Title: A review of outcomes used in nutritional trials in Pediatric Critical Care

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Clinical relevancy statement: Trials within pediatric intensive care are often single centre and underpowered, requiring systematic review with meta-analyses to more generate definitive answers to questions. Our review of paediatric nutrition clinical trial outcomes indicates a lack of clarity and consistency which can impede this comparison of trials. Nutritional outcomes, particularly in the domains of energy targets and feed intolerance were not well defined and their definitions inconsistent. The generation of a core outcome set will aid future researchers to robustly evaluate nutritional interventions within pediatric intensive care.

Key words: Pediatric Critical Care Nutrition, Core outcome set; Pediatric Intensive Care; Child

Abstract

Background: Generating robust evidence within Pediatric Intensive Care (PIC) can be challenging because of low patient numbers and patient heterogeneity. Systematic reviews may overcome small study biases but are limited by lack of standardisation in outcome measures and their definition. Trials of nutritional interventions in PIC are increasing, thus we wanted to examine the outcome measures being used in these trials.

Objective: To systematically describe outcome measures used when a nutritional intervention has been evaluated in a PIC randomized controlled trial.

Methods: A systematic literature review of all studies involving a PIC trial of a nutritional intervention was undertaken from 1 January 1996 until 20 February 2018.

Results: Thirty-one trials met the criteria and were reviewed. They included a total of 3346 patients across all trials. Thirty-nine primary outcomes and 93 secondary outcomes were found. These were categorized into PIC-related outcomes (infection, intensive care dependency, organ dysfunction / long-term functional and mortality) and nutritional outcomes (energy targets, nutritional parameters and feeding tolerance). We found large variation in the outcome measures used. Outcome domains of energy targets, feeding tolerance and infection were not adequately defined.

Conclusions: Large variations in the outcome measures chosen and their definitions exist within PIC nutritional trials. Optimal nutritional outcomes for PIC must be agreed and defined, specifically domains of nutrition efficiency, nutrition tolerance and non-nutritional PIC outcomes. The next step is to conduct an International Delphi study to gain expert consensus and develop a core outcome set to be reported in future pediatric nutrition trials.

Introduction

Pediatric Intensive Care (PIC) is a smaller specialty than adult or neonatal intensive care, in terms of patient numbers. Many trials within PIC are small, conducted within a single center and often underpowered (1). Therefore, there is often a need to undertake systematic reviews to generate more robust evidence. However, systematic reviews rely on consistency in outcome measures for a meta-analysis (2,3,4). Conducting systematic reviews can be problematic, due to the heterogeneity of outcome measures used, with many not able to adequately combine results to produce clear answers. The variation in outcome definitions can lead to differences in occurrence and estimates of treatment effect, which in systematic review can dilute the real effect (5).

It is vital that trials are registered and their protocols made publicly available to reduce the risk of selective outcome reporting (4). In 2013, a comprehensive review of PIC randomised controlled trials (1) analyzed 248 trials from 1879 until April 2013 and found 82% were single centre, with mostly small sample sizes. Of these, 63% examined medications, 11% devices and 8% were nutritional interventions. Critically, primary outcome measures were identified in only 67% of trials, suggesting a need for the agreement around appropriate outcome measures.

One way to improve consistency in the outcomes reported for an intervention is by developing an agreed, standardized collection of specific outcomes, a 'core outcome set' (COS) (2). A COS promotes the reporting of these outcomes, defined in a consistent manner (as a minimum) in future PIC Nutrition trials. The Core Outcome Measures in Effectiveness Trials (COMET) database has registered over 300 studies aiming to develop core outcome sets. Within both adult and neonatal intensive care work is underway to define a COS for nutritional trials (6), it is now time to undertake this in PIC. Currently, knowledge of the outcomes used within PIC nutrition trials is lacking. Our review is the first step in developing a COS for trials of nutritional interventions in PIC.

Methods

Our aim was to systematically describe all outcome measures used when a nutritional intervention has been evaluated in a Pediatric Intensive Care (PIC) randomised controlled trial (RCT) since 1 January 1996. The study population included all children from birth (>37 weeks' gestation term infants) until the age of 17 years. Trials were targeted because the development of a COS relates primarily to randomized controlled studies where an intervention is tested (2).

A systematic literature search was undertaken of all studies involving a trial of a nutritional intervention in PIC from 1 January 1996 until 20 February 2018. Medline (United States National Library of Medicine), Excerpta Medica Database (EMBASE), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Allied and Complementary Medicine Database (AMED), British Nursing Index (BNI), Health Business Elite (HBE), Health Management Information Consortium (HMIC) and PsychINFO (American Psychological Association) databases were searched. The search terms used were: 1. Young (adult OR people OR person) 2. (adolescent OR teenage) 3. (pediatric OR paediatric OR child OR infant*) 4. (PICU or PIC OR ((critical OR intensive) (care OR unit)) 5. (((enteral OR parenteral OR venous OR total OR deliver) ADJ4 nutrition*) OR TPN OR CVN OR PPN OR EN) 6. 1 OR 2 OR 3. 7. 5 AND 5 AND 6. 8. ((randomized OR randomised) OR RCT OR intervention). 9. 7 AND 8. Additionally, trial citations were also extracted from the online database picutrials.net. The study was registered with the Core Outcome Measures in Effectiveness Trials (COMET) initiative online organization. http://www.comet-initiative.org (7).

Adult intensive care trials were excluded. Specifically, neonatal intensive care trials were also excluded but PIC trials including term newborn infants were analyzed. We also excluded pilot studies, to avoid including preliminary interventions where outcomes may have been subject to

adaptation prior to a larger study being performed. One reviewer (KG) conducted the search and independently screened articles for eligibility using titles and abstracts of papers initially. Full texts including supplementary material were then retrieved. The searches and trial selection were then reviewed by the two other authors (LT, FV) to confirm inclusion. Figure 1 shows the screening process.

The trial aims, primary and secondary trial outcome measures, together with their definitions were extracted using a standardized data extraction tool. The database was reviewed by all the authors during the process to confirm trial inclusion and how outcomes measured were categorized. The most common outcomes, were defined as primary outcomes reported by more than one trial and secondary outcomes reported by at least 5 trials.

Descriptions of outcome definitions was based on written information provided in the published paper. We pragmatically classified outcomes as being adequately or not adequately defined. An adequately defined outcome was where the metric was specified and fully described together with a measurement time point. Outcomes not described in detail (meeting the criteria above) or leaving ambiguous interpretation were designated as 'not adequately defined'. The outcomes were extracted by author KG and reviewed by the other authors LT and FV.

Results

The search identified an initial 302 studies (mainly non-nutritional intervention studies) and after careful review of 50 studies where a nutritional intervention was investigated in PIC, 31 randomized PIC nutrition trials met the inclusion criteria and were included in the final analysis (8 – 38) (Figure 1). A range of nutritional interventions were studied which included early versus late enteral nutrition (26, 30, 33), early versus late parenteral nutrition (8), feeding supplements/

prokinetics/ immune enhancing formulas/ drugs (9, 11, 13, 14, 17, 18, 20, 21, 23, 24, 28, 29, 34, 35, 37), intermittent versus continuous feeding (16, 22, 38, 25, 27), high protein/high energy/high lipid containing feeds (10, 15, 19, 31, 32, 36) and the use of protocolized feeding regimens (12).

Primary and secondary outcomes were separated into two categories: pediatric intensive care and nutritional outcomes respectively (Table 1). The PIC outcome domains included newly acquired infection, markers of inflammation, intensive care dependency or marker of dependency, organ dysfunction, long term functional status and mortality.

Newly acquired infection broken down into specific outcome categories included the occurrence or reduced incidence of nosocomial infection (10/20), rates of ventilator associated pneumonia (3/20) and sepsis (7/20). Markers of inflammation outcomes specifically included changes in cytokine (5/10), C-reactive protein (3/10) and lymphocytes levels (2/10), which were all adequately defined (Table 1).

Outcomes related to intensive care dependency included length of stay (intensive care and / or hospital stay) which accounted for 22/38 ICU dependency outcomes and other markers of dependency forming the rest, 16/38. These markers included the duration of mechanical ventilation most commonly (13/38) together with the number of readmissions to PIC within 48 hours of discharge, the duration of haemodynamic support and the proportion of patients receiving renal replacement therapy each accounting for a single outcome.

Organ dysfunction domain outcomes included for example, duration of inotropic support (24), markers of liver dysfunction (8), changes in PELOD (Pediatric Logistic Organ Dysfunction) scores (14), differences in the PRISM (Pediatric Risk of Mortality) and PIM2 (Pediatric Index of Mortality 2) scores respectively (15, 12). Long term functional status outcomes were defined using specific scoring systems such as the pediatric overall performance category and pediatric cerebral

performance category scores respectively (12). This was the only trial which examined long term functional status beyond discharge from hospital.

The nutritional outcomes included nutrient and energy targets, biochemical or metabolic parameters and feeding tolerance. Nutrient and energy target outcomes included both an assessment of nutrient and or energy delivery in relation to targets (12, 16, 25, 31, 34, 38) and adequacy of nutrient delivery (37) (Table 2). Outcomes designated as biochemical or metabolic parameters included those related to a specific change in a marker; for example, serum zinc levels (13), a change in drug requirement (e.g. insulin requirement) (30) or a change in body balance (e.g. whole-body protein (15) or nitrogen balance (29) (Table 4). Outcomes related to feeding tolerance included complications related to feeding such as vomiting, diarrhoea, high gastric residual volume and / or pulmonary aspiration (Table 3).

The trials used *39 different* primary outcome measures, with some trials using multiple outcomes (8, 9, 16, 17, 18, 25, 28, 29, 32, 33, 37, 38). The most frequently reported primary outcome measures were ones using a biochemical/metabolic parameter (15/52), infection or inflammation outcome (13/52), intensive care dependency (11/52) or nutrient/energy target (8/52). Outcomes of feeding tolerance (including adverse events) (4/52) and mortality (3/52) were the least common.

Ninety-three different secondary outcomes measures were used. Intensive care dependency, which included length of stay in PIC or hospital and markers of dependency including length of mechanical ventilation, hemodynamic support and renal replacement therapy, was the most commonly reported secondary outcome measure (27/93). Other outcome measures used commonly as secondary outcomes included feeding tolerance (14/93), organ dysfunction / long term functional status (13/93) and newly acquired infection or markers of inflammation (13/93).

Figure 2 outlines the most common outcomes, highlighting primary outcomes reported by more than one trial and secondary outcomes reported by at least 5 trials.

Outcomes that were not adequately defined, were those outcomes related to nutrient or energy targets (1/9), newly acquired infection (13/20) and feeding tolerance (12/18) (Tables 1, 2 and 3). In all but one trial, when energy targets were used as a primary outcome, their definitions were not stated and fully explained with clear measurement time points (Table 2). Specifically, outcomes examining the time to reach a daily energy target and the percentage of daily energy target achieved lacked an explanation of how the daily energy target was calculated. Others defined how this target was calculated, through dietetic assessment of feeding goals with an estimation of basal energy expenditure based on patient specific factors (12). Only one trial clearly specified a metric, fully describing and defining its primary outcome with a measurement time point, using indirect calorimetry on which to base its energy target (31).

Definitions used for outcomes related to markers of inflammation, intensive care dependency, organ dysfunction, long term functional status and nutrition specific biochemical and metabolic parameters were better defined (Tables 1 and 4).

Discussion

This is the first paper to review and report outcome measures used in trials of PIC nutritional interventions. Thirty-one trials used a broad range of outcome measures, with 39 primary and 93 secondary outcomes in total. Thirty-nine percent of trials used more than one primary outcome measure. This is not uncommon, with evidence that 20% of trials use more than two primary outcome measures and 5% more than five (3). Evidence from adult nutritional trials also shows wide variation in the outcome measures used (39).

The most frequently measured primary and secondary outcome was intensive care dependency, specifically PIC length of stay. There is increasing evidence that inadequate nutrition can prolong intensive care stay, increase duration of mechanical ventilation and worsen clinical outcomes (40, 41, 42). Nonetheless, its limitation as an outcome measure is the potential variation in practice between centers and the impact of multiple confounders. Pediatric Intensive Care Units (PICUs) may or may not be mixed high dependency and intensive care, and length of stay may be subject to bias because of organizational policies on PIC discharge criteria or ward bed shortages. Interestingly, one trial appeared to acknowledge and overcome this outcome limitation by using an adjusted duration of ICU dependency primary outcome. This defined discharge from PIC as the time when a patient was ready from discharge from PIC, specifically when they no longer required or were no longer at risk for needing vital organ support (8).

Mortality was very rarely used as a primary outcome measure in the PIC nutrition trials we evaluated. Mortality continues to fall gradually and its rate in PIC has been <4% in the United Kingdom from 2015-2017 (43) in contrast to higher rates in adult intensive care. Given its infrequent occurrence, mortality is unlikely to demonstrate statistical significance when used to test a pediatric nutritional intervention.

Apart from infection related outcomes, all other PIC outcomes were well defined. The link between malnutrition and infection is well-established (44). Children have low reserves of energy and protein sources compared to adults. This, together with their higher metabolic rates puts them at greater risk of malnutrition which can predispose them to immunodeficiency. Certainly, there is increasing evidence that lower energy intake is associated with adverse outcomes including infection and length of intensive care stay in infants with congenital heart disease (41). Infection itself is a broad term, and how nosocomial infection and/or sepsis were defined was often not stated. Without clear definitions the strength of these infection related outcomes will widely differ

between centers potentially reducing the internal validity of a study (39). We found that infection outcomes were more clearly defined when an objective measure was chosen, for example, bacterial infection rate (28) where a specific microbial pathogen was identified and the number of antibiotic free days (13). Definitions were more ambiguous when a more subjective outcome measure was used, for example the rate of clinical sepsis (30) which in one study was defined as the presence of one of the following: positive blood culture, significant rise in C-reactive protein, thrombocytopenia (or fall >150 without surgery), disorientation, ileus, hypotension, hypothermia, metabolic acidosis, decreased progression of wound healing, and pulmonary, hepatic or renal failure along with systemic antibiotic treatment. If these outcomes are to be robustly evaluated in future meta-analyses of trials clear and objective definitions of these terms will be essential.

We found that longer-term outcome measures, specifically the evaluation of patients after discharge from hospital were rarely used in PIC nutrition trials (12). In adult critical care, it is increasingly recognized that a nutritional intervention may show a beneficial impact on patients in the longer term (39). Core outcomes chosen for PIC will need to consider and reflect this potential impact, particularly in light of our higher survival rate of >96% (43). It is important to foresee the potential short and long-term outcomes of an intervention being studied.

Overall, the nutritional outcomes were less well defined than PIC outcomes. The commonest specific nutritional primary outcome was time to reach energy goal. This outcome is logical and easy to measure, thus proving an attractive choice for trials. Knowing that children in intensive care often fail to achieve even 50% of their predicted energy targets by day 3 (45) justifies this as a useful outcome measure. Unintended underfeeding and overfeeding from inaccurate estimations of energy requirements in children is associated with poor outcomes (46), with evidence that achieving two thirds of target goals was beneficial (47). However, exactly what amount of energy intake we should be targeting within differing intensive care illness phases and pathological

processes is unknown. Treating all critically ill children as a homogenous group is misleading and over simplistic. Failure to account for baseline nutritional status at PIC admission, by lack of any validated tool for use in PIC, contributes to the ambiguity.

Energy target outcomes specifically were often binary in nature (yes/no) without detailing energy intake in kilocalories per day or equations that were used to estimate energy intakes. Only one trial clearly specified a metric, fully describing and defining its primary outcome with a measurement time point using indirect calorimetry on which to base its energy target (31, Table 2). Although indirect calorimetry is recommended as the gold standard for assessing energy expenditure after the acute phase of illness (46), it is not widely available or indeed feasible in some PIC patients (48).

Biochemical and metabolic parameters as a group within the nutritional outcomes were adequately defined (Table 4). Specific blood markers related to the trial intervention and measurements of protein, fat and glucose metabolism had a specified metric, fully described together with a measurement time point. Objective measurements as used for these outcomes are likely to make well defined outcomes for nutritional trials in the future. A core outcome set may not need to include very specific outcomes such as these but any nutritional trial could add outcome measures such as these tailored to the intervention being tested.

One of the least common primary outcomes used was feeding tolerance (including adverse events) (4/53). Rates of feeding complications or adverse event outcomes were used more commonly as secondary outcomes (14/93). Specific feeding complications varied between trials, as did their definitions (Table 3). This variability led to complications often being combined when their individual occurrence rates may have been significantly different, for example vomiting, and pulmonary aspiration (25, 38).

Recent evidence shows that feed intolerance is the commonest cause of stopping feeds (40). In the reviewed trials, when gastric residual volume (GRV) was used to define feed intolerance, varying thresholds were used (16, 22, Table 3). The assessment of GRV remains a controversial issue without any evidence to support the practice or to know what maximal volume or level is significant (40, 49, 50). Despite this, feed intolerance based upon GRV is known to be the most common cited reason amongst PIC healthcare professionals for stopping or withholding enteral nutrition (40). However, heterogeneity in its definition makes the comparison of studies difficult and meta-analysis impossible (39, 51) and this is probably why it was rarely used. A pragmatic consistent agreement on the definition of feed intolerance is likely to aid its use as an outcome measure in future nutrition trials.

Without comprehensive definitions, specific nutritional outcomes are likely to be subjective and open to bias. Despite this the optimal nutritional support strategy is still not established (52); the timing, dosing and combination of nutrients delivered to critically ill children requires robustly designed studies. These should take into account patient heterogeneity (in terms of primary diagnosis, nutritional status, etc), their metabolic state (hypo / hypermetabolism) and include well defined outcome measures.

Adherence to recent guidance for trial protocols (53) would help researchers provide clear, transparent and clearly defined study outcomes. Pediatric trials are known for their challenges which include small patient numbers, differences in pathophysiology, patient age and physiological states, to add to difficulties in recruitment (54). Often these trials, as a result, are underpowered to show a treatment effect. Reporting a set of core outcomes would reduce the variability encountered when comparing trials and pooling their results.

There are some limitations that warrant mentioning, our search was limited to randomized controlled trials and therefore we were not comprehensive in evaluating all outcomes used in

nutritional studies. Nonetheless, we did review trials back to 1996 to give a detailed overview of the outcomes previously used to evaluate a PIC nutritional intervention within trials.

The next step following this review is to undertake an international Delphi study to agree COS for trials of nutritional interventions in PIC. Experts from around the world would vote on a clear definition of non-nutritional outcomes and nutritional outcomes to be used in nutritional intervention trials. Importantly the nutritional outcomes could also be used in non-nutritional intervention trials that may also want to explore these outcomes. Once a COS is agreed and published, this will be actively disseminated. This should ultimately enhance the consistency and clarity of reporting of outcomes both in randomized trials and all studies of nutritional interventions in the PICU population in future trials.

Conclusion

Large variation in outcome measures and their definitions exists within pediatric critical care nutritional trials. If nutritional interventions are to impact outcomes of critical illness, it is now essential that they are defined consistently and objectively. Optimal nutritional outcomes for PIC should now be agreed and defined. Ideally, these would include outcome domains of nutrition efficiency, nutrition tolerance and non-nutritional PIC outcomes. The priority of each domain will depend on the research question and the nutritional intervention being tested. The next step is to conduct an International Delphi study to gain expert consensus for a standardized core outcome set to be reported in all future pediatric nutrition trials. Importantly, as others have mentioned (2,5), this outcome set would not be prohibitive to the inclusion of other specific outcomes related to the intervention being tested. It would rather act as an essential core baseline to aid future worldwide collaboration, minimizing bias involved in systematic review of pediatric critical care trials.

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