# Early Feeding in Acute Pancreatitis in Children: A Randomized Controlled Trial

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abstract

**BACKGROUND:** Studies have increasingly challenged the traditional management of acute pancreatitis (AP) with bowel rest. However, these studies used a low-fat diet or transgastric feeding and only included adults. Aiming to generate higher-quality prospective pediatric data, we compared the traditional approach of fasting and intravenous fluids and early enteral feeding with standard diet or formula.

**METHODS:** Randomized controlled trial of children (2–18 years) with mild-moderate AP. Patients were randomly assigned 1:1 to initial fasting and intravenous fluids or an immediate, unrestricted diet. Pain scores, blood measures, and cross-sectional imaging were recorded throughout admission and follow-up. The primary outcome was time to discharge, and secondary outcomes were clinical and biochemical resolution and local and systemic complication rates.

**RESULTS:** Of 33 patients (17 [52%] boys, mean age of 11.5 [±4.8] years), 18 (55%) were randomly assigned to early feeding and 15 (45%) were randomly assigned to initial fasting. We recorded the median (interquartile range [IQR]) time to discharge (2.6 [IQR 2.0 to 4.0] vs 2.9 [IQR 1.8 to 5.6]; $P$ = .95), reduction in serum lipase levels by day 2 (58% [IQR 2% to 85%] vs 48% [IQR 3% to 71%]; $P$ = .65), and readmission rates (1 of 18 [6%] vs 2 of 15 [13%]; $P$ = .22) between the early feeding and fasting cohorts, respectively. Immediate or delayed complication rates did not differ. Patients randomly assigned to early feeding had weight gain of 1.3 kg (IQR 0.29 to 3.6) at follow-up, compared with weight loss of 0.8 kg (IQR −2.1 to 0.7) in fasted patients ($P$ = .028).

**CONCLUSIONS:** This is the first randomized controlled trial in pediatric AP. There was no difference between early commencement of a standard oral diet and initial fast in any of the major outcome measures.

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Dr Ledder conceptualized and designed the study, coordinated and supervised data collection, collected data, conducted the data analysis, drafted the initial manuscript, and reviewed and revised the final draft; Dr Duvoisin, Ms Lekar, and Drs Lopez and Singh designed the data collection instruments, collected data, and reviewed the manuscript; Ms Dehlsen, Drs Lev-Tzion, Orlanski-Meyer, Shteyer, Krishnan, and Gupta, and Prof Lemberg collected data and critically reviewed the manuscript; Drs Cohen and Ooi designed the study, coordinated and supervised data collection, collected data, conducted the data analysis, and reviewed the final draft; (Continued)

**WHAT'S KNOWN ON THIS SUBJECT:** Early enteral feeding is beneficial in acute pancreatitis; however, evidence is limited to low-fat or transgastric feeding. There are no prospective data, and only limited retrospective data, in pediatric AP. Initial fasting is still widely practiced by pediatric gastroenterologists.

**WHAT THIS STUDY ADDS:** This randomized controlled trial study reveals equivalent outcomes between initial fasting and early commencement of a standard, full-fat diet in mild-moderate AP in children. This provides needed evidence to encourage implementation of early unrestricted diet in these patients.

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Although severe acute pancreatitis (AP) in children is less common than in adults, it can nonetheless cause significant morbidity and even mortality.[1,2] Treatment of AP traditionally relied on complete bowel rest with intravenous (IV) fluids followed by a low-fat diet, with the aim of minimizing the activity of an already inflamed pancreas. Multiple studies in adults have since revealed that early enteral feeding is well tolerated and has significant benefits over fasting or parenteral nutrition, including morbidity, mortality, and a shorter hospital length of stay.[3–8] There is a paucity of pediatric studies, mainly retrospective in nature, with minimal prospective data[9,10] and no randomized trials. The majority of studies to date used nasojejunal feeds or low-fat feeds, presumably to minimize potential pancreatic stimulation.[11] Several animal models of AP suggest that pancreatic secretion, and particularly pancreatic secretory response to cholecystokinin, may diminish early after the onset of AP.[12] Hence, it would seem that feeding may not stimulate the inflamed pancreas, and the assumed concern of exacerbating an already inflamed pancreas may be overstated.

Despite the mounting evidence to the contrary, a survey of practice revealed that the overwhelming majority of pediatric gastroenterologists treat patients with AP with initial fasting and only slowly reintroduce feeds depending on the clinical improvement.[13,14] Indeed, despite recent expert recommendations supporting early feeding in AP, this recommendation is based on retrospective pediatric data and expert opinion extrapolated from adult data.[10,15–18] Therefore, we aimed to prospectively determine if early feeding of children with mild-moderate AP would lead to shorter hospitalization and if it is safer and better tolerated compared with standard practice in the first randomized controlled trial in pediatric AP.

## METHODS

This randomized controlled trial, conducted between 2015 and 2018, included children 2 to 18 years of age diagnosed with AP as per the INSPPIRE (International Study Group of Pediatric Pancreatitis: In Search for a Cure) consensus definition, which requires at least 2 of the following: (1) abdominal pain compatible with AP, (2) serum lipase and/or amylase levels ≥3 times the upper limit of normal, and (3) imaging findings of AP.[14] Patients were excluded if (1) they had signs of severe pancreatitis associated with organ dysfunction (systolic blood pressure <90 mm Hg, $Pao_2$ level <60, creatinine level >2 mg/dL, or gastrointestinal bleeding >500 mL per 24 hours)[19] or required ICU admission; (2) they had a biliary cause of pancreatitis; (3) they had autoimmune pancreatitis; (4) they had high-grade traumatic pancreatitis, defined as partial or complete disruption of the pancreatic duct; and (5) they had any other conditions restricting enteral nutrition. To ensure early commencement of the diet in those patients randomly assigned to early feeding, patients in whom AP was thought to have started >24 hours before presentation were excluded.

After informed consent by both parents, patients were randomly assigned 1:1 by treating the physician at each site using sealed envelopes kept on site in the participating centers. Those patients allocated to initial fasting were treated as per the commonly practiced standard of care: initial nil by mouth (NBM) with IV fluids, followed by a low-fat oral diet once pain resolved and serum amylase and/or lipase levels decreased and/or according to the discretion of the treating physician. IV fluids were administered as directed by the treating physician on the basis of standard maintenance rates, with boluses or increased rates administered on the basis of clinical or biochemical evidence of hypovolemia. The early enteral feeding group was offered an unrestricted diet immediately after random assignment and encouraged to commence oral feeding as soon as possible at a level tolerated by the patient. Nasogastric or nasojejunal tube insertion for administration of polymeric enteral feeds of standard fat concentrations was considered if a patient in the early feeding group was unable or considered unlikely to commence oral feeding within 24 hours of symptom onset. The treating physician, independent of the research team, retained the right to request a different treatment approach if deemed necessary for medical reasons. If such a case were to occur, the child was to be excluded from the study.

In addition to an abdominal ultrasound at admission, patients were reviewed daily with serial blood measures (blood cell count, liver profile, serum electrolyte level, C-reactive protein [CRP] level, erythrocyte sedimentation rate, lipase and/or amylase level), twice-daily pain scores (Wong-Baker Faces Pain Rating Scale[20]), analgesia use, weight, and detailed dietary intake, which was calculated by the team dietician as the patient-specific percentage of the estimated energy requirement (EER). Morbidity, including, but not limited to, hemodynamic instability, sepsis, PICU admission, or PICU team review, was recorded. To confirm full resolution and identify local complications, patients were followed-up at 30 to 60 days post discharge with repeat blood measures (as per blood cell counts during admission) and an abdominal ultrasound.

The primary outcome was time to ready for discharge and was based on 3 criteria: (1) 2 consecutive "no pain"

ratings on the pain score, (2) no analgesic requirement apart from as-required doses of oral acetaminophen, and (3) an oral diet meeting 75% to 100% of the EER.[21] Secondary outcomes included length of hospital stay, time to clinical and biochemical resolution of AP, and local and systemic complication rates.

The trial was conducted in 3 tertiary medical centers: Sydney Children's Hospital, Randwick, Australia; Shaare Zedek Medical Center, Jerusalem, Israel; and Dana-Dwek Children's Hospital, Tel Aviv, Israel. Trial data were recorded on case report forms at each center, and deidentified data were transferred to the data coordination center at Shaare Zedek Medical Center. This study was reviewed and approved independently by each of the treating centers' medical ethics review boards and is listed on ClinicalTrials.gov (identifier NCT02814071).

### Sample Size

We calculated the sample size, assuming a mean length of hospital admission of 3 ± 1 day and aiming to detect a 30% reduction in length of hospital admission with a power of 80% and a significance level of 5%, which required a total of 32 patients to be recruited.

### Statistical Analysis

Data are presented as mean ± SD or median with interquartile range (IQR), as appropriate for the distribution normality. Primary and secondary outcomes were compared by using the $\chi^2$ test or Fisher's exact test for categorical variables and Student's $t$ test or Wilcoxon rank test for continuous variables. Statistical analyses were performed by using SPSS (version 21.0; IBM SPSS Statistics, IBM Corporation, Armonk, NY), with $P < .05$ taken as the significance threshold.

## RESULTS

Thirty-three patients were recruited; 18 (55%) were randomly assigned to early enteral feeding, and 15 (45%) were assigned to initial fasting and IV fluids. All recruited patients completed the protocol, and no patients were excluded or withdrawn from the study after treatment allocation (Fig 1). There was no difference between the 2 cohorts in age, weight, pain scores, and serum amylase and lipase levels at presentation (Table 1). The median (IQR) time to commencement of enteral feeding was 19.3 (10.9–26.8) hours in the early feeding group, compared with 34.7 (22–76.8) in the initial fasting group ($P$ = .004), and there was a consistent trend to earlier attainment of at least 50% EER and >75% EER in the early feeding group than in the initial fasting group (Table 2). One patient in the early feeding group had partial nasogastric nutrition supplementation initially; no patients in either group requiring exclusive nasogastric or nasojejunal feeds, and no patients received parenteral nutrition. No patient allocated to early feeding had feeding delayed by the treating physician over clinical or other concerns.

There was no difference in the primary outcome of time elapsed until ready for discharge. Both cohorts had equal time to pain free status, as defined by Wong-Baker pain scales, and there was no difference in serum amylase or lipase levels at discharge or in weight changes throughout the admission (Table 2, Fig 2). One child allocated to initial fasting developed a small pancreatic pseudocyst that self-resolved, and there were no other localized findings on imaging or systemic complications in either cohort throughout the admission.

Two patients from the initial fasting group were readmitted with recurrence of pain and symptoms from AP, 1 of whom was discharged before achieving adequate pain control and was represented for further inpatient management. A second patient from the initial fasting group was readmitted with relapsed pancreatitis 3 weeks after discharge and an additional rise in the serum lipase level despite near normalization on discharge. In contrast, no patient from the early feeding group was readmitted. One child from the early feeding group was readmitted 5 days after initial discharge with self-limiting diarrhea

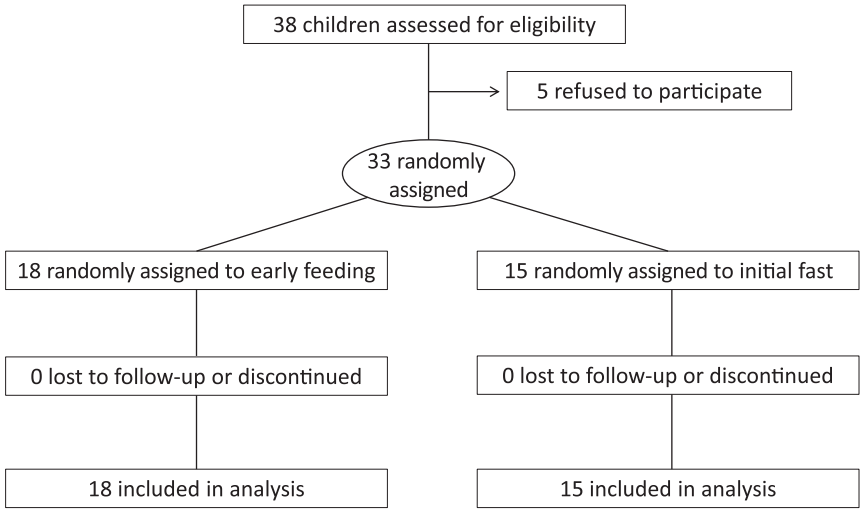


**FIGURE 1**
Consolidated Standards of Reporting Trials study flow diagram.

**TABLE 1** Baseline Characteristics

| | NBM or IVFs | Early Feeding | Significance, *P* |
|---|---|---|---|
| No. | 15 | 18 | — |
| Male sex, *n* (%) | 9 (60) | 8 (44) | .39 |
| Age, y, mean (±SD) | 11.6 (±5.2) | 11.5 (±4.6) | .93 |
| BMI, mean (±SD) | 20.1 (±4.7) | 19.3 (±4.6) | .73 |
| Lipase, U/L, median (IQR) | 637 (286 to 1750) | 1326 (631 to 2360) | .28 |
| Amylase, U/L, median (IQR) | 314 (173 to 809) | 579 (334 to 1763) | .21 |
| Pain score, median (IQR) | 6 (4 to 8) | 7.5 (6 to 8.5) | .33 |

IVF, intravenous fluid; —, not applicable.

persisting for 2 days and was diagnosed by the pediatric team with gastroenteritis; however, no viral agent was identified.

The median follow-up time was 49 (IQR 40 to 57) days. At follow-up, there was a significant difference between the groups in weight, with a median weight gain of 1.3 kg (IQR 0.29 to 3.6) noticed in the early feeding group, as opposed to a weight loss of 0.8 kg (IQR −2.1 to 0.7) in the initial fasting group ($P$ = .028). There were no differences detected in blood results, and there was a trend toward lower serum lipase levels in the early feeding group that failed to reach significance (Table 2). No local pancreatic complications were detected on any patients on the follow-up ultrasound.

## DISCUSSION

To the best of our knowledge, this study is the first randomized controlled trial of any type in pediatric AP. We demonstrated that early commencement of a full-fat diet in children with mild-moderate AP is safe and has no difference in outcomes compared with initial fasting and a subsequent low-fat diet.

This study contributes to earlier cumulative adult data revealing a benefit of enteral nutrition over fasting, particularly in severe AP.[3–8] Initially, management of AP was predicated on avoidance of pancreatic stimulation. As such, nasojejunal feeds were predominantly used in studies of early enteral feeding. Eatock et al[22] challenged this premise in a trial in which patients with severe AP were randomly assigned to nasogastric or nasojejunal administration of low-fat feeds within 72 hours, with no difference detected in outcomes.

**TABLE 2** Patient Outcomes

| | NBM or IVFs | Early Feeding | *P* |
|---|---|---|---|
| Time to cessation of fast, h, median (IQR) | 34.7 (22 to 76.8) | 19.3 (10.9 to 26.8) | .004 |
| EER day 2, *n*/*N* (%) | | | |
| >50% | 4/15 (27) | 9/18 (50) | .19 |
| >75% | 1/15 (7) | 5/18 (28) | .13 |
| EER day 3, *n*/*N* (%) | | | |
| >50% | 8/15 (53) | 15/18 (83) | .067 |
| >75% | 6/15 (40) | 12/18 (67) | .13 |
| Time to pain free, d, median (IQR) | 2 (1 to 4) | 2 (1 to 3) | .95 |
| Days until ready to discharge, median (IQR) | 2.9 (1.8 to 5.6) | 2.6 (2.0 to 4.0) | .56 |
| Reduction in lipase levels on day 2, %, median (IQR) | 48 (3 to 71) | 58 (2 to 85) | .65 |
| Reduction in amylase levels on day 2, %, median (IQR) | 36 (−16 to 45) | 23 (3 to 59) | .56 |
| Lipase at discharge, U/L, median (IQR) | 188 (27 to 348) | 190 (90 to 284) | .94 |
| Amylase at discharge, U/L, median (IQR) | 108 (61 to 327) | 172 (120 to 861) | .095 |
| Lipase at follow-up, U/L, median (IQR) | 50 (15.5 to 371) | 30.5 (18.8 to 88.3) | .815 |
| Amylase at follow-up, U/L, median (IQR) | 92 (60 to 213) | 85.5 (67.8 to 152) | .91 |
| Readmission, *n* (%) | 2 (13) | 1 (6) | .22 |
| Relapse pancreatitis, *n* (%) | 1 (6) | 0 (0) | .30 |
| Δ in wt until discharge, kg, median (IQR) | 0.0 (−0.2 to 0.3) | 0 (−0.49 to 0.3) | .82 |
| Δ in wt until follow-up, kg, median (IQR) | −0.8 (−2.1 to 0.7) | 1.3 (0.29 to 3.6) | .028 |

IVF, intravenous fluid; Δ, difference.

There has been more recent mounting evidence that early and immediate feeding of patients may also be beneficial. Eckerwall et al[23] randomly assigned 60 adult patients with mild AP (APACHE level <8, CRP level <150) to fasting or an immediate oral diet. There was no difference in outcome measures (pain, amylase level, CRP level); however, immediate feeders had a shorter hospital stay. In an additional randomized unblended trial by Lariño-Noia et al,[3] the authors also concluded that early refeeding with a full-caloric, low-fat diet is a safe and well-tolerated practice that also shortens length of hospital stay. Since then, further studies and meta-analyses in adults have conclusively revealed the benefits of early enteral nutrition, with reduced rates of multiorgan failure, less systemic infections, fewer operative interventions, reduced overall morbidity, shorter hospital length of stay, and a lower overall mortality.[3–7] Potential mechanisms of this benefit have been proposed, including the likelihood of enteral nutrition better maintaining integrity and function of intestinal mucosa[24,25] and reducing gut-origin sepsis.[26] Bakker et al[5] somewhat challenged the notion of timing of onset of a diet with similar rates of major infections and mortality in patients with severe AP who received nasojejunal feeds within 24 hours and an oral diet within 72 hours.

It should be noted that in the majority of these trials, low-fat feeds were administered, seemingly for pancreatic protection. Several animal models of pancreatitis of various severities suggest that the inflamed pancreas does not respond to further stimulation, and low-fat feeds may not be required.[12] In these models, the exocrine pancreas gradually

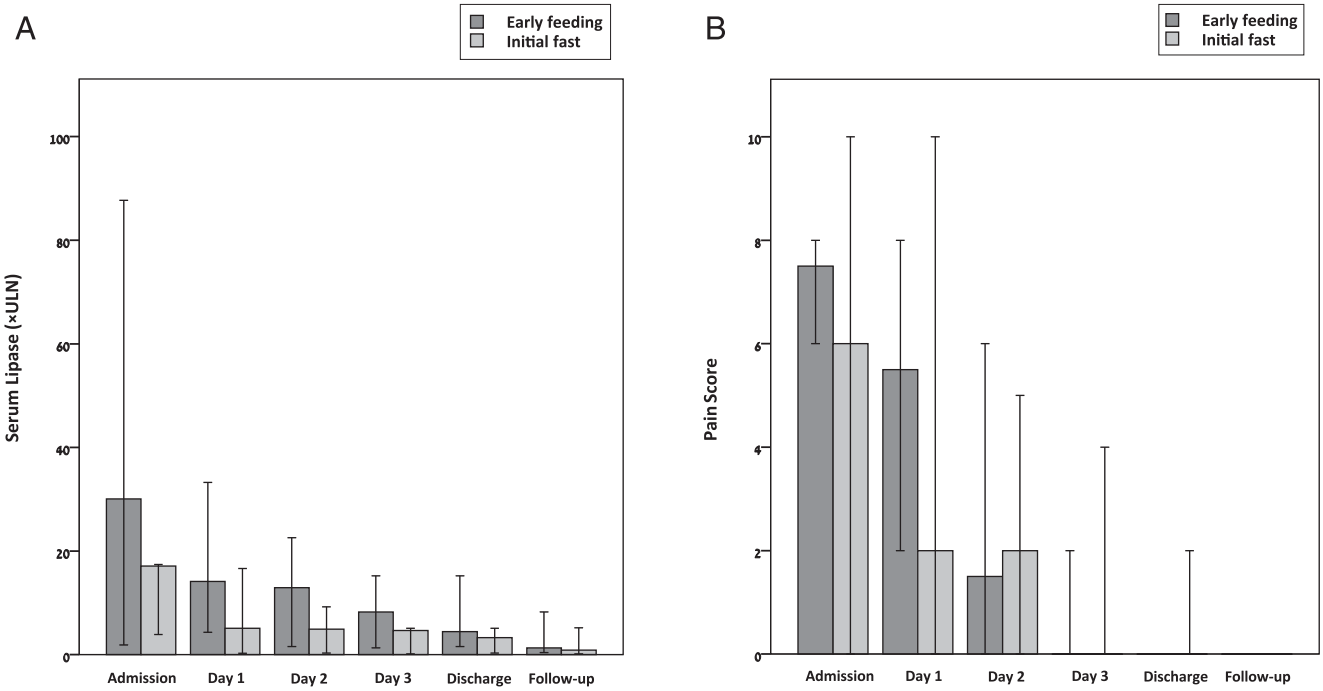


**FIGURE 2**
Secondary outcome measures. A, Serum lipase (×ULN). B, Pain scores (Wong-Baker Faces Pain Rating Scale). ULN, upper limit of normal.

became resistant to cholecystokinin stimulation after the onset of AP, with cholecystokinin-stimulated secretion almost abolished in vivo and in vitro at the time of maximal histologic damage. Basal pancreatic secretion was also reduced during inflammation. The time course of improvement of secretory function after acute experimental pancreatitis depended on the severity of the pancreatitis.[12] Data suggest that pancreatic secretion, and particularly cholecystokinin-stimulated pancreatic secretion, may also be reduced in patients early after the onset of AP.[12]

Although it may be assumed that outcomes of management in pediatric AP would be comparable with those in adult AP, pediatric AP has some noted differences from adult AP. The etiologies of pediatric AP are diverse and differ from those of adult AP, as do the severity and the outcome of pediatric AP.[27] Hence, extrapolation from adult data may not necessarily guide our practice accurately or effectively. Until recently, data on nutrition in pediatric AP was based on a small number of retrospective studies,[10,18,28–30] only 1 of which included >24 patients. More recently, Ellery et al[9] compared 30 prospectively recruited patients with mild AP who were allowed to eat at their discretion with 92 patients from a retrospective cohort who were allowed to eat on the basis of traditional practice. The patient-directed nutrition cohort had a shorter length of NBM and a shorter hospital stay than the historical cohort. Although this important study further supported the benefit of early nutrition in AP, this study commenced a low-fat diet, as opposed to a standard diet in our study. Although we did not demonstrate the same benefit in discharge time, both groups in our study had a discharge time comparable with that of the later prospective cohort in the study by Ellery et al,[9] likely representing a change over time in discharge practices in mild-moderate AP.

We recruited patients with mild or moderate AP on the basis of data suggesting a possible risk of early enteral nutrition in severe AP.[31] Although there was no difference in the outcome measures at discharge between both groups, those patients on early feeding with a full diet gained weight at the last follow-up, whereas those patients in the fasting group lost weight. Although this difference in weight was statistically significant, its clinical significance is open to speculation because further follow-up anthropomorphic data or pubertal assessment was not included in the study protocol. It should be noted that early feeding in the literature is considered feeding within 24 to 72 hours; hence, both groups were exposed to oral nutrition at a relatively early stage. This may plausibly explain the lack of difference in most outcome measures in this study.

Besides the unnecessary discomfort and distress of fasting for a child, the potential benefits of early enteral nutrition in AP are numerous. Some centers use nasojejunal feeding to minimize pancreatic stimulation, and

this is often sited under radiologic guidance. Forgoing this intervention not only is more comfortable for patients but also reduces unnecessary exposure to ionizing radiation.

Our study had some limitations. Firstly, despite it being one of the largest trials relating to nutrition in pediatric AP and the only wholly prospective trial, the numbers are still limited. Complicated disease course in pediatric pancreatitis, including both local and systemic complications, is less frequent than in adult AP,[27] and the smaller sample size may not adequately reflect all cases. In addition, we only recruited patients with mild-moderate AP, and we excluded traumatic and biliary pancreatitis to obtain a more homogenous cohort and minimize the impact of other factors, which may influence recovery. The etiology of pancreatitis was also not extensively investigated beyond more routine blood markers and imaging. Hence, these results may not necessarily be extrapolated to all AP cases.

Adequate hydration has been demonstrated to influence clinical outcomes in pediatric AP.[18] Although IV fluid administration in our study was at the discretion of the treating physician, it is plausible that children in the initial fasting group may have been inadequately hydrated compared with those in the early feeding group with access to oral hydration. This was not specifically controlled for in this study, and hence it is unclear if this influenced the outcomes. It goes without saying that all patients with AP require adequate hydration, whether enteral or IV.

After the commencement of our trial, formal classification guidelines relating to pediatric AP severity were published.[19] In the interest of standardization between centers and to facilitate rapid recruitment, the classification of severe AP in our study was based on fixed cutoff values as described above. Although these inclusion criteria may not necessarily fully correlate with recent formal guidelines, when later assessed, all children recruited had mild-moderate AP, as defined by the recent guidelines.

## CONCLUSIONS

The burden of pediatric AP is significant,[17,32] and measures to improve management have benefits on both the individual and the health system as a whole. We demonstrated the safety of early commencement of a full-fat diet in pediatric AP, with no impact on disease duration, length of hospital stay, or complication rates. These findings provide important supportive data to current recommendations relating to early feeding in pediatric AP, preventing unnecessary fasting in young patients with AP. Indeed, fasting of children with mild-moderate AP may now be considered inappropriate in most circumstances, both in clinical care and in future studies. Considering extensive cumulative data to date in mild-moderate AP, although rare in pediatrics, attention need be given to a similar multicenter trial in severe pediatric AP, for which the benefits of early nutrition may potentially be more far-reaching.

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## ABBREVIATIONS

AP: acute pancreatitis
CRP: C-reactive protein
EER: estimated energy requirement
IQR: interquartile range
IV: intravenous
NBM: nil by mouth

and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.Deidentified individual participant data (including data dictionaries) will be made available, in addition to study protocols, the statistical analysis plan, and the informed consent form. The data will be made available, after publication, to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal. Proposals should be submitted to orenl@szmc.org.il.

This trial has been registered at www.clinicaltrials.gov (identifier NCT02814071).

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