

Title

Nutritional status deterioration occurs frequently during childrens' intensive care unit stay

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Statement of Authorship

Authors' contribution: TG, FCA, EJ and FVV, designed the study, collected and participated to interpretation of data. CG, CFC, EG and AP helped to design the study and to collect data. FB and BGLR helped designing and analyzing the data. LT participated to interpretation of data and provided English editing of the paper. All authors were involved in writing the paper and had final approval of the submitted and published versions.

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Article Tweet

Nutritional status deterioration is frequent during pediatric intensive care stay

ABSTRACT

OBJECTIVE: malnutrition and faltering growth at pediatric intensive care unit (PICU) admission have been related to suboptimal outcomes. However, little is known about nutritional status deterioration during PICU stay, as critical illness is characterized by a profound and complex metabolism shift, which affects energy requirements and protein turnover. We aim to describe faltering growth occurrence during PICU stay.

DESIGN: single center prospective observational study

SETTING: 23 bed general pediatric intensive care unit, Lyon, France.

PATIENTS: all critically ill children aged 0 to 18 years with length of stay longer than 5 days were included (September 2013 - December 2015)

INTERVENTIONS: weight and height/length were measured at admission and weight was monitored during PICU stay, in order to calculate body mass index for age (BMI) z-score. Faltering growth was defined as BMI z-score decline over PICU stay. Children admitted during the first year of the study and who presented with faltering growth were followed after PICU discharge for 3 months.

MEASUREMENTS and MAIN RESULTS: we analyzed 579 admissions. Of them, 10.2% presented a BMI z-score decline greater than 1 standard deviation and 27.8% greater than 0.5. Admission severity risk scores and prolonged PICU stay accounted for 4% of the variability in nutritional status deterioration. Follow up of post PICU discharge nutritional status showed recovery within 3 months in most patients.

CONCLUSION: nutritional deterioration is frequent and often intense in critically ill children with length of stay greater than 5 days. Future research should focus on how targeted nutritional therapies can minimize PICU faltering growth and improve post-PICU rehabilitation.

Introduction

Recent recommendations published by a North American pediatric intensive care (PICU) malnutrition workgroup insist on the need to describe critically ill children's nutritional status according to a holistic approach, combining admission nutritional status assessment to dynamic nutritional status assessment before and during PICU stay, in order to integrate malnutrition etiology and consequences in its interpretation (1). Malnutrition at admission has indeed been related to various suboptimal outcomes in critically ill children (2–5). Similarly, patients experiencing recent faltering growth prior to PICU admission also present with longer length of PICU stay (6). However, limited data is available on nutritional status shift during PICU stay (7–9). Nutritional status deterioration frequency, intensity and the impact on outcomes such as acquired infections or rehabilitation remain unclear.

Critically ill children experience a profound metabolic shift in relation to inflammatory stress, resulting in an increased catabolism and loss of body mass (10–12). Young children who normally undergo rapid growth may also present with faltering growth in the PICU setting. Nutritional deterioration assessment should be based on PICU faltering growth monitoring (also called failure to thrive), defined, according to Bouma et al. (13), as a weight loss or a decline of nutritional indices such as weight for age z-scores, body mass index for age z-scores or weight for height z-scores.

The aim of this study was to describe PICU acquired faltering growth, based on the occurrence of nutritional status deterioration during PICU admission. Its definition relied on nutritional indices z-score monitoring, when a significant decline of these indices was encountered. We aimed to describe faltering growth frequency and to identify associated patients' characteristics and outcomes. This may help identifying at risk children and individualizing nutritional strategies in the future.

Material and methods

A prospective observational single center study was conducted between September 2013 and December 2015 in Lyon-France university children's hospital 23-bed PICU. This PICU admits children aged 0 to 18 years old (preterm infants and cardiac patients are admitted in other units and where not included in the study). Nutritional support followed local written guidelines, based on 2009 American society of parenteral and enteral nutrition (ASPEN) guidelines and international expert consensus (14,15). Local guidelines are also in accordance with 2017 updated ASPEN guidelines (16) especially regarding energy and protein goals. They consisted of early enteral nutritional as first line nutritional support, preferential use of gastric continuous feeding, onset of parenteral support at day 2 to 4 when needed. Study ethical approval was obtained in 2012 (institutional review board: Lyon-Sud-Est 2; number 00009118) and waiver of consent was obtained.

All consecutive children (including neonates aged 4 to 28 days at PICU admission) admitted to this unit during the conduct of the study were included. Their data were analyzed if their length of PICU stay was longer than 5 days, which was considered the time sufficient to present with PICU acquired faltering growth (17). When multiple admissions occurred for the same patient, only the first admission was used.

To allow for nutritional status assessment at admission and for its monitoring during PICU stay, anthropometric measurements were performed (weight and height or length) at admission, and repeated on a daily basis (weight), as per local guidelines and practices. Prior to the conduct of the study, the nursing team had been trained to perform anthropometric measurements, as described by Valla et al. (18), using appropriate weighing devices and calipers (height and length were extrapolated from ulna length, as described by Gauld et al. (19) for children above one meter), in order to guarantee optimal assessment. Anthropometric measurements allowed for nutritional indices calculation which were expressed as z-scores according to World Health Organization (WHO) growth standards (when age ranges were appropriate and according to gender), using WHO ANTHRO and WHO ANTHROPLUS online software (20–22); i.e. z-scores of body mass index for age (BMI),

weight for age (WAZ), height/length for age (HAz) and weight for height/length (WHz).

Undernutrition was considered if WHO BMI z-score was below -2 standard deviation (SD).

PICU faltering growth was defined, as per Mehta et al. and Bouma et al (1,13), as a z-score decline of nutritional parameters of at least 1 SD. We chose BMI z-score in the overall population because WHO standards do not provide data of WHz for children older than 5 years. Risk of PICU faltering growth and PICU faltering growth were defined when children presented with a BMI deterioration over PICU stay between 0.5 and 1SD and above 1SD respectively. We also analyzed a subgroup of young children under the age of 24 months, who may present a higher faltering growth risk. We used WAZ decline, as BMI is less accurate in the youngest and according to WHO guidelines. Similar cut off values were used to define risk of and PICU faltering growth. Weight monitoring over PICU stay allowed determining the lowest BMI z-score and WAZ. The time delay between admission and date of lowest BMI and WAZ was also recorded, and other nutritional indices (i.e. WHz, HAz and percentage of weight loss) were simultaneously calculated.

Patients' characteristics were further recorded to assess their potential association with PICU faltering growth. These included admission profile parameters, i.e. gender, age, pediatric logistic organ dysfunction score: PELOD, pediatric index of mortality score: PIM2, chronic medical condition (onset of chronic condition at least 3 months prior to PICU admission) and surgical admission, admission diagnosis (i.e. trauma, respiratory failure, metabolic/kidney failure, gastro-intestinal/liver failure, sepsis, shock, neurologic failure, other). These further included PICU parameters, i.e. nutritional support type (enteral versus parenteral nutrition) and use of neuroblocking agents, death, length of PICU stay, mechanical ventilation duration, and acquired infections (i.e. ventilation acquired pneumonia, urinary tract infection, septicemia, others, according to the Center of Disease Control definition)

Patient's post discharge follow-up: [all](#) children recruited during the first year of the study and presenting with a BMI z-score decline greater than 0.5 SD were followed after PICU discharge until

BMI z-score caught up PICU admission value and up to a maximum of 3 months after discharge.

Pediatric units where children had been discharged after PICU stay were asked to assess nutritional status, following WHO guidelines. Parents were also contacted by phone (one, two and three months after PICU discharge) and asked to report the most recent weight measured by a healthcare professional or by themselves.

Statistical analysis: all nutritional indices are expressed in z-scores according to age (when appropriate) and gender, and to WHO references. Categorical variables were expressed as numbers (n) and percentages. The hypothesis of normal distribution was tested with Kolmogorov-Smirnov test and histograms and quantitative variables were expressed as medians and interquartile range (IQR 25-75). Categorical variables were compared using the chi-square test. Quantitative variables were compared between groups using Kruskal-Wallis non-parametric test, and linear parameters with Pearson's correlation test. Linear regression was undertaken to identify factors associated with PICU faltering growth, including age and weight as potential confounders and significant variables ($p < 0.05$) identified in univariate regression and ANOVA (i.e. patients' characteristics described above). The statistical tests were two tailed and the level of significance was set to 5% ($p < 0.05$). Statistical analyses were conducted using IBM SPSS® Statistics version 24.0 (IBM® Armonk, NY, USA).

Results

Out of the 1732 admissions recorded during the conduct of the study, 579 (33.4%) admissions that spent longer than 5 days on PICU were analyzed (see patient flow chart in figure 1). Of them, 320 (55%) were children younger than 24 months. Patients' characteristics are presented in table 1. At PICU admission, the median (IQR 25-75) age was 13.6 months (1.9 - 96.1) and weight 9.0 Kg (4.1 - 23.0); 60% were males. Patients' nutritional status data are presented in table 2, figure 2 and supplemental digital content 1. At admission, undernutrition (WHO BMI z-Score $< -2SD$) was

diagnosed in 15%. Respiratory failure was the predominant admission diagnosis, followed by neurologic failure (status epilepticus, brain injury, encephalitis, meningitis and neuro-surgery).

The lowest PICU BMI z-score was encountered at 4.9 (IQR 0.0 ; 6.4) days from admission in the overall population, and 6.0 (IQR 4.2 ; 10.4) days in the subgroup who presented BMI z-score decrease greater than 0.5 SD. During their PICU stay, 10.2% of the children presented with an absolute decline of BMI z-score greater than 1SD (faltering growth) and 27.8% presented a decline greater than 0.5SD (risk of faltering growth). Similarly, in the subgroup of children younger than 2 years, WAz decline was greater than 0.5SD in 26.8%.

Overall population analysis

In the overall population (supplemental digital content 2), a significantly greater decline in BMI z-score was seen in association with greater age, in better-nourished children, in children who received neuromuscular blocking agents or mechanical ventilation, in children with higher severity illness scores (PELOD and PIM2) and in children with neurologic failure or sepsis. These children presented with significantly longer ventilation duration and length of stay, and more frequent acquired infections. In the multivariable linear regression model, PIM2 score and Length of stay remained significantly associated with BMI z-score decline, as shown in table 3 (R^2 0.036 ; $p < 0.01$).

Analysis of children under the age of 24 months

In this subgroup of children (supplemental digital content 3), a significantly greater decline in WAz was encountered in better-nourished children (defined as per admission BMI z-score or WAz), and in children presenting with higher admission weight and higher PELOD scores. These children presented with significantly longer length of PICU stay. In the multivariable linear regression model, admission WAz remained significantly inversely associated with WAz decline, as shown in table 4 (R^2 0.036 ; $p < 0.01$).

Children's post PICU discharge follow up

Out of the 70 children who presented with a greater than 0.5 SD decline of BMI z-score during the first year of the study, 8 (11%) were lost to follow up. The follow up group presented with similar admission characteristics and outcomes compared to the overall group, as shown in supplemental digital content 4. Out of the 62 children followed up, 4 died prior to hospital discharge without BMI recovery. BMI caught up with PICU admission values prior to PICU discharge in 2 children and in 31, 17, and 3 children within 1, 2 and 3 months post PICU discharge respectively. Only 5 (8%) children did not catch up at 3 months. Four of these 5 children had no nutritional support after PICU discharge, whereas 20 (39%) out of the 51 followed up children who recovered received enteral or parenteral nutrition after PICU discharge (30 of them were already receiving enteral or parenteral nutrition at PICU admission because of various chronic underlying condition).

Discussion

Monitoring of nutritional status during PICU admission defined according to BMI z-score or WAZ showed that PICU acquired faltering growth was an early, relatively frequent and significant phenomenon in critically ill children with length of stay greater than 5 days. High admission illness severity scores, the absence of malnutrition at admission and an increased length of stay were associated with nutritional status deterioration.

Growth stops in case of underfeeding or in case of negative imbalance between nutritional intakes and requirements. During critical illness, children are challenging to feed because of feeding intolerance (e.g. gastroparesis, gut dysmotility and gut inflammation impair nutrient absorption); this often leads to underfeeding which has been shown to be associated with suboptimal outcomes (23,24). Furthermore, large shifts affecting carbohydrate, protein and lipid metabolism and additional nutrient losses (drains, wounds, renal replacement therapy, etc) occur in the PICU setting,

resulting in even greater imbalances between nutritional intakes and requirements (25). As a consequence, critically ill children are at high risk of faltering growth.

Our results showed high occurrence of faltering growth during PICU stay with more than a quarter of children presenting with a BMI z-score decline greater than 0.5 SD and 24% with more than 5% weight loss. Moreover, this phenomenon occurs rapidly after PICU admission, whereas faltering growth in relation to chronic disease usually tends to happen after several weeks of disease. This is in contrast with Hulst et al. (7) results who found that faltering growth (based on WAZ decline) occurred in preterms and neonates but not in older critically ill children. Their children sample size was however limited. When they examined other nutritional indices such as mid upper arm circumference and triceps skinfold, their cohort did present with faltering growth during admission. Kelleher et al. found that young infants undergoing stage 1 Norwood surgery for hypoplastic left heart syndrome presented similar body weights at PICU admission and at discharge (median length of stay 13 days); this group did present with faltering growth, as they are normally expected to grow fast in the first month of life (9). However, these patients belong to a specific nutritional high-risk group (congenital heart disease) and were not included in the current study. Surprisingly, no further papers studying weight evolution in PICU could be found in the pediatric literature, despite the plethora available to describe the high frequency of malnutrition at PICU admission and its association to suboptimal outcomes (2,6,17,26). PICU health care professionals have limited impact on pre-PICU nutritional status; however, they can increase the awareness of their pediatric colleagues to the risks of malnutrition in PICU, especially in surgical wards responsible for children planned for elective surgery which will require PICU admission. PICU healthcare professionals could eventually play a greater role preventing or minimizing faltering growth occurrence during PICU stay. Nutritional status deterioration was more likely to occur in well-nourished children at admission. Possibly, under-nourished patients were identified and received optimized nutritional care, compared to well-nourished children. Another explanation may be that chronically undernourished

children might present with a different metabolism to spare energy costs of metabolism, with a less significant impact of critical illness on their metabolism shift. This hypothesis is supported by Briassoulis et al. study which has shown a contrasting combination of hypo-metabolism and over-feeding in a malnourished group of critically ill children; indeed, common resting energy expenditure equations, such as Schofield, failed to predict measured resting energy expenditure accurately (27).

Following BMI z-score or WAZ does not allow for differentiating overall faltering growth and fat mass / lean mass loss. Other parameters may be better at assessing body composition shifts. Muscle mass has previously (17) been monitored over PICU stay in a small population of critically ill children: quadriceps femoris muscle thickness measured with ultrasonography and used as a surrogate of muscle mass. This showed significant, intense and early decrease over PICU stay; at day 5, muscle mass had decreased by almost 10%, and more as PICU stay was prolonged. We did not encounter such high values of weight loss in our overall population but still we found an absolute difference of 0.4 SD between BMI admission and PICU lowest values. Critically ill children experience a profound shift in their metabolism(15), with transient hypo-metabolism and an important protein turnover (increased muscular breakdown, decreased muscular anabolism), in order to enable protein neo-synthesis (inflammation, wound healing, etc.) which partly explains muscle mass loss and weight loss. Together with a pattern of early hypo-metabolism, longitudinal activation of metabolic-hormones and heat shock proteins, and repression of bioenergetics and innate immunity have been shown in septic children and adults (28,29). The long-term impact of this phenomenon should be further investigated post PICU discharge, as physical rehabilitation may be negatively impacted.

Length of stay and severity of illness accounted for nutritional status deterioration. Indeed, in relation to PICU admission diagnosis, or potential complications, these parameters may combine to prolong the metabolism shift and feeding difficulties simultaneously. Conversely, nutritional status deterioration may impact PICU outcomes. Acquired undernutrition and muscle loss may contribute to PICU weakness and ventilation weaning failure. Finally, malnutrition at PICU admission and

faltering growth at admission have been associated with suboptimal outcomes (2,6,26); it is plausible that faltering growth during PICU admission may have a similar impact.

Catch up growth after PICU discharge was rapid most of the time. Most patients did not need nutritional support after hospital discharge. The ones found to be under enteral or parenteral support were most likely, but not all, receiving artificial nutrition in a similar manner prior to PICU admission, because of various underlying chronic conditions. However, children with acute brain injury often required prolonged nutritional support because of new onset of cerebral palsy, or swallowing issues. It is interesting to note that the few patients who did not catch up growth at three months post PICU discharge, did not receive any form of nutritional support. Better collaboration is needed with pediatric teams who manage these children after PICU discharge (clinicians, dieticians, nurses), in order to make them aware of post PICU syndrome issues, rehabilitation and follow up needs, including nutrition. Hulst et al. (7) found similar results in their study cohort: nutritional status was found to be improved 6 months post PICU discharge, compared to PICU admission nutritional status, with less than 10% suffering from undernutrition. However, no study has assessed long term functional outcomes so far, in relation to weight loss or faltering growth, such as muscle strength, muscle function, and quality of life.

This study has some limitations that need to be acknowledged. First, anthropometric measurement accuracy remains questionable in the PICU setting especially because of potential fluid overload (or dehydration) at admission. Mid upper arm circumference is less influenced by fluid shift, and may be a more accurate marker of nutritional status in the PICU setting. However, WHO do not provide references for children above the age of 5 years, which limits its use in a large part of PICU patients. The use of ulna length extrapolation to assess height may also have led to a measurement bias; anthropometric measurements were also performed by trained nurses rather than experts, which may also have impacted measurement accuracy. During post PICU weight follow up, parents'

reporting of weight measurement may also have impacted accuracy of reported values. Secondly, nutritional intake data were not collected, and their impact on nutritional status deterioration could not be assessed. However, children admitted to our unit are fed according to local written guidelines, with known good guideline compliance by our team. In addition, body composition was not assessed, its monitoring would further improve the understanding of the pathophysiology of faltering growth, assessing muscle mass, fat mass, but also micronutrient status. Finally, the power of the study did not allow for analyzing sub-groups based on admission diagnosis.

Conclusion

Nutritional deterioration is frequent and often intense in critically ill children with length of stay greater than 5 days. Future research should focus on how targeted nutritional therapies can minimize PICU faltering growth and improve post-PICU rehabilitation.

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Figure legend

Figure 1: Patient flow chart.

PICU (pediatric intensive care unit) admissions were recorded between September 2013 and December 2015. Post PICU discharge follow up was conducted in patients admitted in the first year of the study only.

Figure 2: Nutritional status deterioration over PICU stay.

Weight for age z-score (WAZ) and BMI z-score decrease significantly during PICU admission in children under 24 months and in the overall population respectively. (Adm: PICU admission)

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