

## Restoration of energy level in the early phase of acute pediatric pancreatitis

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### Abstract

Acute pancreatitis (AP) is a serious inflammatory disease with rising incidence both in the adult and pediatric populations. It has been shown that mitochondrial injury and energy depletion are the earliest intracellular events in the early phase of AP. Moreover, it has been revealed that restoration of intracellular ATP level restores cellular functions and defends the cells from death. We have recently shown in a systematic review and meta-analysis that early enteral feeding is beneficial in adults; however, no reviews are available concerning the effect of early enteral feeding in pediatric AP. In this minireview, our aim was to systematically analyse the literature on the treatment

of acute pediatric pancreatitis. The preferred reporting items for systematic review (PRISMA-P) were followed, and the question was drafted based on participants, intervention, comparison and outcomes: P: patients under the age of twenty-one suffering from acute pancreatitis; I: early enteral nutrition (per os and nasogastric- or nasojejunal tube started within 48 h); C: nil per os therapy; O: length of hospitalization, need for treatment at an intensive care unit, development of severe AP, lung injury (including lung oedema and pleural effusion), white blood cell count and pain score on admission. Altogether, 632 articles (PubMed: 131; EMBASE: 501) were found. After detailed screening of eligible papers, five of them met inclusion criteria. Only retrospective clinical trials were available. Due to insufficient information from the authors, it was only possible to address length of hospitalization as an outcome of the study. Our mini-meta-analysis showed that early enteral nutrition significantly ( $SD = 0.806$ ,  $P = 0.034$ ) decreases length of hospitalization compared with nil per os diet in acute pediatric pancreatitis. In this minireview, we clearly show that early enteral nutrition, started within 24-48 h, is beneficial in acute pediatric pancreatitis. Prospective studies and better presentation of research are crucially needed to achieve a higher level of evidence.

**Key words:** Pediatric pancreatitis; Enteral nutrition; Nil per os diet; ATP restoration; Length of hospitalization

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**Core tip:** Acute pancreatitis is a serious inflammatory disease with rising incidence both in adult and pediatric medicine. Despite the existing research activities in this field, no specific therapy is available to treat this disease. Results in basic science strongly suggest that early energy restoration could be the first-line treatment for acute pancreatitis. Our minireview suggests that early enteral nutrition should have priority in the treatment of acute pediatric pancreatitis.

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## INTRODUCTION

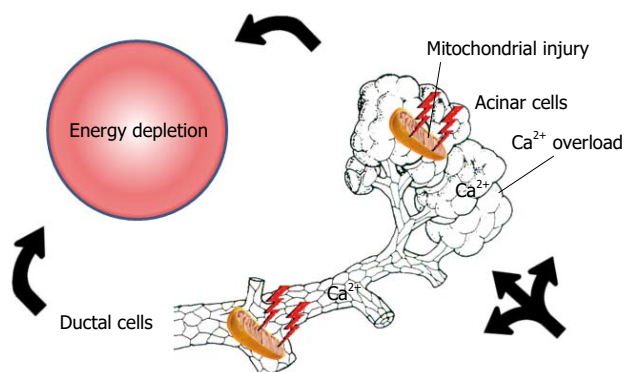
Acute pancreatitis (AP) is a serious inflammatory disease with rising incidence both in adult and pediatric populations<sup>[1,2]</sup>. Common characteristics in both age groups are that no specific therapy is available to

treat the disease and that the general supportive treatments at the early phase of the disease are usually volume resuscitation and a nil per os (NPO) diet<sup>[3-6]</sup>. However, while there is clear evidence in the literature that volume therapy is beneficial, the latter treatment is questionable.

One of the main reasons for the debate is that the pathogenesis of the disease clearly suggests the opposite. Irrespective of the etiological factors, mitochondrial damage and energy depletion are the leading intracellular responses in the early phase of the disease in the exocrine pancreas<sup>[7-10]</sup>. Bile acids<sup>[11-14]</sup>, ethanol, fatty acids and their non-oxidative metabolites, fatty acid ethyl esters<sup>[8,9,15-18]</sup> were shown to elevate the intracellular  $Ca^{2+}$  concentration, causing mitochondrial damage and a resultant decrease of intracellular ATP concentration. This will lead to inhibited fluid and bicarbonate secretion and CFTR  $Cl^-$  channel dysfunction in the ductal cells and secretory block and intracellular trypsinogen activation in the acinar cells (Figure 1)<sup>[9,16,19,20]</sup>. Very importantly, restoration of ATP levels both in acinar and ductal cells prevents (at least in part) the toxic effects of the etiological factors<sup>[7,21,22]</sup> noted above. These data strongly suggest that an energy supply, for example, *via* enteral nutrition, should be beneficial for patients as compared to nil energy.

Notably, early enteral nutrition (EEN) either *via* oral, nasogastric- or nasojejunal tube feeding is beneficial as regards systemic infections, complications, multi-organ failure, need for surgical interventions and mortality<sup>[6,23-30]</sup>. Enteral nutrition has already been proven to be beneficial in other inflammatory gastrointestinal diseases. The first-line recommendation to induce remission in pediatric Crohn's disease is exclusive enteral nutrition<sup>[31]</sup>. Enteral nutrition could also be effective in the maintenance of pediatric inflammatory bowel disease remission<sup>[32]</sup>. With regard to acute pancreatitis, three of the recent and most up-to-date guidelines for acute pancreatitis in adults clearly show the positive effect of enteral nutrition in moderate and severe AP<sup>[6,23,24]</sup>. Besides the energy supply, enteral nutrition in patients can also have other advantages as a first-line treatment for patients. It is well documented that the gut plays an important role as an immune barrier in the immune system and that EEN facilitates this barrier function. EEN significantly decreases pathogenic bacteria in the stool, alteration of intestinal flora and levels of serum endotoxins. EEN has a favourable effect on immune dysregulation caused by severe acute pancreatitis, which can reduce APACHE II scores, pancreatic sepsis, initial incidences of systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome<sup>[33,34]</sup>.

Recent meta-analyses of adult data showed that EEN is beneficial in all severity groups in AP; however, no systematic review is available concerning the role of EEN in pediatrics<sup>[35]</sup>. Therefore, the aim was to review



**Figure 1** Early events in acute pancreatitis. Bile acids, ethanol, fatty acids or their non-oxidative metabolites, fatty acid ethyl esters, induce calcium overload, causing mitochondrial damage and a resultant decrease in intracellular ATP concentration both in acinar and ductal cells. This will lead to general energy depletion in the pancreas.

the literature to analyse the effect of EEN vs NPO therapy on the outcome of acute pediatric pancreatitis (APP) and aggregate the information in APP leading to a higher statistical power and more robust point estimate than is possible from the individual studies.

The preferred reporting items for systematic review and meta-analysis protocol (PRISMA-P) were followed<sup>[36]</sup>. Our structured literature search was based on the participants, intervention, comparison and outcomes format: P: patients under the age of twenty-one suffering from acute pancreatitis; I: early enteral nutrition (per os and nasogastric- or nasojejunal tube started within 48 h); C: NPO therapy [per os/nasogastric- or enteral tube after 48 h and total parenteral nutrition (TPN) within or after 48 h]; O: length of hospitalization, need for intensive care unit (ICU), complications, necessity of antibiotics, surgical/non-surgical interventions and mortality.

In February 2016, a literature search was performed on the PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) and EMBASE (<https://www.embase.com>) databases using the following Medical Subject Headings and search terms: "pediatric" OR "paediatric" AND "pancreatitis". The search was limited to human studies, full-text publications with abstracts in English with no time period, resulting in 632 articles altogether (PubMed: 131; EMBASE: 501).

The articles were checked separately. Meta-analyses, reviews, case reports and articles on chronic pancreatitis were excluded and duplicates were removed (Figure 2). Potentially eligible papers were selected, and, finally, five of them with relevant data on EEN or/with NPO therapy in acute pediatric pancreatitis in patients under twenty-one years old were included (Table 1)<sup>[37-41]</sup>. To reduce the risk of bias, the literature search was independently performed by three researchers following the inclusion criteria noted above.

The details in the collected articles were checked, and only articles where both EEN and NPO were presented separately were used. Two articles met this

**Table 1** Studies included in the quantitative synthesis

Ref.	Data	Groups	NO. of patients
Abu-El-Haija <i>et al</i> <sup>[37]</sup> , 2016	Yes	EEN	24
		NPO	14
Flores-Calderón <i>et al</i> <sup>[41]</sup> , 2009		Only NPO	18
Goh <i>et al</i> <sup>[40]</sup> , 2003		Only NPO	12
Raizner <i>et al</i> <sup>[39]</sup> , 2013		Only NPO	7
Szabo <i>et al</i> <sup>[38]</sup> , 2015	Yes	EEN + IVF lo	55
		NPO + IVF lo	20
	Yes	EEN + IVF hi	96
		NPO + IVF hi	30

EEN: Early enteral nutrition; NPO: Nil per os.

criterion. The two articles contained three separate data pairs, where EEN was compared to NPO (Figure 3). The following parameters were collected: length of hospitalization (LOH), need for treatment at an ICU, development of severe AP, lung injury (including lung oedema and pleural effusion), white blood cell count and pain score on admission. Only one of the five investigated parameters (LOH) contained a minimum of three items, which were analysed statistically.

The meta-analytic calculation was made with Comprehensive MetaAnalysis (V3) software using the random effects model (the DerSimonian-Laird method). We calculated a weighted standard difference in means and 95%CI. In the case of one study (Abu-El-Haija *et al*<sup>[37]</sup>, 2016), we converted the median and range values to means and standard deviation using the modified Hozo's formula by Wan *et al*<sup>[42]</sup>. For a visual inspection, we used a forest plot.

Figure 3 shows the parameters collected from the articles. It was only possible to perform forest plot analyses on LOH. EEN significantly decreased LOH (SD = 0.806,  $P = 0.034$ ) compared to the standard NPO diet (Figure 3).

## DISCUSSION

Several therapeutic recommendations are available in the literature on nutrition in acute pancreatitis. The IAP/APA guideline suggests enteral tube feeding as the first-line therapy in patients requiring nutritional support with predicted severe and severe acute pancreatitis<sup>[6]</sup>. According to the Japanese guideline, enteral nutrition in the early phase of severe acute pancreatitis can decrease the incidence of complications and elevate the survival rate<sup>[24]</sup>. Recent meta-analyses of adult studies revealed that EEN decreases mortality, rate of interventions and the incidence of multi-organ failure in severe acute pancreatitis. Moreover, group analyses of 17 parameters including laboratory parameters (such as CRP and white blood cells) and symptoms (such as pain or presence of SIRS) suggested that EEN also has merits in mild acute pancreatitis. Since the incidence of APP has risen in the past twenty years (with 3.6 and 13.2/100000 children affected annually), we

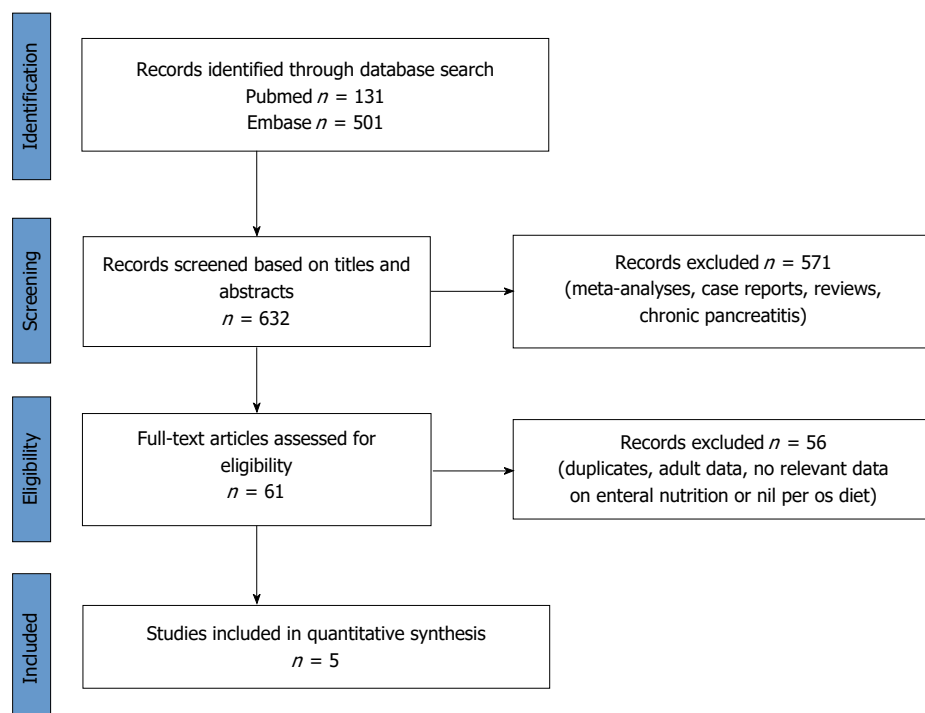


Figure 2 Flow chart on the methods used in the literature search.

Ref.	Therapy	n	LOH	Need for ICU	Severe AP	Lung injury	WBC	Pain score
Abu-El-Hajja <i>et al</i> <sup>[37]</sup> , 2016	EEN (< 24 h)	24	81.7 h					
	NPO (< 24 h)	14	94.7 h					
Szabo <i>et al</i> <sup>[38]</sup> , 2015	NPO (< 48 h) + IVF lo (< 24 h)	20	7.1 d (1.01 SE)	20.0% (8.94 SE)	35.0% (10.7 SE)	11	13.60 (6.44 SD)	4.95 (3.75 SD)
	EEN (< 48 h) + IVF lo (< 24 h)	55	2.8 d (0.24 SE)	1.8% (1.80 SE)	9.1% (3.88 SE)	21	9.89 (3.89 SD)	4.62 (3.50 SD)
	NPO (< 48 h) + IVF hi (< 24 h)	30	5.0 d (0.58 SE)	13.0% (6.21 SE)	17.0% (6.80 SE)	14	13.30 (4.76 SD)	6.08 (3.19 SD)
	EEN (< 48 h) + IVF hi (< 24 h)	96	3.2 d (0.22 SE)	1.0% (1.04 SE)	4.2% (2.04 SE)	4	11.30 (5.25 SD)	5.47 (3.57 SD)

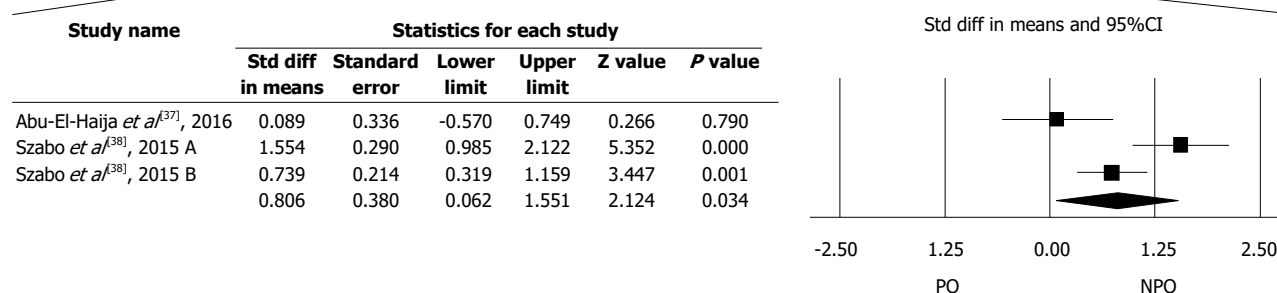


Figure 3 Two articles contained three separate data pairs where early enteral nutrition was compared to nil per os. LOH: Length of hospitalization; EEN: Early enteral nutrition; NPO: Nil per os. ICU: Intensive care unit; AP: Acute pancreatitis; WBC: White blood cell count.

systematically reviewed the literature to understand whether there is any beneficial effect of EEN vs NPO in children<sup>[43,44]</sup>.

We faced several difficulties during our review: (1) APP is still underdiagnosed, thus decreasing the possibility of performing clinical trials<sup>[45]</sup>; (2) the number of studies on the management of these patients is very low, and there is still only a small number of studies focused on understanding the characteristics of the disease<sup>[46]</sup>; (3) the studies have not focused on the early management of the patients; the groups

were therefore not separated; and (4) finally, but very importantly, the methods sections and the quality of data presentation in these articles are very low. Consequently, in many cases, it was impossible to obtain quality analysable data from the manuscripts for a proper broad-spectrum meta-analysis<sup>[37-39]</sup>.

By the end of the search, we identified five articles containing relevant data on nutritional management during the early phase of APP. Raizner *et al*<sup>[39]</sup> published a retrospective analysis involving seven children with necrotizing pancreatitis. All the children received a

strict NPO diet, five patients received TPN and just one patient was treated with nasojejunal feeding for seven days. All the children required a prolonged hospital stay (with a mean of 20 d) for acute complications, with three of them suffering from late complications<sup>[39]</sup>. Goh *et al.*<sup>[40]</sup> included twelve patients in their retrospective study. One patient needed a distal pancreatectomy, and eleven patients recovered with conservative management, with none of them receiving EEN. Two patients had acute complications, and two patients had recurrent AP<sup>[40]</sup>. Flores-Calderon *et al.*<sup>[41]</sup> studied eighteen patients with acute pancreatitis caused by L-asparaginase due to acute lymphoblastic leukemia. All the patients were treated with bowel resting for a mean of 22 d, fourteen of the patients received TPN and four had an elementary diet. Two of the patients required intensive care unit admission, with local complications developing in twelve patients. None of the patients died from complications related to AP. Although these studies point out several disadvantages of that NPO diet, none of them could be enrolled in our meta-analysis.

Finally, it was possible to collect three sets of analysable data pairs where both NPO and EEN were present. Abu-El-Haija *et al.*<sup>[37]</sup> conducted a prospective study of 38 children suffering from mild AP and retrospectively investigated the relationship of nutrition with pain and LOS. EEN feeding meant per os feeding and NPO was identified as oral feeding not being allowed for 24 h. Importantly, EEN, even with high fat intake, did not cause an elevation in pain in children, suggesting that EEN is a well tolerable nutritional possibility in children. The fact that LOS was much shorter in group EEN vs NPO points to EEN as a better way of treating APP<sup>[37]</sup>. The most advanced study was performed by Szabo *et al.*<sup>[38]</sup>, where several parameters were collected to understand the effect of EEN on the course of APP. Two hundred and one children suffering from mild AP were enrolled retrospectively. They compared EEN vs NPO both with and without aggressive fluid resuscitation. Fluid therapy was administered during the first 24 h, and the type of nutrition was determined during the first 48 h. Besides the beneficial effects of EEN on LOS, they also showed that EEN reduces the severity of the disease. Although our aim was to perform a meta-analysis on several parameters to understand the differences between EEN and NPO, we were only able to perform the statistical analyses on LOS, which clearly showed that EEN is not only a safe method of nutrition but also substantially decreases LOS, resulting in a better and less expensive treatment of mild APP<sup>[38]</sup>.

## CONCLUSION

The information collected by basic scientists, retrospective clinical studies and meta-analyses suggests that EEN should have priority in treating APP. However, it is perhaps self-evident that randomized multicenter clinical intervention trials would be crucial to achieving

a higher level of evidence.

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