Intermittent fasting in paediatric critical illness: The properties and potential beneficial effects of an overnight fast in the PICU

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1. Introduction

Although nutritional support for critically ill children has been considered an essential cornerstone of therapy in paediatric intensive care units (PICUs) worldwide, current recommendations are still predominantly based on observational studies. For decades, associations between undernourishment and impaired outcome have led to feeding interventions to attenuate nutritional deficits during PICU admission [1–3]. Therefore, nutritional support has traditionally focused on early and high macronutrient intake [1,4]. Spreading the daily nutritional target over a 24 h period is perceived to be more feasible and probably beneficial; the hypothesis being that this would circumvent enteral feeding intolerance and thereby it would be easier to reach high target intake early. However, the ongoing controversy on the optimal amount and timing of administration of artificial nutrition might conceal the fact that there is no hard evidence for continuous 24 h feeding in critically ill children [5]. Moreover, the potential benefit of a fasting response on the convalescence of critical illness has been overlooked for decades. Recent studies presented mechanistic pathways of a ‘fasting response’ with endocrine changes, activated autophagy, and increased ketogenesis to benefit the critically ill patient [6–10]. Although speculative, a daily intermittent fasting strategy may mimic such a ‘fasting response’ and could exert its beneficial effects while providing sufficient amounts of nutrition. Indeed, numerous murine, preclinical and clinical studies have shown that intermittent fasting strategies protect against diseases and promote cellular and organ health [11,12]. Until now, available studies examining intermittent versus continuous feeding in critically ill children have focused on the nutritional intake and on the occurrence of gastrointestinal complaints as outcomes. We aimed to review the potential nutritional and non-nutritional advantages of an intermittent
feeding/fasting strategy during paediatric critical illness, as well as the practical considerations to be taken into account for such an intervention in this vulnerable population.

2. Current evidence for intermittent versus continuous nutrition in the paediatric intensive care unit

Experts worldwide agree that there are insufficient data to make evidence-based recommendations on either intermittent or continuous feeding in critically ill children [5,13]. To our knowledge, until now only 5 articles were published that investigated intermittent versus continuous feeding in critically ill children, two of which described the same research population (Table 1) [14–18]. When reviewing the available evidence of intermittent versus continuous feeding, one needs to take the commonly used definitions into account. Intermittent feeding in the broad sense comprises any feeding strategy other than providing nutrition with a constant infusion rate over 24 h. Numerous strategies of intermittent feeding can be distinguished, depending on the time and duration of the fasting period [19]. With cyclic feeding, nutrition is administered by an electric feeding pump, either gastric or postpyloric, as with continuous feeding. However, nutrition is not administered for 24 h per day, but feeding periods might vary between as short as 8 h/day and as long as 18 h/day. With bolus feeding, nutrition is administered via syringe or gravity drip over a very short period for 6–12 times a day. This method, which can only be used in patients with gastric tubes (to prevent dumping syndrome if fed postpyloric), closely resembles normal feeding patterns in neonates and infants. In between these methods is the intermittent feeding pattern, in which nutrition can be administered both by feeding pump as well as by gravity drip for 4–8 times a day over a defined time period, with an administration time usually between half an hour and 2 h. When reviewing the available literature several issues arise (Table 1). The methodology of intermittent feeding was often poorly described and very heterogeneous with different interval periods. However, in all studies, nutrition, whether intermittent or continuous, was administered for 24 h per day. Summarizing these studies, intermittent feeding using the bolus or intermittent feeding strategy seems feasible and safe, but as none of the studies has focused on the impact of an

<table>
<thead>
<tr>
<th>Year, author</th>
<th>Patients, number intervention/control</th>
<th>Intervention method</th>
<th>Control method</th>
<th>Fasting period</th>
<th>Primary Outcome</th>
<th>Findings</th>
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<tr>
<td>2003, Horn D. and Chaboyer W.</td>
<td>Age 0–13 years. Exclusion criteria: history of diarrhea or vomiting 24 h before randomization, anticipated transfer &lt;72 h, need for a specific gastric feeding protocol. N = 23/22</td>
<td>Intermittent gastric feeding: 2 hourly feeding of 20–30 min via syringe or gravity method 24 h/day</td>
<td>Continuous gastric feeding (by feeding pump)</td>
<td>Max. 1 h and 40 min</td>
<td>Feeding tolerance: number of stools, prevalence of diarrhea and prevalence of vomiting</td>
<td>No significant differences in the number of stools per day (p = 0.83), the prevalence of diarrhea (p = 0.30) and vomiting (p = 0.19)</td>
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<td>2004, Horn D., Chaboyer W., Schluter P.J.</td>
<td>Age 0–13 years. Exclusion criteria: history of diarrhea or vomiting 24 h before randomization, anticipated transfer &lt;72 h, need for a specific gastric feeding protocol. N = 23/22</td>
<td>Intermittent gastric feeding: 2-hourly feeding of 20–30 min via syringe or gravity method 24 h/day</td>
<td>Continuous gastric feeding (by feeding pump)</td>
<td>Max. 1 h and 40 min</td>
<td>Fourth hourly gastric residual volume (GRV)</td>
<td>No overall difference in median GRV/kg values and no difference in 4th hourly GRV&gt;5 ml/kg (p-values not provided).</td>
</tr>
<tr>
<td>2016, Fayazi S., Adineh M., Zahraei Fard S., Farokh Payam H., Ahmadie Batvandy Z.</td>
<td>Age 5–17 years. Inclusion criteria: expected enteral nutrition for 7 days, standard food formula. Exclusion criteria: gastrointestinal bleeding, nasojejunal tube, gastrostomy, jejunostomy, food absorption disorders, history of surgery for removing part of the gastrointestinal tract, not able to elevate the head off the bed for 30°. N = 30/30</td>
<td>Intermittent gastric feeding: interruption periods not clearly described, every 4 h for 24 h/day</td>
<td>Continuous gastric feeding (by feeding pump)</td>
<td>Max. 4 h</td>
<td>Reaching caloric target and complications (diarrhoea and vomiting)</td>
<td>Significantly less time needed to reach caloric target intake in the continuous group (P = 0.001). No significant difference in gastrointestinal complications</td>
</tr>
<tr>
<td>2016, Sonmez Düzkaya D., Yildiz S.</td>
<td>Age 1 month – 18 years, Inclusion criteria: requiring mechanical ventilation &gt;48 h. Exclusion criteria: pneumonia, known pulmonary infections, tracheotomy, illnesses related to the gastrointestinal system, use of neuromuscular blocking medication. N = 20/20</td>
<td>Intermittent gastric feeding: interruption periods not clearly described, 24 h/day</td>
<td>Continuous duodenal feeding (by feeding pump)</td>
<td>Not clearly described</td>
<td>Rate of ventilator acquired pneumonia (VAP)</td>
<td>No statistically significant difference in ventilator-associated pneumonia (p = 0.66)</td>
</tr>
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<td>2019, Brown A.M., Fisher E., Forbes M.L.</td>
<td>Age 1 month – 12 years, Inclusion criteria: intubated within 24 h of PICU admission. Exclusion criteria: primary gastrointestinal pathology or surgery, EN not started within 48 h, EN started prior to PICU admission, percutaneous gastric tube. N = 11/14</td>
<td>Bolus gastric feeding (every hour), 24 h/day</td>
<td>Continuous gastric feeding</td>
<td>Max. 1 h</td>
<td>The attainment of target energy and protein intake.</td>
<td>Significantly higher energy intake (p = 0.001) and protein intake (p = 0.006) at 24 h in patients in the bolus feeding group. No statistical difference between the groups at 48 h for either energy or protein intake.</td>
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(extended) fasting period, no conclusion on the impact of cyclic feeding can be drawn.

Extending our view toward the experience in neonatal ICUs, a recent meta-analysis in low birth weight preterm neonates reported less time needed to reach full feed with intermittent feeding in comparison with continuous feeding [20]. Moreover, this meta-analysis found no significant differences in feeding intolerance, serious complications and growth parameters. Nevertheless, all the included studies used bolus feeding as the intermittent feeding strategy. Regarding adult ICU patients, two systematic reviews on intermittent feeding were recently published [21,22]. Despite large heterogeneity of the included studies, the authors drew a cautious conclusion that intermittent feeding in intensive care seems more beneficial. To summarize, there is no evidence that either continuous or intermittent feeding strategies are superior to improve clinical outcome, or even improve the performance to safely achieve macronutrient target intakes. However, the potential impact of the fasting response of intermittent feeding/fasting is missing with the fasting periods being poorly described, mainly concerning bolus feeding, and endpoints merely including the nutritional intake or gastro-intestinal complaints.

3. From ‘caloric restriction’ to ‘time-restricted feeding’

The narrow focus on the nutritional intake and the gastrointestinal tolerance of the previous studies conceals the recent reconsideration of high nutritional target intakes during the acute phase of critical illness. Indeed, recent recommendations and guidelines from the leading societies have adapted their recommendations to withhold supplemental parenteral nutrition and to lower the overall caloric target intake during the first week in PICU to reach 0.67—1 times Resting Energy Expenditure (REE) [5,13,23]. These adaptations were predominantly based on a large multicentre RCT (PEPaNIC), which showed that withholding supplemental parenteral nutrition (PN), while providing micronutrients, during the first week of paediatric critical illness was clinically superior to an early start of PN (<24 h) [24,25]. This novel strategy, in which low macronutrient intakes were accepted during the first week of PICU, improved short-as well as long-term outcome of critically ill children, independent of age or nutritional status [24,26—29]. These counterintuitive findings, corroborating those from adult ICU studies [30], were attributed to a ‘fasting response’, characterized by increased ketogenesis and endocrine response [7,24,30,31]. The low nutritional intake and the response herein resembled ‘caloric restriction’ strategies, which have consistently shown to have clear disease-modifying abilities in animal and human studies on a wide range of diseases [32—48]. One may hypothesize that further withholding nutritional support may amplify these beneficial effects. However, it is currently unclear when safe fasting ends and when the potential detrimental effects of starvation start during paediatric critical illness. Therefore, increasing the cumulative macronutrient deficit during the first week and/or extending nutrient restriction beyond the first week may be inappropriate. Especially in children, who are in the early phase of their life when the foundation of growth and neurocognitive development are laid, this might have both short-term and long-term consequences. A safer strategy might be based on ‘time-restricted feeding’, a form of the increasingly popular so-called ‘intermittent fasting’ strategy. With this strategy, intermittent periods of feeding interruption, long enough for the occurrence of a ‘fasting response’, are incorporated in feeding regimens without the restriction of total nutritional/caloric intake [12,49]. In humans different intermittent fasting regimens were investigated such as the daily time-restricted feeding protocol, alternate-day fasting and period fasting (e.g. fasting 2 or more days per week) [11,12,49]. Given the nature of this review on exploring intermittent fasting in the paediatric ICU setting, we will focus only on daily time-restricted feeding, which is considered to be the classical form of intermittent fasting and probably the most feasible strategy in this population. This strategy restricts food intake to a 8—12 h time period per day, resulting in a 14—18 h feeding interruption period, without a restriction in the total amount of nutritional intake [11,49]. Such an alternative ‘fasting mimicking’ strategy takes advantage of the mechanistic pathways of the ‘fasting response’ without a reduction in caloric/nutritional intake on a daily basis.

4. The properties and mechanisms of ‘intermittent fasting’ in health

The intermittent fasting strategy is based on metabolic switching between a nutrient abundant period and a feeding interruption period (and back), triggering multiple metabolic and endocrine changes [11,49]. During the feeding period with energy and amino acids readily available, glucose is used as energy source, fat is stored in adipose tissue, and a metabolic pathway designed to promote anabolism and growth is activated. When feeding is interrupted for an extended period (usually 14—18 h) a cascade of cellular signalling, metabolic adaptations and neuroendocrine responses are triggered (Fig. 1) [11,12].

4.1. Ketone body metabolism

One key element of the hypothesized beneficial effects of intermittent fasting is the production of ketone bodies [11]. Fasting leads to reduced blood glucose levels and subsequent decreased hepatic glycogen stores [50]. This triggers lipolysis and fatty acid mobilization, resulting in the production of ketone bodies (especially β-hydroxybutyrate) [50,51]. These ketones are actively transported into the cell where they are metabolized to generate adenosine triphosphate (ATP) [52]. Ketone body metabolism is presumed to have multiple advantages over glucose metabolism. Firstly ketones can cross the blood—brain barrier [52], thereby contributing to the preservation of brain function. Secondly, they are very efficient, as they consume less oxygen per molecule oxidized and provide more energy (ATP) than other metabolites, such as pyruvate [53]. Concomitantly, in a well-orchestrated manner, ketones activate numerous signalling molecules, such as nicotinamide adenine dinucleotide (NAD+)-dependent deacetylase activity of sirtuins (SIRTs), which help defend against oxidative stress and activate autophagy [52,54,55]. These processes are also activated by the features of ketone body metabolism independent of the interference of signalling molecules [53,56]. Ketones also act as strong regulators of cellular pathways and gene expression, involved with stress resistance (neuro)plasticity and mitochondrial biogenesis, such as nuclear factor kb (NF-kb) [57], brain-derived neurotrophic factor (BDNF) [57,58], and cyclic AMP response element-binding protein (CREB) [11,41,59].

4.2. Autophagy

In addition to ketogenesis, the low levels of circulating glucose, insulin and amino acids result in the down-regulation of mammalian target of rapamycin (mTOR) and thus inhibition of protein synthesis, while further increasing activation of autophagy and mitochondrial biogenesis [41,55]. Moreover, energy shortage stimulates adenosine monophosphate (AMP)-activated protein kinase (AMPK), a master bioenergetics sensor, through a rise in the AMP/ATP ratio, which in turn increases autophagy activation and mitochondrial biogenesis as well [41,55]. As autophagy eliminates macromolecular debris, such as damaged organelles and protein
aggregates, this is a process that is crucial for cellular integrity and function [60]. Furthermore, autophagy plays a role in the recycling of macronutrients and metabolites and in diverse aspects of innate and adaptive immunity [55, 60–62].

4.3. Circadian rhythm

An additional potentially beneficial property of the intermittent fasting strategy is based on the interplay with the circadian rhythm, the 24-h rhythm that is present in a large part of human physiology. The circadian clock orchestrates various cellular and organ systems such as sleep–wake cycles, body temperature, cardiovascular activity, gastro-intestinal functions, neuro-cognition and endocrine systems [12]. One of the functions of the circadian rhythm is anticipatory homeostasis: preparing the body for what is expected to come, such as nutritional intake during the day. For example, intestinal motility is lower at night and melatonin, the hormone involved with sleep, inhibits gastric acid excretion during the night [63–65]. Metabolic activity is subject to similar circadian control: insulin secretion and sensitivity dip during the night, leading to impaired glucose tolerance [66, 67]. Likewise, several important components in lipid metabolism, such as Apo-C-III and PPAR-α, are also directly regulated by the circadian clock [68, 69]. The relationship between circadian rhythms, organ function and feeding time, however, is not one-directional, but rather an intricate crosstalk. Each cell in the human body has its own internal clock, which consists of a transcriptional-translational feedback loop of so-called clock genes. This molecular time-keeping mechanism involves the expression of transcription factors CLOCK (circadian locomotor output cycles kaput) and BMAL1 (brain and muscle Arnt-like 1) to enable transcription of Periods (PER1–3) and Cryptochromes (CRY1–2), which in turn repress CLOCK and BMAL transcription [12]. Each of the core clock genes act as a transcription factor for a wide variety of other genes leading to circadian expression of up to 43% of protein-coding genes [70], and thereby govern key cellular processes, including cell proliferation. These molecular clocks do not require any input to keep ticking, but they may be corrected or synchronised by both internal and external stimuli. Daylight is the most important entrainment signal to the central clock, which is located in the suprachiasmatic nuclei (SCN) of the hypothalamus [12]. Nutrient intake, or more correctly the feeding/fasting response, is the most powerful Zeitgeber for the peripheral clock system [12, 71]. Fasting orchestrates the circadian rhythm and its physiology through a NAD⁺ and ketone body (β-hydroxybutyrate) induced activation of SIRT1, and AMPK induced phosphorylation of CRY1 to regulate CLOCK:BMAL1 activation [71–75]. This fasting-induced control of the circadian rhythm is so strong that the peripheral clocks of mice (nocturnal animals) when tube-fed during daytime, take on diurnal rhythms, leading to complete misalignment of central and peripheral rhythms [76]. Indeed, the effects on circadian health induced by intermittent fasting are intertwined directly or indirectly with the metabolic effects.

5. Potential benefits of an intermittent fasting strategy during paediatric critical illness

Apart from the increasing popularity as a method to treat or prevent overweight and/or obesity, intermittent fasting has shown a broad spectrum of health benefits unrelated to weight loss as well. Mainly in animal models it has shown robust health benefits on aging and life span, but also disease-modifying effects on a wide range of chronic diseases [32, 34, 35, 40, 43, 45, 77–79]. Summarized briefly, intermittent fasting has shown its value in obesity [36], diabetes mellitus [80], cardiovascular health [33, 37, 81], and autoimmune diseases [44], and is hypothesized to even benefit therapy in cancer [38, 39, 82] and neurodegenerative disorders [41].
Intermittent fasting might have multiple potential benefits in paediatric critical illness as well (Fig. 2).

5.1. Metabolic effects

Metabolic disturbances such as insulin resistance and its related impaired glucose homeostasis and dyslipidaemia are common during critical illness and all these manifestations are strongly associated with impaired outcome [83–89]. Intermittent feeding appears to improve hepatic insulin sensitivity with subsequent lowering of insulin requirements to maintain euglycaemia in non-critically ill patients and in pigs [36,90–92]. The effect of intermittent fasting on critical illness related dyslipidaemia has not been investigated and also the results on lipid metabolism in clinical studies outside the adult ICU are conflicting [93]. Nonetheless, although the implications of an intermittent fasting strategy on dysglycaemia and dyslipidaemia have not been investigated in a critical care setting, the possibilities are easy to conceptualize. Indeed, beyond this metabolic setting, several pathways involved in intermittent fasting described in the previous paragraph have also been implicated in the recovery of paediatric critical illness.

5.2. Ketone bodies

Some clinical critical care studies indicate that ketone bodies might be protective to the detrimental effects of critical illness [7]. Indeed, increased ketogenesis statistically mediated part of the clinical superiority of withholding parenteral nutrition during paediatric crucial illness [7]. Moreover, normocaloric high fat diets, so-called ketogenic diets, have shown to protect against brain injury in rodents [94–97] and have been proven successful in children with refractory epilepsy [98,99]. Finally, ketogenesis has been hypothesized to explain why premorbid mild overweight/obesity is protective against critical illness-induced muscle wasting and weakness [100].

5.3. Autophagy

The fasting–induced activation of autophagy has also been put forward as explanatory mechanism for beneficial effects on outcome in clinical studies omitting early PN in an ICU setting [9,101,102]. Its inactivation leads to accumulating damage and a pro-inflammatory state, which has been hypothesized to mediate critical illness–induced organ failure [8,102]. Several animal studies and clinical studies have verified a protective role of autophagy in the recovery of critical illness [8,103–106]. Both for ketogenesis as well as autophagy the (theoretical) properties of intermittent fasting during critical illness probably depend on the duration and intensity of the fasting response. Nevertheless, the findings of the studies mentioned before provide indications that the metabolic switching from a fasting period to a feeding period might be beneficial, specifically for critically ill patients.

5.4. Circadian rhythm

Based on insights of circadian rhythm studies, intermittent feeding with an overnight fasting period may deliver food to the gastro-intestinal tract at a time when gut motility, secretory activity and metabolism are attuned to food processing and nutrient uptake. Through this mechanism, feeding tolerance and glycaemic
control may actually be improved by intermittent fasting, despite higher hourly nutritional loads during the feeding window. Its entraining role on the peripheral circadian rhythm may be even more beneficial. During critical illness the circadian rhythm impacts various pathophysiological mechanisms, and vice versa, critical illness and the PICU environment influence the circadian rhythm. Disruption of circadian rhythm is associated with impaired outcome in critically ill adults [107–110] and children [111] and preventing circadian disruption has been hypothesized to improve tissue repair and thus wound healing, immune response, metabolism, sleep, and delirium in critically ill patients.

6. Critical illness related complications mitigated by intermittent fasting

In the previous paragraphs we translated well proven mechanisms and benefits of ‘intermittent fasting’ and ‘circadian rhythm’ investigated in murine, preclinical, and clinical studies to the critical care setting. In addition, some other distinct properties of critical illness leading to impaired outcome exist, which might be mitigated by an intermittent feeding/fasting strategy as well.

6.1. Ischemia-reperfusion injury

Ischemia-reperfusion injury is the paradoxical tissue damage caused when blood supply returns to tissue after a period of ischemia, threatening the function and viability of tissue and organs. Ischemia-reperfusion injury is a common cause of single- or multi-organ failure in the course of critical illness [112]. In multiple murine studies a fasting period prior to an ischemic insult has shown to reduce ischemia-reperfusion injury of head, kidney, heart and liver [45,113–120]. Furthermore, fasting has shown to reduce tissue damage, improve functional outcome, and mitigate cognitive deficits in a murine model of traumatic injury to head or spine [113,121–123]. Also in a clinical setting involving human ischemia-reperfusion injury after kidney transplantation, preoperative dietary restriction improved postoperative recovery [124]. Most of these studies have used fasting as preconditioning feature. Whether the beneficial properties of fasting only act as prevention of ischemia-reperfusion or could also act as therapeutic intervention after its occurrence remains to be investigated.

6.2. Muscle protein catabolism

Acute skeletal muscle wasting due to excessive protein catabolism is one of the most devastating conditions during critical illness [125]. It has been associated with worse morbidity and even mortality during hospitalization and beyond [126–132]. Continuous feeding is presumed to contribute to impaired muscle protein synthesis because of the ‘muscle-full effect’ in which continuously high amounts of amino acids suppress myofibrillar protein synthesis [133]. An advantageous feature of intermittent feeding is the creation of amino acid (specifically leucine) peak concentrations to enable muscle protein anabolism, potentially increasing (muscle) protein synthesis [134]. However, a recent single-blinded RCT did not find a significant effect of intermittent feeding versus continuous feeding on the preservation of muscle mass in 121 critically ill adults [134]. The intermittent feeding strategy of six 4-hourly feeds per 24 h for a median duration of four days [range 0–10 days] did not prevent the loss of rectus femoris muscle, despite improved protein and energy delivery and increased peak concentrations of plasma leucine [134]. Thus, although a 4 h feeding interruption period appears capable to produce amino acid peak concentrations during critical illness, it was not possible to overcome muscle wasting during the acute phase of critical illness.

6.3. Gastro-intestinal intolerance

Nutritional delivery is a major concern during critical illness. Aside from the well-known barriers (failure to prioritize nutrition, procedural interruptions), feeding intolerance appears to be a prevalent but poorly understood phenomenon in critically ill patients [135,136]. Impaired gastric and intestinal motility, but also impaired nutritional uptake due to intestinal ischemia or oedema are probably pathophysiological features [137]. A clear definition of feeding intolerance is lacking, but a pragmatic definition is the reduction or cessation of EN due to clinical manifestations of GI dysfunction such as vomiting, large gastric residual volumes or diarrhoea [137,138]. Theoretically, intermittent feeding could reduce feeding intolerance, through beneficial effects on gastrointestinal hormones and by enhancing splanchnic blood flow [139,140]. Moreover, intermittent feeding could improve GI motility and nutrient (amino acid) uptake as a result of pulsatile changes in GI hormones such as ghrelin, cholecystokinin, glucagon-like peptide-1 and peptide YY [91,92,139,141]. However, the effect of intermittent feeding/fasting on enterohormonal response has not yet been investigated in the ICU setting, adult nor paediatric.

6.4. Delirium

Delirium is a common problem in critically ill children that is associated with worse clinical outcome [142–144]. The disturbance of circadian rhythm and/or sleep has been put forward as a probable cause of this delirium [145]. Indeed, treatments targeting to improve sleep such as melatonin supplementation, earplug placement, and environmental noise and light reduction, have shown promising results in reducing delirium in critically ill adults [146–148]. Theoretically, preservation of circadian rhythm by implementing an overnight fast could help reduce delirium even without the need of pharmacological intervention.

7. Considerations for the implementation of intermittent fasting in critically ill children

The previous paragraphs envisioned the potential benefit of intermittent fasting during critical illness both from fasting in itself as well from the phenomenon of metabolic switching. Intermittent fasting strategies have been investigated mostly as a lifestyle intervention and it is unclear whether they could benefit critically ill children in an acute setting as well. Obviously, to be beneficial, the intermittent fasting strategy would need to exert its effect already within a few days, given the median length-of-stay in PICU. Withholding parenteral nutrition during paediatric critical illness already exerted its beneficial effects within the first few days [24,149], which suggests that an (intermittent) fasting strategy might have impact very rapidly. In addition to the duration of the intermittent fasting strategy, the length of the daily fasting period requires some consideration in critically ill children. Indeed, the optimal duration of the feeding and fasting periods to be feasible and safe, as well as effective, remains unclear. First, to be effective, the optimal fasting period would have to allow a fasting response (marked by ketogenesis) to exert the potential beneficial effects. It is likely that this would be both influenced by critical illness and by age. Indeed, critically ill patients might have a reduced fatty acid metabolism and impaired ketogenesis [150,151]. This could indicate a slower or less pronounced ketogenesis during critical illness. Nevertheless, this appears to be most prominent in lean patients, which might explain the observations that mild overweight/obesity is protective during critical illness [152–154]. The optimal fasting period might be age-dependent as well. Neonates and infants have limited glycogen stores as compared to older children and adults, which allows for an
earlier ketogenesis during fasting (Fig. 3) [50]. A significant ketogenesis was already observed 0–7 h (median 36 min [IQR 18–74]) after admission in critically ill children in the PEPaNIC RCT [7]. A similar secondary analysis of the adult EPANIC RCT, investigating withholding PN in critically ill adults, showed that ketone levels were only modestly elevated, as compared with the paediatric population [31]. This indicates that aside from the nutritional intake and/or status prior to PICU admission, ketogenesis during critical illness also depends on age. Interestingly, the increased ketogenesis in critically ill children statistically mediated part of the beneficial impact of withholding parenteral nutrition on weaning from respiratory support and on time to live PICU discharge [7]. In contrast, the (modest) rise in ketones found in the adult study did not independently associate with the outcome benefit of withholding PN [31]. Moreover, both in the children as well as in the adults, the ketogenic response was not associated with the decreased incidence of nosocomial infections due to withholding PN [7,31]. This could indicate other mediating mechanisms exerted during the fasting response parallel to ketogenesis, such as autophagy. Although the role of the fasting induced activation of autophagy in mediating recovery from critical illness has been put forward in several animal and human studies, the duration of the fasting period to activate autophagy is uncertain [6,8].

A fasting period sufficient to exert the hypothesized benefits of intermittent fasting would still need to be feasible and safe for a critically ill child. To be feasible, and to prevent it from becoming a caloric restriction intervention, the daily feeding period would need to be sufficient to allow current target intakes to be achieved, taking into account well-known barriers to deliver nutrition such as feeding intolerance. Moreover, for the intervention to be safe, the condensed period of feeding would have to be sufficient to prevent the increased intake to cause ischemic intestinal injury as well. Furthermore, the fasting period should not lead to hypoglycaemia incidents. The latter is an obvious concern in neonates and infants, because of their limited glycogen stores [155]. Therefore, the optimal fasting period might be shorter in neonates and infants than in older children or adults. In addition to the potential risk of hypoglycaemia during the fasting periods, one needs also to be aware of the increased risk of glucose variability during intermittent feeding and fasting, as glucose variability has been hypothesized to be harmful during critical illness [156,157].

Additionally, fasting might contribute to variability in drug metabolism, and thus drug levels, by its effects on metabolizing enzyme activity [158]. This is particularly relevant for drugs with a small therapeutic range or for patients who are subject to other factors that contribute to variability in drug metabolism, such as inflammation [158].

Another issue that arises is the provision of parenteral nutrition. Although it is currently recommended to consider supplementing parenteral nutrition only after the first week in PICU, parenteral nutrition is provided to a considerable part of the PICU population. Even though cyclic parenteral nutrition is common and beneficial in patients with chronic intestinal failure, several concerns would come to mind for such intervention in critically ill children, such as swift changes in glucose level, changes in fluid levels or fluid overload, as well as hypercapnia [159]. However, a recent report in fourteen high-risk surgical neonates showed that cyclic parenteral nutrition, with a fasting period of 4 h and a slow tapering protocol, started as early as from the first day of life, was safe and efficacious [160]. Whether a fasting period of 4 h would suffice to exert the hypothesized benefits of intermittent fasting is uncertain.

Although the concept of intermittent fasting has not been investigated in a PICU setting, one recent study in adults has provided valuable insight. In a randomized cross-over 24-h pilot study (ICU-FM-1) in 70 critically ill adults a 12-h feeding period was alternated with a 12-h fasting period on day 8 after admission to the ICU [8]. In this population, ketones were already increased after 4 h of fasting, but on the other hand autophagy markers were largely unaffected [8]. However, these tests were performed on blood samples, which might not be a valid method to assess autophagy at the level of other tissues [6]. This was the first study focussing on a prolonged fasting period during critical illness and it certainly opens clinical and research perspectives, despite some issues that limit its translation to a PICU setting. First, the daily nutritional target intake in the former study was reduced by 50 %, which renders it unsuitable for a clinical study over a prolonged period, in which case the nutritional intake cannot be proportionally increased. Second, the 12-h feeding and fasting periods might not be feasible or safe in neonates and infants as explained above. Third, given the immediate effect of the nutritional intervention observed in the PEPaNIC RCT [24,149,161], intermittent fasting should also already be initiated when early enteral nutrition (EN) is being administered in PICUs. Nonetheless, this pilot study fuels the expectations of an intermittent fasting strategy to obtain a fasting response of which the clinical impact requires to be investigated in a clinical setting.

8. Conclusion

Continuous 24 h feeding is currently regarded standard of care in paediatric ICUs despite the lack of evidence of superiority over intermittent feeding. Available studies on intermittent feeding in PICU have only examined the effects of bolus feeding, provided 24 h a day, and showed inconsistent results on surrogate outcomes. An intermittent feeding strategy, especially a strategy that allows for an extended overnight fasting period, might have beneficial effects in critically ill children. Although the optimal duration of the feeding and fasting periods is still unclear, a time-restricted feeding strategy might exert its beneficial effects by stimulation of ketone body metabolism and autophagy, its beneficial effect on circadian rhythm and various other processes involved during critical illness.

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All authors contributed to the design of the review; KV and SV wrote the initial manuscript and constructed the figures and tables;
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Conflicts of interest

The authors declare that they have no competing interest.

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References


