate and severe AP (defined as the presence of organ failure and/or local or systemic complications) [32]. Patients were monitored daily for nutritional and clinical outcomes, and pre-defined discharge criteria were applied to all patients. This study showed that refeeding directed by patient hunger reduced the hospital length of stay (by an average of 2 days) without causing a greater risk of OFI, compared to that of patients in the conventional arm.

The protocols of studies by Li *et al.* and Zhao *et al.* allowed patients to decide when to eat, but both required patients to follow a conventional stepwise diet [31,32]. As of yet, there are no published studies that allow patients to choose the option of when and what they would eat. The ongoing Patient-Intitiated and ConTrolled Oral Refeeding (PICTOR) randomized trial at Auckland City Hospital (Auckland, New Zealand) compares the metabolic, nutritional and clinical outcomes of patients who direct their own refeeding, compared to patients in the conventional stepwise oral refeeding protocol [33]. Patients with AP without ongoing need for opiates are randomized to either conventional stepwise oral refeeding or patient-controlled refeeding, which allows patients to choose what to eat and when to eat at their discretion. Patients are monitored daily and outcomes are recorded in a detailed patient symptom diary. Discharge is at the discretion of the treating teams. First study results are expected in 2016.

Expert commentary

Finding the answers to these three questions is essential for the optimization of nutritional management in AP. By ensuring that patients begin refeeding at the right time, with the right type of food, it is expected that we will see a reduction in the frequency of OFI and, subsequently, improved patient QoL, reduced length of hospitalization and a resulting reduction in treatment costs.

The current evidence suggests that both light and full diets are just as well tolerated as the conventional stepwise diet, as no study has reported any difference in OFI rates between the study groups. The effect of these diets on length of hospitalization has proved to be more variable: two studies have shown that commencing refeeding on a light or full solid diet resulted in a reduction in hospital stay [7,8], whereas others have not [6,9,11]. Study-level factors should be considered when investigating OFI, and further studies that use pre-defined discharge criteria are needed to confirm these findings. However, given the best available evidence of the safety of light and full diets, it appears that the CLD step of refeeding may be safely omitted.

The published superiority randomized trials seem to be consistent in inferring that early refeeding is well tolerated and, in some studies, has been shown to reduce the length of hospitalization. While different studies used a range of cues to begin refeeding, none of the investigated approaches improved the

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tolerance of oral refeeding. Furthermore, none of the studies were designed to be a non-inferiority trial, which is the preferred study design for demonstrating that the new strategy is at least not worse than the conventional one [34]. It is argued that rather than sporadically investigating various subjective or objective cues or arbitrary pre-defined time schedules, a more robust approach to determine when to start feeding in an individual patient with AP is to embrace the recently introduced concept of 'gut rousing' and use it as a unified framework to systematically investigate the optimal timing of oral refeeding. The gut rousing concept postulates that maintenance of gut function or reduction of gut dysfunction is the key to improve nutrition-related and clinical outcomes in patients with AP [35]. Hence, the introduction of feed (either orally or enterally) may have a therapeutic role. Based on the best available evidence, all patients with AP should be kept nil per os until the initial liberal intravenous fluid resuscitation and opiate analgesia is tapered (usually the first 24 h after admission). Oral refeeding should begin around 24–48 h after admission in patients with normal gut function, while patients showing signs of gut dysfunction should have tube feeding introduced.

Five-year view

Despite the recent increase in the number of publications investigating the nutritional management of AP, there are still large gaps in the literature that need to be addressed over the next 5 years. When investigating the question of what patients should receive as the initial meal in refeeding, the majority of studies have compared the outcomes of interventional diets to those of the conventional stepwise diet. However, the evidence comparing different interventions to each other is sparse and, in some cases, completely missing (Table 1).

Also, very few studies have been conducted to investigate the role of patient-centered care in oral refeeding. While there are some studies that have begun this process of investigation [27,28,31–33], there is still much room for further research in this area (Figure 1). At present, patients are not very involved in the decision-making for their care. While it may not be appropriate or feasible for patients to be involved in all areas of their care, it is important to think critically about areas in which they can be included in the decision-making. Indicators such as lipase levels or CT scans, and the ability to initiate enteral feeding should arguably be directed by the treating team; however, this does not mean that patients cannot be involved in the discussion regarding when they should restart oral intake and what they should eat.

Over the next 5 years, the research focus of oral refeeding in AP will continue to broaden, in order to promote more holistic management of patients. The concept of gut rousing provides a valuable framework that allows nutrition to be considered in the context of overall medical management of AP (including the functionality of the gut, administration of opioid analgesics and resuscitation fluids), rather than in isolation [35]. Broader perspectives in research are needed to elucidate the risk factors of OFI and inform appropriate interventions to reduce OFI occurrence. Future research should also attempt to encapsulate other outcomes such as patient QoL, which is essential for holistic patient health and can be profoundly impacted by complications such as OFI.

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Key issues

- Oral feeding intolerance is a common complication in acute pancreatitis that has a considerable burden.
- Light and full diets as the first meal are as well tolerated as a clear liquid diet, and may reduce the length of hospitalization.
- As a guideline, feeding of patients with acute pancreatitis should, in general, be started on the second day after hospital admission: enteral tube feeding in patients with gut dysfunction and oral refeeding in patients with normal gut function.
- 'Gut rousing' is a valuable framework to direct further research on early management of patients with acute pancreatitis, including interventional studies of different oral refeeding practices.
- Individualized patient-directed refeeding regimes have the potential to reduce hospital length of stay without increasing the risk of oral feeding intolerance.
- Refeeding decisions should be coherent between wider treating teams and with a patient-centered focus.

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