Title: Considerations for nutrition support in critically ill children with COVID-19 and paediatric inflammatory multisystem syndrome temporally associated with COVID-19

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Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in Wuhan,China, December 2019 (2). The World Health Organization (WHO) declared the outbreak of SARS-CoV-2 disease (COVID-19) a pandemic in March 2020, and to date there have been over 3.5 million cases, 250,000 deaths affecting 215 countries around the world (3). Although children remain largely unaffected and only represent 2% of cases (4), a cumulative pediatric infection proportion model of 50% estimates there would be 37 million children infected with SARS-CoV-2, of which almost 100,000 would require hospitalization for severe pneumonia and nearly 11,000 would require admission to Paediatric Intensive Care unit (PICU) (5). It is anticipated this current pandemic will last for months, if not years with significant health implications for children with regards to short and longer term nutritional support and recovery.

There are reports of children COVID-19 or COVID-19 like symptoms with hyperinflammatory multisystem syndrome, ARDS, gastrointestinal and atypical Kawasaki disease presenting to PICU worldwide paediatric hyper-inflammatory syndrome temporally associated with COVID-19, for which there are important nutrition support considerations. As a result, the European Society of Pediatric and Neonatal Intensive Care – Metabolism, Endocrine and Nutrition group (ESPNIC-MEN) and paediatric nutritionists working in PICUs are being consulted regarding nutrition management of critically ill children with COVID-19 or COVID-19 like symptoms. Therefore, the aim of this editorial is to provide an adaptation of nutrition support recommendations for the overall population of critically ill children, to provide further refined recommendations for critically ill children presenting with COVID-19 or paediatric hyper-inflammatory syndrome temporally associated with COVID-19. They are based on the ESPNIC-MEN section recommendations published in January 2020 (6) and Surviving Sepsis Campaign recommendations from February 2020 (7). These recommendations cover the acute, stable and rehabilitation phases (Table 1, Table 2).***Clinical presentation of critically ill children with severe* SARS-CoV-2 disease**

In adults, the severity of COVID-19 disease is postulated to arise from renin-angiotensin system (RAS) and the angiotensin-converting enzyme (ACE)2 receptor on cells which the virus uses as a mode of cell entry. Individuals with high ACE2 levels e.g. diabetes or low levels e.g. hypertension may have a dysregulated response leading to pulmonary inflammation and acute respiratory distress syndrome (ARDS) (8, 9). Although ACE2 receptors are predominantly found in the respiratory mucosa, they have been found to be expressed in the gastrointestinal tract, which may facilitate viral entry into the epithelial cells within the gastrointestinal tract (10, 11).

ARDS induced hypoxia, inotrope resistant shock, dehydration from fever, vomiting and diarrhoea, elevated liver enzymes, coagulation dysfunction, rhabdomyolysis including other manifestations suggests injuries to vital organs (12, 13). ARDS remains a rare clinical feature of COVID19 in paediatrics. However, very recently clinicians have been reporting a rise in the number of children of all ages presenting with a paediatric multisystem inflammatory syndrome associated with COVID-19, eventually leading to hyperinflammatory shock and associated with myocarditis; common features of this syndrome are toxic shock syndrome, atypical Kawasaki Disease, macrophage activation syndrome and bacterial sepsis with cardiac inflammation; serum blood measures are similar to severe COVID-19, although many have negative SARS-CoV-2 real-time reverse transcription (rRT-PCR) tests while some present with positive SARS CoV2 serology (13-15).

In children atypical Kawasaki disease symptoms include vasculitis changes in peripheral and visceral arteries including cerebrovascular, renal and gastrointestinal systems (13, 15). Gastrointestinal tract involvement is reported in approximately 20–35% of atypical Kawasaki disease cases with varying clinical manifestations such as vomiting, diarrhoea, abdominal pain, abdominal distension, jaundice, paralytic ileus, hepatomegaly, and ultrasound findings of hydrops of the gallbladder, pancreatitis, gastrointestinal obstruction/ pseudo-obstruction (13, 16).

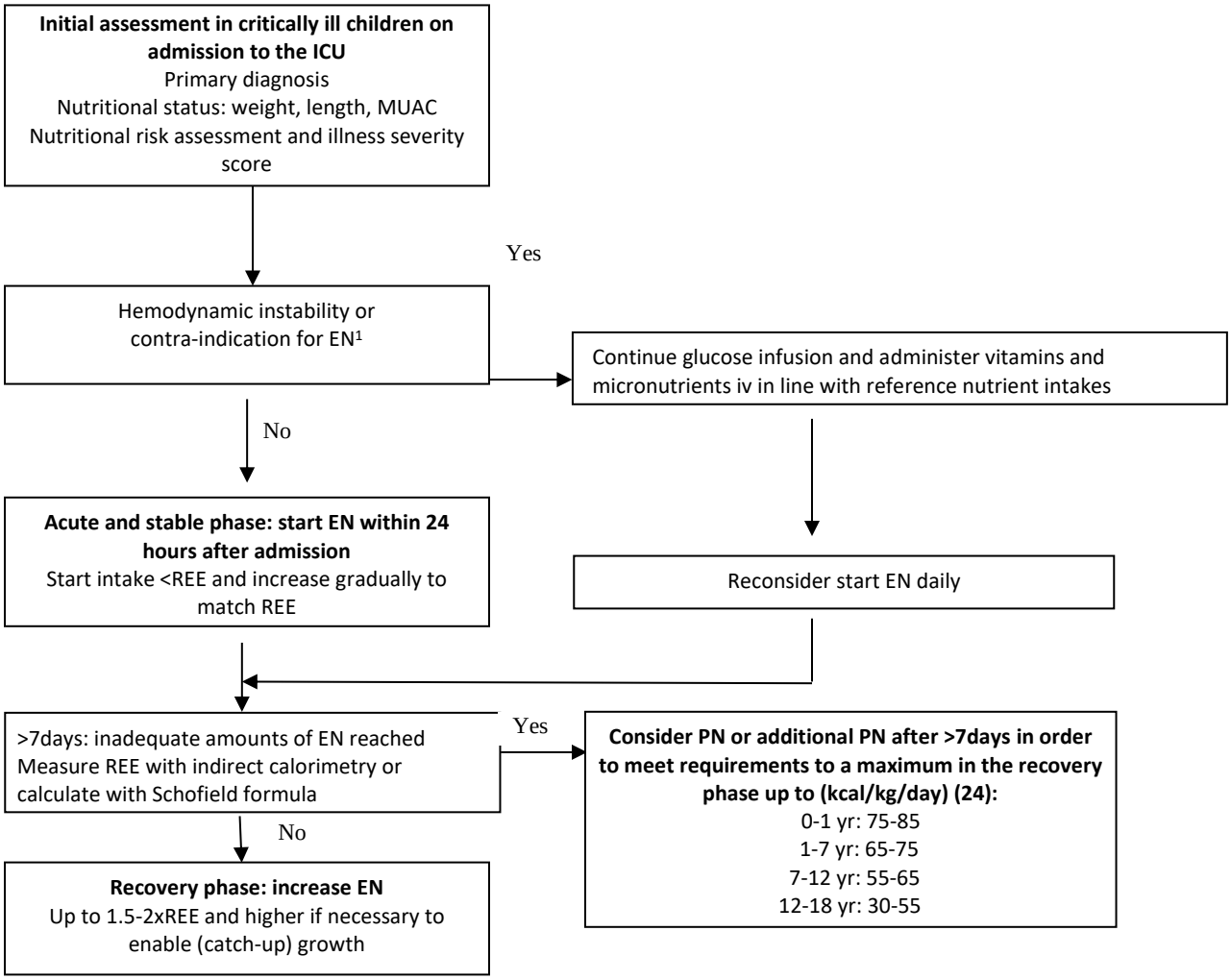
Considerations for nutrition support in COVID-19 and paediatric inflammatory multisystem syndrome temporally associated with COVID-19

Gastrointestinal symptoms reported amongst children and adults in Wuhan in the later stages of the epidemic with COVID-19 were thought to arise from infected epithelial cells (10). Although less than 10% of children with COVID-19 develop diarrhea or vomiting, reports of prolonged reverse transcription-polymerase chain reaction (RT-PCR) positivity in the stool has raised the concern of faeco-oral transmission (11). The newer gastrointestinal and atypical Kawasaki disease presentation may mean that feeding is more delayed than usual in some children, especially if this is indicative of a novel COVID-19 direct intraluminal viral process, (PCRs negative in stool to date).

The cornerstones of nutrition recommendations for critically ill children remain early enteral feeding within 24 hours of admission, energy requirements not to exceed resting energy expenditure during the acute phase and parenteral nutrition to be withheld during the first 7 days of admission (Figure 1, Table 1). For critically ill children with severe COVID-19 and COVID-19 like symptoms there are a number of different nutritional considerations including; 1) severe gastrointestinal or cardiac manifestations and inotrope resistance shock may mean usual early enteral feeding is not be possible, and nutrition support using the enteral route may be delayed for up to 7 days or more, 2) the placement of naso-enteric tube is considered aerosol producing and as such appropriate personal protective equipment should be worn, 3) children who are nursed prone or in a medically induced coma may tolerated post-pyloric feeds better, 4) measurement of GRV is not recommended unless there is repeated vomiting and no possibility to increase gastric enteral feeding (measured additional care should be taken using personal protective equipment (PPE) as SARS-COV 2 virus has been found in the gastrointestinal lumen, 5) there is no evidence to support supra-physiological doses of micronutrient supplementation above the reference nutrient intake, including zinc and 6) as children may have undergone a prolonged admission to PICU, nutrition support may be required well into the recovery period to ensure adequate and appropriate nutrition recovery, particularly as significant pro-inflammatory response (17) and lean body mass deficits have been reported in obese adults with COVID-19 (18)(Table 2).

Table 1: Summary of nutrition requirements during acute, stable and recovery phase of paediatric critical illness (1, 7, 19-21)

	Acute phase	**Stable phase**	**Recovery phase**
Enteral nutrition (Preferred route)			
Energy	It is recommended to commence early enteral nutrition (EN) within 24 hours of admission unless contraindicated (e.g. inadequate signs of systemic perfusion and rising lactate)		EN may need to be continued for longer into the recovery phase to support physical and nutritional rehabilitation
Protein (g/kg/day)	1-2	2-3	3-4
Parenteral nutrition			
Energy	< resting energy expenditure (REE)	1.3-1.5xREE	2xREE
Carbohydrates mg/kg/min (g/kg/day) Newborn 28 d-10 kg 11-30 kg 31-45 kg >45 kg	 2.5-5 (3.6-7.2) 2-4 (2.9 -5.8) 1.5-2.5 (1.4-2.2) 1-1.5 (1.4-2.2) 0.5-1 (0.7-1.4)	 5-10 (7.2-14) 4-6 (5.8 – 8.6) 2-4 (2.8-5.8) 1.5-3 (2.2-4.3) 1-2 (1.4-2.9)	 5-10 (7.2-14) 6-10 (8.6-14) 3-6 (4.3-8.6) 3-4 (4.3-5.8) 2-3 (2.9-4.3)
Protein (g/kg/day)	0	1-2	2-3



MUAC= mid upper arm circumference, iv=intravenous, EN= enteral nutrition, PN = parenteral nutrition, REE = resting energy expenditure [1]Contraindications for EN: Severe gastro-intestinal symptoms with concern for intestinal ischemia, hemodynamic instability (1)

Figure 1: Nutritional strategy in paediatric intensive care patients

Table 2: Considerations for nutrition support in critically ill children with COVID-19 and Paediatric inflammatory multisystem syndrome temporal systems (PMS-TS) (6, 7)

Question	Recommendation for critically ill children (6)	COVID-19 adapted recommendations
In critically ill children, when should enteral nutrition (EN) be commenced and how should it be increased?	• It is recommended to commence early EN within 24 hours of admission unless contraindicated (e.g. inadequate signs of systemic perfusion and rising lactate) • It is recommended to increase EN in a stepwise fashion until goal for delivery is achieved using a feeding protocol or guideline	• For children with the newer gastrointestinal and atypical Kawasaki disease presentation may mean that feeding is more delayed than usual in some children, especially if this indicative of a novel COVID-19 direct intraluminal viral process, (PCRs negative in stool to date) • Corticosteroid and high dose aspirin may increase the risk of gastritis and children may benefit from prophylactic treatment to prevent upper gastrointestinal bleeding (22) • Some of these children are reported to have body mass index > 91st centile; energy requirements should be calculated on using ideal body weight (23)
In critically ill children on hemodynamic support (vasoactive medications, extracorporeal life support ECLS) does enteral feeding compared to no enteral feeding affect outcomes?	• Early EN is recommended in term neonates/ children who are stable on ECLS • Early EN is recommended in term neonates/ children who are stable on pharmaceutical hemodynamic support	• However, in children who continue to require fluid resuscitation or escalating doses of vasoactive agents (e.g. inadequate signs of systemic perfusion and rising lactate), with evidence of severe gastrointestinal dysfunction and atypical Kawasaki disease, EN may be withheld for up to 7 days (6, 7)
What are critically ill children requirements?	• In the acute phase, energy intake provided to critically ill children should not exceed resting energy expenditure • After the acute phase, energy intake provided to critically ill children should account for energy debt, physical activity, rehabilitation and growth • Measuring resting energy expenditure using a validated indirect calorimeter should be considered to guide nutritional support or Schofield equations (24) are recommended to estimate resting energy expenditure	• Due to the gastrointestinal and atypical Kawasaki disease EN support may need to be continued for longer into the recovery phase until sufficient oral intake is consistently achieved to support physical and nutritional rehabilitation (19) • An unknown is whether muscle mass loss may be more pronounced in children with severe disease and energy, protein deficits should be avoided • The use of indirect calorimetry (IC) should be risk assessed with benefits of using it against Schofield equations (24), as limiting ventilator circuit disconnection will reduce virus aerosolization

	• For critically ill infants and children on enteral nutrition a minimum enteral protein intake of 1.5 g/kg/d can be considered to avoid negative protein balance	
In critically ill children, do different feed formulas (polymeric vs. semi-elemental feed, standard vs. enriched formula) impact on clinical outcomes?	• Polymeric feeds should be considered as the first choice for EN in most critically ill children, unless there are contraindications • Protein and energy-dense formulations may be considered to support achievement of nutritional requirements in fluid-restricted critically ill children • Peptide-based formulations may be considered to improve tolerance and progression of enteral feeding in children for whom polymeric formulations are poorly tolerated or contra-indicated	• COVID 19 paediatric multisystem inflammatory syndrome may be associated with severe gastrointestinal symptoms, which may prevent early EN, or impact on its tolerance (16) • In those where enteral feeding is possible a peptide based feed may be better tolerated (25)
In critically ill children, does continuous feeding compared to intermittent bolus gastric feeding impact on outcomes?	• There is no evidence to suggest that either continuous or intermittent/bolus feeds are superior in delivering gastric feeds in critically ill children • In children with gastrointestinal symptoms continuous feeds may be better tolerated with or without a two- four hour feed break within 24 hour day (25)	
In critically ill children, does gastric feeding compared to post-pyloric feeding impact on clinical outcomes?	• Gastric feeding is as safe as post pyloric feeding in the majority of critically ill children • Gastric feeding is not inferior to post pyloric feeding in the most critically ill children	• Gastric feeding is recommended over post-pyloric feeding in children with severe sepsis/ shock • In an awake children (e.g. not sedated / intubated, the placement of naso-gastric tube is considered of naso-gastric tube is considered to be an aerosol generating procedure (AGP) and care should be taken to ensure health care professional safety by wearing full personal protective equipment (6, 7) • For children placed prone or those at increased risk of vomiting or those with high gastric-residual volumes, post-pyloric feeding may be superior • In children where high levels of sedation including opioids or muscle relaxants gastric emptying may be delayed necessitating the use post pyloric feeding

		• In an awake children, (e.g. not sedated / intubated) insertion of a naso-jejunal tube) may require more time and risk associated with this AGP
In critically ill children does routine Gastric Residual Volume (GRV) to guide enteral feeding impact on outcomes?	• Routine measurement of GRV in critically ill children is not recommended	• Routine measurement of GRV is not recommended (6, 7). COVID-19 has been found in gastric and intestinal epithelial cells (10) and as such additional care should be taken to ensure health care professional safety by wearing personal protective equipment • If GRV is measured, caution should be used avoiding contact with the aspirate to avoid HCP contamination • The use of closed draining systems are recommended if feeding is not possible
In critically ill children, when should Parenteral Nutrition (PN) be started?	• Withholding PN for up to one week can be considered in critically ill term neonates and children, independent of nutritional status, while providing micronutrients (26) • ESPGHAN/ESPEN recommendations on (21) routine biochemistry should be completed prior to commencement including triglyceride levels (which may be high as a result of severe inflammatory response) and monitored throughout PICU stay (7)	
In critically ill children, does pharmaconutrition (glutamine, lipids and/or micronutrients) impact on clinical outcomes?	• There is insufficient evidence to recommend the use of pharmaconutrition in critically ill children	• As this is such a novel infection, there may be negative unintended consequences particularly if supra-physiological doses of micronutrients are given (27) • There is no evidence to support the use of supplemental glutamine, which in severe sepsis may promote the release of inflammatory mediators (28) • *In-vitro* models of zinc supplementation have been shown to have antiviral activity through inhibition of SARS-CoV RNA polymerase, as well as down regulation of inflammatory pathways. However, there is no currently no evidence to support zinc supplementation in children with COVID-19 (29)

Nutritional rehabilitation following PICU

The duration required for recovery is unknown so far. If children have experienced severe disease physical and nutritional rehabilitation may be required for a number of weeks. It may also be important to consider baseline nutritional status as obese critically ill children (non-COVID) with a high body mass index and excessive visceral at baseline are significantly more likely to have persistent acquired impairment at hospital discharge (30). During recovery higher energy and protein intake may be required up to twice the resting energy expenditure depending on age (19) until nutritional deficits are replete. There is a paucity of information relating to nutritional recovery in children following critical illness. Close monitoring of nutritional status in addition to nutrition support may be required post discharge as longer functional term outcomes, including the persistence of acquired functional impairment relative to skeletal muscle mass deficits, have been associated with duration of mechanical ventilation, use of vasoactive medications and duration of PICU stay (31).

In addition, the impact of paediatric critical illness on feeding and feeding difficulties post-discharge remains unknown (32). Adult survs of critical care report significant changes to their ability to eat, with reduced appetite, altered taste and food preferences lasting up to 3 months post ICU discharge, which is likely to be an important consideration in children (33). Adult recommendations post-recovery include the use of enteral and oral nutrition support (34, 35). As such EN support should continue after discharge from PICU until children are able to eat able to consume > 75% of their nutrition requirements from food alone. Micronutrient supplementation may also be required to support catch up growth and muscle mass deposition, and serum levels should be measured once the inflammatory response has resolved and CRP is within normal range (27, 36).

Limitations

Whilst the considerations for nutrition support in critically ill children, are based on a peer review publication (ref), the addition of statements pertaining to the nutrition management of children with COVID-19 and paediatric inflammatory multisystem syndrome temporally associated with COVID-19 are extrapolated from

other patient groups, as there is a paucity of published evidence based nutrition therapy in critically ill children with COVID-19.

Conclusion

Early enteral feeding critically ill children with COVID-19 and COVID-19 like symptoms should be considered. However, in those with significant gastrointestinal issues or inotrope resistance shock this may not be possible for several days. Clinicians should account for gastrointestinal intolerance, taking factors influencing this tolerance into account, and we recommend deciding early about post-pyloric feeding and intuiting this if appropriate. In the acute phase, energy intake provided to critically ill children should not exceed resting energy expenditure and postponing parenteral nutrition for 7 days may be considered. The placement of naso-enteric tubes is considered AGP and as such appropriate personal protective equipment should be worn and there is no evidence to support supra-physiological doses of micronutrient supplementation including zinc during the acute phase. As children may have had a prolonged admission to PICU, nutrition support may be required well into the recovery period to ensure adequate and appropriate nutrition recovery.

Conflicts of interest

None to declare

Author contributions

Authors made the following contribution to the manuscript: (1) LVM, FV, SCATV formulated the original idea, (2) LVM drafted the manuscript (3) LVM, KJ, CJC, CM,LL, LT FV and SCATV reviewed and revised the manuscript for important intellectual content, (4) and all authors provided final approval of the version to be submitted.

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