Évaluation nutritionnelle systémique de l'enfant en réanimation pédiatrique

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Résumé

La malnutrition à l'admission en réanimation pédiatrique est fréquente et associée à une augmentation de la morbi-mortalité. Néanmoins, la plupart des études, limitées à une évaluation statique du statut nutritionnel, ne permettent pas une analyse fine de l'impact de la malnutrition. Une approche systémique associerait en plus d'une évaluation nutritionnelle statique, une analyse dynamique dans le temps, une analyse de la composition corporelle et une analyse physiopathologique et étiologique.

Cette approche globale a été appliquée dans 4 études prospectives observationnelles, incluant des enfants sévèrement agressés de plus de 36 semaines d'âge corrigé.

Il en ressort que la dénutrition globale à l'admission est fréquente (23,7%) et que la cassure des courbes de croissance avant l'admission est associée à une augmentation de la durée de séjour de 3 jours. L'enfant sévèrement agressé présente à l'admission des taux plasmatiques abaissés de 6 micronutriments impliqués dans le stress oxydant (Sélénium, Zinc, Cuivre, Vitamines C, E et bêta-carotène), proportionnellement au nombre de défaillances d'organe. La dénutrition globale et la fonte musculaire acquises en cours de séjour sont des phénomènes fréquents, précoces et importants, associés à une durée de séjour prolongée.

Les changements métaboliques liés à l'agression sévère conduisent à une dénutrition. Ces processus adaptatifs sont parfois dépassés et la dénutrition pourra à son tour aggraver le pronostic. La bonne compréhension de la physiopathologie sous-jacente et un suivi systémique et systématique du statut nutritionnel sont les éléments indispensables à l'évaluation des stratégies nutritionnelles.

Mots-clés

Malnutrition ; Dénutrition ; Evaluation Nutritionnelle ; Pédiatrie ; Réanimation ; Fonte Musculaire ; Micronutriments ; Stress Oxydant ; Pronostic

Titre anglais

Holistic nutritional assessment in critically ill children

Résumé anglais

Malnutrition at pediatric Intensive care unit (PICU) admission is frequent and associated with impaired outcomes. However, most studies have focused solely on a static definition. A holistic approach would improve the description of malnutrition: this would include both a static and dynamic assessment of nutritional status, together with body composition assessment and with malnutrition classified based on its patho-physiology and etiology.

This holistic assessment of malnutrition has been applied and examined in four observational studies which included critically ill children older than 36 gestational weeks (corrected age).

These found that malnutrition was frequent at PICU admission (27.3%) and faltering growth prior to PICU admission was associated with an increased length of PICU stay (+3 days). Critically ill children present at admission with decreased plasma levels of 6 micro-nutrients (Selenium, Copper, Zinc, Vitamin C, E and beta-carotene) involved in anti-oxidative stress pathways. Nutritional status deterioration during PICU stay, and associated muscle mass loss occurred frequently and were intense. This early phenomenon was associated with extended length of PICU stay.

A profound critical illness related metabolic shift leads to malnutrition as an adaptive process. However, malnutrition may also negatively impact on outcomes in this setting. These studies have led to a clearer understanding of the underlying patho-physiology. This, combined with a more systematic and holistic nutritional assessment, will enable implementation and assessment of nutritional strategies aiming to improve the functional outcome of critically ill children.

Keywords

Malnutrition; undernutrition; nutritional status assessment; children; critically ill; pediatric intensive care; micronutrients; oxidative stress; muscle wasting; outcome

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Cadre de la thèse

La thèse présentée dans ce document traite du statut nutritionnel des enfants admis en réanimation pédiatrique, et dénommés « enfants sévèrement malades » ou « enfants sévèrement agressés » (critically ill children). Les nouveau-nés de moins de 36 semaines d'aménorrhée et les enfants de moins de 36 semaines d'âge corrigé ne rentrent pas dans le cadre de ce travail de thèse.

Terminologie employée dans ce travail de thèse (traduction anglaise) et dans la littérature

Le terme « **alimentation** » désigne classiquement l'alimentation « normale », libre, orale.

Le terme « **nutrition** » désigne classiquement l'alimentation « artificielle », englobant la nutrition entérale et la nutrition parentérale.

Le terme « **malnutrition** » (malnutrition) définit un statut nutritionnel anormal, et englobe la dénutrition (undernutrition, malnourishment, stunting, wasting) et la surcharge pondérale et l'obésité (overnutrition, overnourishment, overweight, obesity). Mais il ne décrit pas a priori la nutrition ni l'alimentation.

La « **sur-nutrition** » (overfeeding) et la « **sous-nutrition** » (underfeeding) correspondent à une nutrition ou une alimentation respectivement trop importante ou insuffisante, au regard des besoins. Mais ces termes ne définissent pas a priori le statut nutritionnel.

1. Introduction

1.1. Importance de l'évaluation nutritionnelle, impact sur le devenir

La prise en charge nutritionnelle fait partie à part entière de la prise en charge globale des patients, adultes et enfants, admis en réanimation.

Les recommandations 2019 de l'ESPEN (European Society for Parenteral and Enteral Nutrition) (1) concernant l'adulte admis en réanimation rappellent la nécessité d'une prise en charge nutritionnelle chez tout patient, surtout si son séjour dépasse 48 heures (niveau de recommandation : bonnes pratiques professionnelles, consensus fort 100%). En effet, la sous-nutrition, autant que la sur-nutrition, est associée à un mauvais devenir (mortalité, morbidité) (2) chez l'adulte. De la même façon, chez l'enfant en réanimation pédiatrique, la sous-nutrition est associée à une morbi-mortalité augmentée (3–5) : la survie serait significativement augmentée chez l'enfant s'il reçoit un pourcentage plus élevé de ses cibles nutritionnelles protéino-énergétiques.

Les recommandations américaines de l'ASPEN (American Society for Parenteral and Enteral Nutrition) et de la SCCM (Society of Critical Care Medicine) de 2017 concernant l'enfant admis en réanimation (6) rappellent quant à l'elles l'importance d'évaluer systématiquement l'état nutritionnel et de le suivre en cours de séjour, de déterminer le plus précisément les besoins nutritionnels individualisés et de s'employer à atteindre ces objectifs en anticipant et suivant la tolérance.

Dans ce travail de thèse, nous nous sommes intéressés à l'étude du statut nutritionnel de l'enfant admis en réanimation pédiatrique, en y appliquant une approche systémique à même d'appréhender la question posée dans sa globalité.

Plusieurs études ont rapporté une association entre le statut nutritionnel à l'admission en réanimation pédiatrique et le devenir des enfants, aussi bien en réanimation pédiatrique polyvalente qu'en réanimation pédiatrique cardiologique. En effet, la dénutrition (7–20), dont la définition varie selon les études, est associée à une augmentation de la mortalité et de la morbidité (infections acquises, durée de séjour, durée de ventilation, dysfonction cardiaque). Ainsi, en 2014, Prince et al. (11) ont montré dans une population britannique de 14 307 enfants sévèrement malades, une association entre le statut nutritionnel à l'admission en réanimation pédiatrique (défini sur la base du z-score du poids pour l'âge) et la mortalité ; cette association définissait une courbe en U, les extrêmes du z-score du poids pour l'âge (< -3,5DS et >+3,5DS) présentant le risque de mortalité maximal alors que les enfants entre +0,5DS et +2,5DS présentaient un risque minimal.

Le surpoids et l'obésité sont également associés à un devenir différent en comparaison d'un statut nutritionnel normal à l'admission. Néanmoins, leur impact reste mal défini, certaines études montrant une amélioration du pronostic, d'autres le contraire (8,11,13,20–25). Il est possible que la prévalence élevée de l'obésité aux Etats-Unis puisse expliquer leurs meilleurs

résultats (plus grandes expertise et expérience des professionnels de santé de réanimation dans la prise en charge ventilatoire et pharmacologique de l'enfant obèse).

1.2. Prévalence de la malnutrition et concept de l'évaluation nutritionnelle systémique

La dénutrition à l'admission en réanimation pédiatrique, définie sur la base de données anthropométriques et d'indices nutritionnels mesurés et calculés à l'admission, a une prévalence élevée, variant de 15 à 25% selon les études (jusqu'à 55% au Brésil), selon la population étudiée et le recrutement des études, et selon les ressources économiques et l'organisation du système de santé (26,7–10,13,16,27). Les enfants atteints de cardiopathie ont une prévalence de dénutrition plus élevée que les autres (28,29), s'expliquant par leurs besoins de base augmentés, l'anorexie liée à l'insuffisance cardiaque et son retentissement respiratoire, l'entéropathie classiquement associée, et la restriction hydrique pouvant compromettre les ingesta (30,31).

Ces données de prévalence ont peu évolué sur les 20 dernières années, et la dénutrition reste donc une problématique fréquente en réanimation pédiatrique (32).

Une seule étude, au design biaisé (protocole de nutrition local conduisant à une sur-nutrition quasi systématique), a suivi l'évolution du statut nutritionnel des enfants sévèrement malades, en cours de séjour et jusqu'à six mois après leur sortie (33). De façon surprenante, les enfants de plus de 28 jours ne présentaient pas ou peu de dénutrition acquise en cours de séjour, contrairement à l'impression générale ressentie par les professionnels de santé impliqués en réanimation pédiatrique (34,35).

En somme, malgré le nombre conséquent de travaux ayant étudié le statut nutritionnel à l'admission et son impact sur le devenir, la description du statut nutritionnel s'est limitée aux données anthropométriques d'admission, en négligeant les autres aspects clés de l'évaluation nutritionnelle. En effet, l'évaluation nutritionnelle de l'enfant en réanimation devrait suivre une approche systémique permettant une analyse globale et dynamique, telle que définie par un consortium d'experts en malnutrition pédiatrique (36,37). (Les recommandations françaises de la haute autorité de santé à paraitre sont également en accord avec cette approche). Pour cela, la démarche d'évaluation nutritionnelle de l'enfant sévèrement malade devrait reposer sur l'association des composantes suivantes :

- **Une composante statique :**

Elle consiste en une évaluation à un instant donné, à l'admission en réanimation notamment, et se base sur des mesures et des indices de statut nutritionnel validés qui seront développés plus loin (Indice de masse corporelle, rapport Poids taille, rapports poids pour l'âge et taille pour l'âge, rapport périmètre brachial pour l'âge).

- **Une composante temporelle dynamique :**

Elle recherche une perte de poids ou une cassure des courbes de croissance, avant l'admission (aiguë ou chronique), en cours de séjour, et à distance de la sortie ; elle consiste

en la répétition dans le temps de la composante statique décrite ci-dessus, tout au long du parcours de soin. Les données antérieures à l'admission doivent être recueillies au travers des dossiers médicaux, et des carnets de santé ; le suivi nutritionnel doit faire partie du suivi du patient en cours de séjour, et dans sa phase de réhabilitation post réanimation.

- **Une composante compartimentale :**

Elle consiste en l'évaluation de la composition corporelle, distinguant, au-delà du statut nutritionnel global, l'évaluation de la masse maigre et de la masse grasse, de la masse musculaire, de l'état d'hydratation (facteur confondant), et le statut en micro-nutriments.

- **Une composante étiologique :**

Elle consiste en la caractérisation de la cause de la malnutrition (pathologie sous-jacente, contexte socio-économique et impact sur l'accès à l'alimentation, régimes déviants de type orthorexique ou de l'anorexie). On différenciera dans ce cadre les causes aiguës et chroniques.

- **Une composante physiopathologique :**

La malnutrition est la conséquence d'un déséquilibre entre les apports et les besoins.

  - Les apports peuvent être inadaptés (insuffisants ou trop importants)

  - L'alimentation ou la prescription nutritionnelle peuvent ne pas être en adéquation avec les besoins. L'intolérance nutritionnelle et les interruptions de la nutrition prescrite peuvent également compromettre les objectifs fixés et prescrits (34,38–40)

  - L'absorption peut être altérée (entéropathie, troubles du transit)

  - Les besoins peuvent être fortement modifiés en contexte de réanimation, de façon quantitative ou qualitative (41,42)

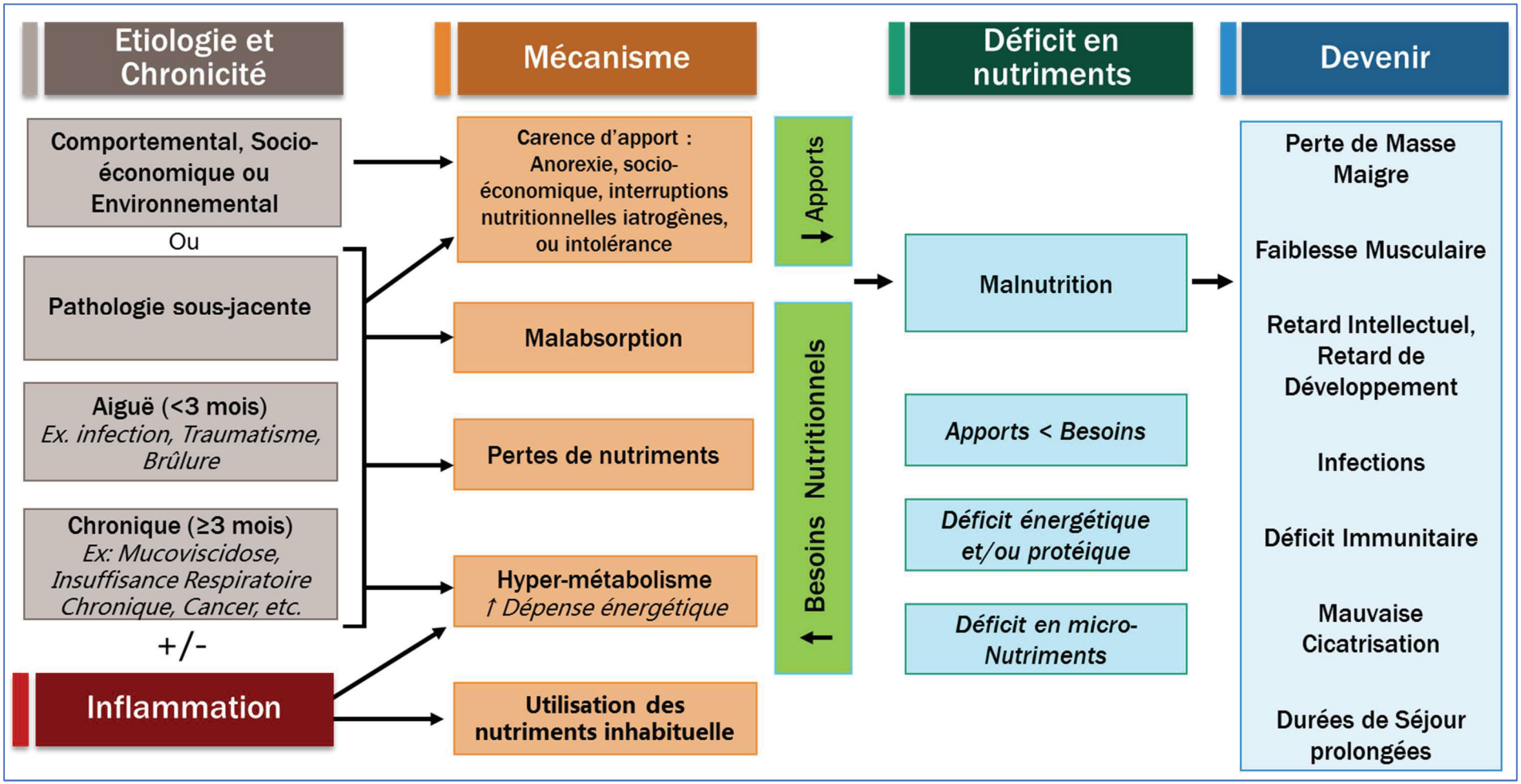
  - Du fait des perturbations métaboliques majeures en lien avec l'affection critique sous-jacente (« orage cytokinique », perturbation neuroendocrines, dys-régulation hormonale, altération du système nerveux autonome, résultant en un catabolisme protéique et lipidique majeur initial)

  - Du fait d'un anabolisme compensatoire secondaire au décours de la phase aiguë (cicatrisation, inflammation, anabolisme protéique et lipidique), requérant des apports protéiques importants

  - Du fait des pertes accrues de nutriments (brûlures, drainages, épuration extrarénale, stomies et fistules)

- **Une composante évolutive et pronostique :**

Elle consiste à rechercher l'impact sur le devenir en évaluant le retentissement physique, psychomoteur, intellectuel, social et psychologique, à court, moyen et long terme (43).



Adapté d'après Mehta et al. 2013 (36)

Définition de la malnutrition chez l'enfant hospitalisé : approche systémique de l'évaluation nutritionnelle

1.3. Difficultés techniques de l'évaluation nutritionnelle en réanimation pédiatrique

L'enfant sévèrement malade présente des caractéristiques intrinsèques tendant à compromettre la fiabilité et / ou la faisabilité de son évaluation nutritionnelle. En effet, la sécurité du patient primera sur cette évaluation nutritionnelle, notamment chez l'enfant instable. L'équipement lourd peut compromettre la faisabilité des techniques d'évaluation nutritionnelle ou leur fiabilité : ventilation invasive sur sonde d'intubation ou trachéotomie, ou non invasive, présence de cathéters vasculaires, de mesure de pression intracrânienne, de sondes digestives ou urinaires, de stomies, de drainages, de circulation extracorporelle (épuration extrarénale ou assistance circulatoire ou respiratoire), pansements et plâtres, etc.

1.4. Outils de l'évaluation nutritionnelle

Classiquement, l'évaluation nutritionnelle de l'enfant sain reposera sur le calcul d'indices nutritionnels, calculés sur la base de mesure anthropométriques. L'enfant est un organisme en croissance, dont le poids, la taille et la composition corporelle évoluent continuellement de la naissance à l'âge adulte. Aussi, les indices nutritionnels utilisés doivent être indexés à l'âge et au sexe, idéalement exprimés en déviation standard (DS) de z-scores (ou en percentiles) et en utilisant des références validées et actualisées, nationales et / ou internationales.

(Dans la suite de ce manuscrit, les indices nutritionnels mentionnés seront toujours indexés à l'âge et au sexe, sans en faire mention systématiquement).

Les indices nutritionnels habituellement utilisés sont l'indice de masse corporelle (IMC), le rapport poids/taille (RPT), le rapport poids pour l'âge (RPA), le rapport taille pour l'âge (RTA), et le rapport périmètre brachial pour l'âge (RPBA). Ces indices seront utiles pour décrire le statut nutritionnel global et préciser le caractère aigu ou chronique de la dénutrition, mais seront peu discriminants pour évaluer la composition corporelle.

La mesure des plis cutanés (tricipital, scapulaire, bicipital) est utile, permettant également le calcul de la circonférence musculaire brachiale ; ce sont des indices de masse maigre et masse grasse ; néanmoins, la faible reproductibilité de la mesure des plis cutanés chez l'enfant compromet la fiabilité de ces mesures par des opérateurs non spécialistes, et en fait un outil peu utile en pratique clinique (44).

Les autres techniques classiquement utilisées pour décrire le statut nutritionnel chez l'enfant ne sont pas validées en réanimation pédiatrique :

La DEXA (absorptiométrie biphotonique à rayons X), l'IRM et le scanner abdominal, qui permettent une évaluation de la masse grasse et de la masse musculaire, ne sont pas envisageables en routine, du fait de l'irradiation ou de la contrainte et du danger que représente le transport d'un enfant instable ou lourdement équipé. En dehors de l'évaluation nutritionnelle, le scanner est par ailleurs bien moins fréquemment utilisé à visée diagnostique chez l'enfant que chez l'adulte en réanimation. L'échographie musculaire n'a

pas montré de reproductibilité suffisante pour son utilisation en pratique courante en réanimation pédiatrique (45).

L'impédancemétrie bio-électrique, mono ou multi fréquence, est un outil utilisable au lit du patient, non invasif et bon marché, mais n'est pas validée en réanimation pédiatrique, notamment à cause des variations hydriques importantes et rapides, qui limitent l'interprétation nutritionnelle des résultats. L'impédancemétrie multifréquence et l'angle de phase ont bien montré un intérêt dans l'évaluation du pronostic général chez l'enfant sévèrement agressé, mais les mesures obtenues doivent être interprétées en considérant l'effet conjoint du statut nutritionnel et du statut d'hydratation qui ont chacun une action propre sur le pronostic (46,47).

La dilution isotopique (utilisant des isotopes stables), bien que non irradiante, est coûteuse et non utilisable en pratique clinique courante (48,49).

Les valeurs plasmatiques des marqueurs biologiques classiquement utilisés dans l'évaluation nutritionnelle de l'enfant (albumine, préalbumine, Retinol Binding Protein, etc.) sont fortement impactées par les variations hydriques (surcharge hydrique principalement), par l'inflammation (même indexée à la CRP), par l'insuffisance hépato-cellulaire, par les fuites (urinaires, digestives, de drain, etc.). Ces marqueurs sont d'interprétation nutritionnelle très limitée dans le contexte de la réanimation pédiatrique (50–54).

Au final, les mesures anthropométriques restent recommandées en pratique courante pour l'évaluation nutritionnelle (6,36). Pourtant, elles ont elles-mêmes leurs limites propres que nous détaillons ci-après.

1.5. Mesures anthropométriques : freins à leur réalisation et leur interprétation

Plusieurs enquêtes auprès des professionnels de santé de réanimation pédiatrique ont identifié comme frein à la réalisation des mesures anthropométriques (34,55,56) :

- la sécurité engagée du patient
- l'absence d'outils adaptés
- l'insuffisance de leurs connaissances ou de leur sensibilisation à cette problématique

1.5.1. **Le poids** :

Il doit être mesuré en théorie à l'admission et en cours de séjour. L'interrogatoire des parents ou la consultation du carnet de santé ou du dossier médical (en cas d'antériorité de séjour) permet également d'estimer le poids. Le poids peut être extrapolé à partir des courbes de croissance, non sans une marge d'erreur. La confrontation de ces différentes méthodes peut aider à réajuster la valeur réelle du poids.

Mesurer le poids n'est pas simple en réanimation pédiatrique : les critères de qualité, comme les critères de l'organisation mondiale de la santé (OMS), ne sont pas directement applicables (57–61), l'enfant étant difficilement mobilisable du fait de l'équipement

technique (sonde d'intubation, drains, cathéters, circulation extra corporelle, etc.). La sécurité doit par ailleurs être garantie. L'enfant est bien généralement dévêtu, mais chez le jeune enfant, les équipements décrits ci-dessus peuvent modifier significativement le poids mesuré. L'utilisation de balances intégrées dans les lits et berceaux / couveuse facilite néanmoins grandement la mesure régulière du poids (35).

Si elle peut être mesurée, la valeur du poids doit néanmoins être interprétée une fois encore dans le contexte du risque d'inflation hydrique, fréquente chez l'enfant en réanimation pédiatrique. Le poids est autant un indicateur nutritionnel qu'un indicateur de surcharge hydrique ; son évolution témoignera soit d'une modification du statut hydrique, soit d'une modification de son statut nutritionnel. Nous ne disposons pas aujourd'hui de marqueurs de surcharge hydrique permettant d'isoler ce facteur confondant de l'interprétation nutritionnelle des mesures de poids. Le bilan entrée-sortie ne peut être considéré comme une méthode fiable, notamment du fait de la variabilité individuelle des pertes insensibles.

1.5.2. La taille :

L'enfant étant un organisme en croissance, la taille déclarative ou figurant sur les papiers d'identité ne peut être considérée comme fiable contrairement à l'adulte. Tout comme le poids, la taille doit être mesurée, mais les critères OMS (57) sont difficiles à réunir (rectitude pour les moins de deux ans mesurés allongés à l'aide d'une toise, station debout pour les plus de deux ans mesurés avec un stadiomètre) et l'équipement du patient compromet l'exactitudes et la sécurité des mesures. Des méthodes d'estimation et d'extrapolation de la taille (44,62–66) ont été validées dans d'autres populations pédiatriques, mais pas en réanimation ; leur utilisation peut entrainer des erreurs (extrapolation de la taille à partir de mesures segmentaires : longueur de l'ulna, du tibia, de la distance talon-genou, de l'envergure, des segments contigus, etc.). L'extrapolation des courbes de croissance peut également aider à corriger les erreurs de mesure.

La mesure de la taille pourra être répétée en cours de séjour prolongé (plusieurs semaines), chez les plus jeunes enfants dont la cinétique de croissance est rapide (35,67). Une stagnation staturale est alors recherchée.

1.5.3. Le périmètre brachial :

La mesure du périmètre brachial est simple et peut être faite en sécurité. Elle se fait à l'aide d'un simple mètre-ruban au niveau du bras, à mi-distance entre le coude et l'épaule. Sa mesure est peu impactée par l'inflation hydrique, ce qui en fait un outil particulièrement intéressant en réanimation pédiatrique. Néanmoins, la précision de la mesure, au mieux à une décimale, ne permet pas de détecter facilement des variations modérées chez les plus jeunes enfants.

Malgré tous les freins à la réalisation des mesures anthropométriques décrits ci-dessus, il est néanmoins possible grâce à un programme de formation et de sensibilisation des équipes soignantes de réanimation pédiatrique d'obtenir de bon résultats en termes d'évaluation nutritionnelle (35). Ainsi, la constitution d'une équipe support de nutrition multi professionnelle et intégrée au service, et le déploiement d'un tel programme éducationnel a montré au travers d'une évaluation des pratiques professionnelles, une augmentation significative du nombre d'enfants mesurés et pesés dans les 24 h suivant l'admission en réanimation pédiatrique polyvalente à Lyon. Les mesures anthropométriques (poids, taille périmètre crânien, périmètre brachial) étaient réalisées chez 32%, 65% et 96% des enfants respectivement en 2011, 2012 et 2013 ($p<0,01$). La reproductibilité et la comparaison à un gold standard n'ont pas été testées dans cette étude. Néanmoins, ces mesures anthropométriques intégrées aux pratiques quotidiennes ont permis la réalisation d'études sur le statut nutritionnel des patients sévèrement malades.

1.6. Définition de la malnutrition

Classiquement, les indices nutritionnels permettent de distinguer chez l'enfant la dénutrition chronique de la dénutrition aiguë (36,37).

- La dénutrition aiguë se manifestera par des z-scores d'IMC, de RPA, de RPT et de RPBA diminués, alors que les z-scores de RTA sont normaux (Les courbes de croissances de poids cassent avant celles de la taille).
- La dénutrition chronique se manifestera par des z-scores de RTA, RPBA, et RPA diminués, mais les z-scores de l'IMC et du RPT peuvent être normalisés ou légèrement diminués.
- La dénutrition aiguë sur fond de dénutrition chronique se manifestera par des z-scores de RTA, RPA, IMC, RPBA, RPT tous diminués.
- En cas d'œdèmes importants, seuls seront pris en compte les z-scores de RTA et RPBA.
- La construction et l'analyses des courbes de croissance (courbe de poids et taille, d'IMC et des autres indices nutritionnels), lorsqu'elles sont possibles, permettent également un diagnostic nutritionnel chez l'enfant.

La définition des seuils de z-score caractérisant un statut nutritionnel normal d'un statut nutritionnel anormal (dénutrition modérée, sévère) n'est pas consensuelle. Néanmoins, Bouma et al. ont résumé les critères d'évaluation de la malnutrition pédiatrique, en se basant sur les recommandations de 2015 de l'Academy of Nutrition and Dietetics et de l'American Society for Parenteral and Enteral Nutrition et sur l'approche nouvelle proposée par le groupe d'expert sur la malnutrition pédiatrique de N. Mehta, décrite précédemment dans ce manuscrit (36,37,68).

La dénutrition sera évaluée soit sur la base de valeurs uniques d'indices nutritionnels, soit sur la base de valeurs multiples, comme présenté dans le tableau 1.

		Dénutrition Légère	Dénutrition Modérée	Dénutrition Sévère
Valeurs uniques (dans le temps) d' indices nutritionnels	z-scores de RPT ou BMI ou RPBA	entre -1 et -1,9DS	entre -2 et -2,9DS	< -3 DS
	z-scores de RTA	-	-	< -3 DS
Valeurs répétées d' indices nutritionnels	vélocité de prise pondérale (pour les moins de 2 ans)	<75% de la norme	<50% de la norme	<25% de la norme
	perte de poids (pour les plus de 2 ans)	5% du poids habituel	7,5% du poids habituel	10% du poids habituel
	décélération des z-scores du RPT	-1 DS	-2 DS	-3 DS
	% des ingesta proteino-énergétiques par rapport aux besoins théoriques.	entre 51 et 75%	entre 26 et 50%	< 25%

Tableau 1 : adapté de Bouma et al. Définition des stades de dénutrition pédiatrique. (37)

RPT : Rapport poids / taille ; RTA : Rapport Taille pour l'âge ; IMC : Indice de masse corporelle ; RPBA : Rapport périmètre brachial pour l'âge ; DS : Déviation standard

L'OMS propose des valeurs de z-score définissant chacun de ces types de dénutrition ; ces normes OMS ont été établies sur la base de données obtenues dans différents pays à travers le monde (58,59,69–71). Même si elles peuvent être sensiblement moins précises ou adaptées que des normes nationales, elles permettent des comparaisons internationales ; par ailleurs, l'évolution dynamique s'affranchit automatiquement des normes choisies, puisqu'elle prend alors en compte la variation des indices nutritionnels, plus que leurs valeurs absolues. Néanmoins, l'OMS, tout comme les normes nationales (françaises, américaines ou autres), ne propose pas des normes pour chaque indice nutritionnel pour toutes les tranches d'âges pédiatriques : ainsi, le RPBA et le RPT ne sont pas disponibles au-delà de 5 ans, ni le RPA au-delà de 10 ans. Seuls l'IMC et le RTA couvrent l'ensemble de la population pédiatrique. Il en résulte que les définitions théoriques précédemment décrites (proposées par Mehta et al., et Bouma et al.) ne peuvent être littéralement appliquées en réanimation pédiatrique. La conception des études nutritionnelles constituant ce travail de thèse a donc essentiellement reposé sur l'analyse des z-scores de l'IMC.

1.7. Evaluation de la masse musculaire

L'évaluation de la masse musculaire fait partie de l'analyse de la composition corporelle. Nous avons précédemment décrit l'impossibilité d'utiliser les techniques habituelles (DEXA, IRM, scanner, impédancemétrie) chez l'enfant sévèrement malade. Il n'y a ainsi pas de méthode validée dans cette sous population. Chez l'adulte (72–75), la mesure échographique de la masse musculaire au lit du patient semble intéressante et reproductible (mesure de l'épaisseur ou de la surface du quadriceps femoris notamment) ; mais chez l'enfant Fivez et al. ont échoué à montrer une bonne reproductibilité de l'étude échographique de la masse musculaire segmentaire (45).

Pourtant, le suivi de la masse musculaire serait utile, afin de mieux décrire le concept, peu étudié en pédiatrie (76–82) mais bien connu en réanimation adulte de « fonte musculaire aiguë en réanimation » (ICU acute muscle wasting) et responsable du syndrome de faiblesse musculaire de réanimation (ICU acquired weakness, frailty) qui compromet le devenir des patients, en retardant le sevrage ventilatoire et la réhabilitation au sens large (83–92).

1.8. Evaluation micro-nutritionnelle (éléments-trace et vitamines)

Eléments-trace (ou oligo-éléments) et vitamines sont des nutriments indispensables. Les patients de réanimation peuvent présenter des carences en micro-nutriments dans plusieurs contextes :

- Dénutrition par carence d'apport (carence globale des apports, régimes déviants orthorexiques, anorexie) (93–95)
- Pertes excessives (éléments-trace et vitamines hydrosolubles dans l'épuration extrarénale, en cas de brûlures étendues, par exemple) (96–99)
- Mobilisation / consommation aiguë des stocks (en cas de stress oxydant par exemple) (81–83)

L'évaluation des réserves en micronutriments n'est pas simple en routine. En effet, les résultats des dosages plasmatiques sont difficiles à obtenir en urgence. Par ailleurs, les dosages plasmatiques, dont les normes pédiatriques ne sont pas toujours validées, ne sont pas nécessairement un reflet parfait des stocks intra tissulaires (pool intracellulaire, protéines de transport). Enfin, en cas de mobilisation aiguë des éléments-trace, en cas de stress oxydant par exemple, l'amélioration clinique s'accompagnera d'une « démobilisation » des stocks, introduisant le concept de « déficit circonstanciel transitoire ». Ainsi, chez l'adulte en réanimation, les résultats des études de supplémentation à forte dose en micro-nutriments (sélénium, zinc, vitamine C) sont contradictoires (1) et une supplémentation à forte dose ne serait recommandée qu'en cas de déficit documenté ; chez l'enfant, les trois études disponibles, dont les biais sont importants, n'ont pas montré de bénéfice significatif (100–102).

1.9. Objectif du travail de thèse réalisé

La malnutrition est donc une problématique fréquente en réanimation pédiatrique et associée à un moins bon pronostic. La littérature pédiatrique reste pourtant très pauvre, et ne propose qu'une approche « simpliste », consistant presque toujours en la description du statut nutritionnel statique à l'admission, et négligeant les composantes dynamiques, étiologiques, physiopathologiques et compartimentales.

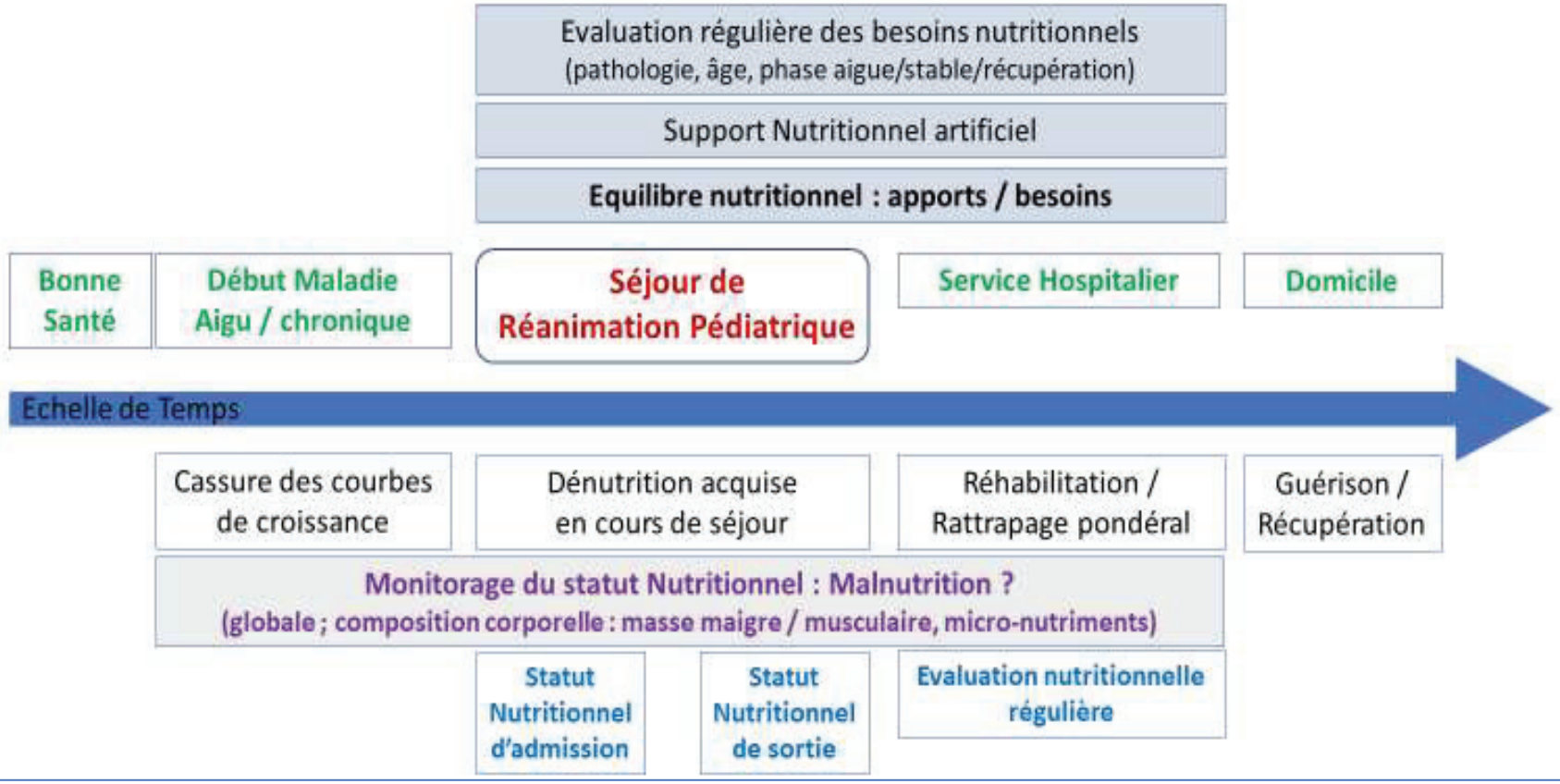
Nous nous proposons dans ce travail de thèse de décrire et analyser le statut nutritionnel en lui appliquant une approche systémique, intégrant chacune de ses composantes. Ce travail sera le préalable à la conception d'études interventionnelles (impliquant des stratégies nutritionnelles et de mobilisation précoce active par exemple), pouvant influencer l'évolution du statut nutritionnel et le devenir global de l'enfant sévèrement malade.

Quatre études publiées seront présentées successivement

- La première est intitulée « cassure des courbes de croissance à l'admission en réanimation pédiatrique : prévalence, facteurs de risque et impact sur le devenir » (« Faltering growth in the critically ill child: prevalence, risk factors, and impaired outcome »). Cette étude publiée en mars 2018 a étudié la composante dynamique du statut nutritionnel avant l'admission en réanimation pédiatrique (103).
- La seconde est intitulée « Fréquente dégradation du statut nutritionnel en cours de séjour en réanimation pédiatrique » (« Nutritional Status Deterioration Occurs Frequently During Children's ICU Stay »). Cette étude publiée en août 2019 a évalué l'évolution du statut nutritionnel global à l'admission, en cours de séjour et jusqu'à trois mois après la sortie de réanimation (104).
- La troisième est intitulée « une diminution de l'épaisseur du quadriceps femoris est fréquemment observée par ultrasonographie en cours de séjour en réanimation pédiatrique (« Thigh Ultrasound Monitoring Identifies Decreases in Quadriceps Femoris Thickness as a Frequent Observation in Critically Ill Children »). Cette étude a été publiée en juin 2017 et a décrit l'évolution de la masse musculaire en cours de séjour (105).
- Enfin, la quatrième est intitulée « modifications des dosages plasmatiques à l'admission en réanimation pédiatrique, liées à l'intensité du stress oxydant » (« Multiple Micronutrient Plasma Level Changes Are Related to Oxidative Stress Intensity in Critically Ill Children »). Cette étude a été publiée en septembre 2018 et décrit le statut micro-nutritionnel à l'admission en réanimation pédiatrique (106).

Le concept général de l'évaluation nutritionnelle systémique appliqué à la réanimation pédiatrique est synthétisé dans le schéma suivant

Evaluation Nutritionnelle
en cours de séjour en réanimation pédiatrique



2. Etudes

2.1. Article n°1

Cassure des courbes de croissance à l'admission en réanimation pédiatrique : prévalence, facteurs de risque et impact sur le devenir

"Faltering growth in the critically ill child: prevalence, risk factors, and impaired outcome"

2.1. Article n°1

Cassure des courbes de croissance à l'admission en réanimation pédiatrique : prévalence, facteurs de risque et impact sur le devenir

"Faltering growth in the critically ill child: prevalence, risk factors, and impaired outcome" (103)

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Valla FV, Berthiller J, Gaillard-Le-Roux B, Ford-Chessel C, Ginhoux T, Rooze S, Cour-Andlauer F, Meyer R, Javouhey E.

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2.1.1. Introduction

La littérature s'est jusqu'ici essentiellement concentrée sur le statut nutritionnel à l'admission, sur la base d'une évaluation statique ne prenant pas en compte l'évolution récente des paramètres anthropométriques. L'objectif de cette étude était de décrire le statut nutritionnel global à l'admission en réanimation pédiatrique, en se basant sur les valeurs brutes des z-scores d'indices nutritionnels calculés à partir des mesures anthropométriques d'admission, et de les comparer aux données des 3 mois précédant l'admission. Nous avons par ailleurs cherché à isoler des facteurs associés à partir des caractéristiques des patients.

2.1.2. Matériel et méthode

Etude prospective observationnelle monocentrique (conduite dans une unité de réanimation pédiatrique non cardiologique, non néonatale, sur 12 mois entre 2012 et 2013).

Ont été inclus tous les enfants de plus de 36SA d'âge corrigé, de 0 à 18 ans.

Des mesures anthropométriques étaient réalisées à l'admission (poids, taille, périmètre brachial). Les mensurations préalables étaient recherchées dans les carnets de santé ou les dossiers médicaux des enfants, afin de construire les courbes de croissance. (Références françaises).

La dénutrition à l'admission était définie sur la base des valeurs de z-score d'IMC (<-2DS dénutrition modérée, <-3DS dénutrition sévère) ; la cassure des courbes de croissance était retenue en cas de diminution du z-score du RPA > 1DS.

2.1.3. Résumé des résultats et discussion

Parmi les 683 séjours analysés, 162 (23,7%) présentaient une forme de dénutrition, statique ou dynamique. Parmi eux, 89 (13,0%) présentaient une dénutrition statique à l'admission, et 81 (11,8%) une cassure des courbes de croissance avant l'admission. Parmi ces 81, seulement 8 avaient un z-score de l'IMC anormal.

L'existence d'une maladie chronique sous-jacente était associée à la dénutrition statique à l'admission et à une cassure des courbes de croissance. Un allongement de la durée de séjour était associé à la cassure des courbes de croissance avant l'admission.

Dans notre étude, la dénutrition statique (13%) est moins fréquente que rapportée dans la littérature, ce qui pourrait s'expliquer par l'absence d'enfants avec cardiopathie dans notre cohorte.

En élargissant la définition de la dénutrition à l'admission à l'association de ses composantes statique et dynamique, la prévalence augmente significativement de 13 à 23,7%. La dénutrition est donc plus fréquente que ne le laisserait penser l'usage simple des indices ponctuels de dénutrition. Par ailleurs, l'association à un moins bon devenir incite à rechercher la cassure des courbes de croissance à l'admission.

Les limites de cette étude tiennent à son caractère monocentrique, et au facteur confondant qu'est la variation du statut hydrique dans ce contexte. Les données antérieures étaient manquantes pour 13% des séjours, mais ces patients ont été analysés dans le groupe non dénutri.

Cette étude évaluait le statut nutritionnel global, sans discrimination quant à la composition corporelle.

2.1.4. article publié

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ORIGINAL ARTICLE

Faltering growth in the critically ill child: prevalence, risk factors, and impaired outcome

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Abstract

Low body mass index (BMI) *z* score is commonly used to define undernutrition, but faltering growth allows for a complementary dynamic assessment of nutritional status. We studied the prevalence of undernutrition and faltering growth at admission in the pediatric intensive care (PICU) setting and their impacts on outcome. All (685) consecutive children (aged 0 to 18 years old) admitted in a single-center PICU over a 1-year period were prospectively enrolled. Nutritional status assessment was based on anthropometric measurements performed at admission and collected from medical files. Undernutrition was considered when *z* score BMI for age was < − 2SD. Faltering growth was considered when the weight for age curve presented a deceleration of > − 1 *z* score in the previous 3 months. Undernutrition was diagnosed in 13% of children enrolled, and faltering growth in 13.7% mostly in children with a normal BMI. Faltering growth was significantly associated with a history of underlying chronic disease, and independently with extended length of PICU stay in a multivariate analysis.

Conclusion: Assessment of nutritional status in critically ill children should include both undernutrition and faltering growth. This study highlights that faltering growth is independently associated with suboptimal outcome in PICU.

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What is Known:
- *Malnutrition, defined according to BMI-for-age z score, is correlated with poor outcome in the critically ill child.*
- *In this setting, nutritional assessment should consist not only of a static assessment based on BMI-for-age z score but also of a dynamic assessment to identify recent faltering growth.*

What is New:
- *Critically ill children frequently present with faltering growth at admission.*
- *Faltering growth is a newly identified independent associated factor of suboptimal outcome in this setting (extended length of stay).*

Keywords Pediatric intensive care unit · Malnutrition · Length of stay · Mechanical ventilation duration · Undernutrition

Abbreviations

BMI	Body mass index
HC	Head circumference
MUAC	Mid upper arm circumference
NutriSIP	French-speaking pediatric intensive care nutrition group
PELOD	Pediatric logistic organ dysfunction score
PICU	Pediatric intensive care unit
PIM2 score	Pediatric Index of Mortality Score 2
SD	Standard deviation
WHO	World Health Organization

Introduction

The cornerstone of an optimal nutritional approach is to evaluate the nutritional status of any patient admitted to a pediatric intensive care unit (PICU), detect malnutrition, define nutritional goals, and adapt nutritional intakes. Undernutrition is common in critically ill children, with data indicating that between 15 and 24% has a poor nutritional status at PICU admission [2, 13, 18, 23, 24]. Undernutrition is known as a cause of morbidity in the critically ill adult, but in critically ill children, only few studies have succeeded to correlate undernutrition at admission to a worsening outcome, defined by an increased length of stay and mortality [4, 15, 22, 24].

A pediatric malnutrition workgroup [20] recently reviewed the literature and proposed an overall approach of malnutrition integrating not only a "static nutritional assessment" based on anthropometric cut-off values but also suggesting a "dynamic nutritional status assessment," distinguishing between illness and non-illness related undernutrition and functional outcome. Indeed, all the previous PICU-based studies have focused on undernourished children, defined by a single assessment of their static nutritional status with cut-off values set by the World Health Organization (WHO). To the best knowledge of the authors, no study to date has performed a dynamic growth assessment and evaluated its correlation with PICU admission profile or outcome. Assessing faltering growth (previously named failure to thrive) is a dynamic approach for assessing growth status and is defined on weight curves as a non-voluntary weight downward crossing of more than two major percentiles. It allows for the detection of poor growth before reaching recommended WHO undernutrition cut-off values [20].

We set out to describe the growth status of children at admission on PICU, focusing not only on undernutrition but also on how faltering growth at admission correlated with patient' profiles and outcomes.

Material and methods

Subjects A single-center prospective study was conducted in our 23 bed-PICU at Lyon University Children Hospital, France. This PICU has a large variety of patients including trauma, infectious disease, hematological disease, surgery, and liver and kidney transplantation, but neither cardiac patients nor preterm infants are admitted to this unit. We included all the patients admitted over 1 year (September 2012–August 2013) in order to prevent a potential seasonal recruitment bias. Patient re-admissions within a month of the previous admission were excluded. Local ethics approval was obtained for the study (EudraCT number 2012-005801-29).

Growth assessment and patient demographics Anthropometric measurements were performed in the first 24 h of admission by the nursing team who had previously been taught measurement techniques as described by Valla et al. [27]. This included measurements of weight, height/length, mid upper arm circumference (MUAC), and head circumference (HC). Triceps skinfold thickness was not performed, as it would be difficult to maintain the level of training to ensure measurement accuracy and reduce between person variability [26]. The methods described by WHO for HC and MUAC measurements were followed. The precise use of scales was monitored (Enterprise 9000 ArjoHuntleigh® beds; SECA757, SECA®; CWB7726, Soehnle®) and nurses were trained to take factors that may influence its accuracy (over hydration or dehydration) into account and to record them. In addition, measurement methods for supine length (skull to heel) for children under 1 m were performed (SECA207, SECA®) and for children > 1 m, ulna length to extrapolate the height as per method described by Gauld et al. was used [7, 8]. This

allowed for calculation of the following nutrition indices: body mass index (BMI), weight for height, weight for age, height for age, MUAC/HC (height extrapolation from ulna length and nutritional indices calculation were automatically made by our computerized flow chart: ICCA-Philips Health Care®).

Our primary outcome was to determine faltering growth (dynamic nutritional assessment) and undernutrition (static nutritional assessment) prevalence at PICU admission. Our secondary outcomes were to analyze the relation of faltering growth and undernutrition with patient outcome. A member (a physician or a dietician) of our PICU nutrition support team was responsible for the interpretation of nutritional indices at PICU admission [19].

Faltering growth was considered on the analysis of weight for age curves in case of non-voluntary weight deceleration greater than 1 z score in the previous 3 months, which is considered similar to the downward crossing of more than two major percentiles described in the literature [14, 20, 21, 29]. Patients' growth was plotted on a growth weight for age curve with all available anthropometric measurements collected from patients' personal and/or hospital medical files (parents brought their child's personal medical files that contained their previous growth parameters performed by local doctors, nurses, schools, etc., which is standard French medical practice). When no weight was available in the previous 3 months, extrapolation of the growth curve based on ancient weights was performed, following the same percentile. Growth curves were then analyzed, using French standards [25] for national comparisons. Admission weight for age was compared to the expected weight for age based on his personal growth curve (or growth curve extrapolation).

Undernutrition was defined according to a "static" approach of nutritional assessment and considered if admission BMI-for-age z score was < -2 SD (severe undernutrition if BMI-for-age z score < -3 SD); French growth charts were used and converted to z scores using the Epinut software (FileMaker Pro Advanced 11, Apple Inc., Cupertino, CA, USA). Every patient's nutritional assessment was reviewed by the nutrition support team who evaluated accuracy of the assessment based on clinical status (i.e., edema, plasters) and whether the assessment accounted for prematurity and used specific growth curves for children with syndromes (when available: e.g., Down syndrome, Duchenne muscular dystrophy) or subjective assessment when required because of anthropometry inaccuracy.

Patient characteristics were collected from medical charts (including age, gender, PIM2 mortality score and organ dysfunction PELOD score, ventilation support, underlying chronic disease, admission profile, and nutrition support) to describe the population and identify risk factors for faltering growth at admission. PICU outcome was assessed on PICU mortality rate, acquired infections (as defined by the Center of Disease Control), length of PICU stay, mechanical ventilation duration, and acquired undernutrition during PICU admission (defined as 5% weight loss during PICU stay).

Statistical analysis

Categorical variables were expressed as numbers (n) and percentages. Quantitative variables were expressed as medians (first–third quartiles). The hypothesis of normal distribution of quantitative variables was tested using the Kolmogorov-Smirnov test and graphically confirmed with histograms. Categorical variables were compared using the chi-square test or Fisher's exact test when the conditions of application of chi-square test were not met. Quantitative variables were compared between groups using Wilcoxon non-parametric test when the hypothesis of normality of distribution was not verified. A logistic regression was conducted in order to identify and quantify risk factors of faltering growth and undernutrition (a univariate analysis was performed, followed by a multivariate analysis including univariate analysis significant variables and potential confounding factors such as age and sex). Linear regression was conducted to identify factors associated with PICU length of stay, invasive ventilation duration, and ventilation duration using simple and multiple linear regression for quantitative variable and ANOVA and ANCOVA for qualitative variables. In both models, age and sex were included in the model as confounding factors as well as significant variables identified in simple linear regression and ANOVA. The statistical tests were bilateral and the level of significance was set to 5% ($p < 0.05$). Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., NC).

Results

Subjects We enrolled 685 patients in the study and completed nutritional assessment and the data analysis on 683 patients. Two patients did not have any kind of nutritional assessment over a weekend and were not included in further analysis (see Fig. 1). The median (Q1–Q3) age was 18.5 (2.7–103.8) months and 41% were girls. The majority were admitted with respiratory failure, followed by neurological diseases. Further characteristics are described in Table 1. The nutrition support team concluded on nutritional status according to the definition described above in 683 patients. In 93 children (13.6%), growth curve assessment was not possible as no previous anthropometric measurements were available (these patients were further analyzed within the "no faltering growth group").

Nutritional status at admission The nutrition support team diagnosed undernutrition or faltering growth in 162 children

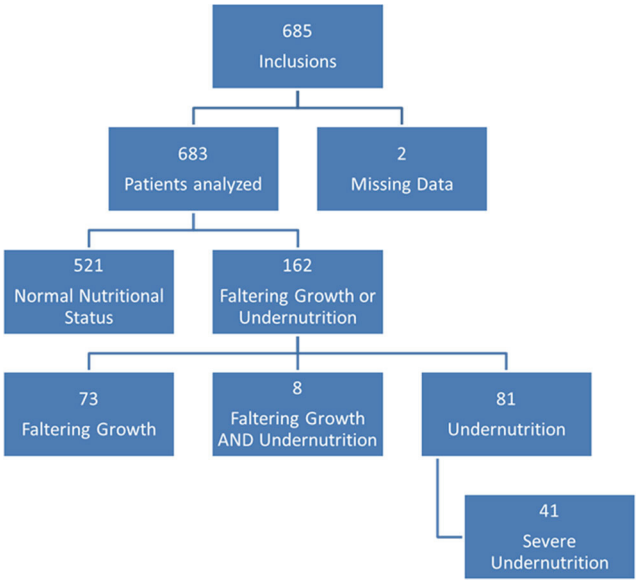

Fig. 1 Patient flow chart (undernutrition is defined as per BMI-for-age *z* score < − 2SD). Static undernutrition and faltering growth (dynamic undernutrition) are two complementary aspects of malnutrition. Each undernourished child may suffer from one of them, or both of them. A child with a BMI for age of + 2SD who loses weight may present with a BMI for age of − 0.5 SD. He would not be considered as presenting with "static undernutrition" according to BMI for age or weight for age, in spite of a 2.5 SD decrease (i.e., faltering growth). A similar decrease of 2.5 SD occurring in a child with an initial BMI for age of 0 SD would then present with a BMI for age of − 2.5. He would be considered as with static undernutrition and faltering growth. Finally, a child with a chronic undernutrition (e.g., BMI for age − 2.5 SD) may follow the − 2.5 SD BMI for age curve and be considered undernourished (static) but without faltering growth. This will depend on the underlying chronic condition and on the nutritional support

(23.7%). Undernutrition was found in 89 children (13.0%). Weight curves showed faltering growth in 81 children (13.7%) and 73 (11.4%) of these 81 children had a normal BMI-for-age *z* score (11.4%) (Table 2 and Fig. 1).

Profile at PICU admission A history of underlying chronic disease was significantly correlated with the risk for being undernourished and/or presenting with faltering growth at admission ($p < 0.0001$) (Table 3). Young age and female gender were also significantly correlated to faltering growth at PICU admission. No association was found with PELOD and PIM2 scores or with surgical versus non-surgical patients in any subgroup.

PICU outcome Our results indicated a significantly ($p = 0.001$) increased PICU length of stay (PICU length of stay increased by 3 supplementary days) in the faltering group only (Table 4). Extended ventilation duration, acquired infections, death, or acquired undernutrition during PICU stay were not significantly different in any group (see Table 5). In a univariate analysis, length of PICU stay and mechanical ventilation duration were both associated to faltering growth, undernutrition/faltering growth, chronic underlying disease, acquired infection, and PIM2 score. In a multivariate analysis, including all these confounding factors, faltering growth was still associated to PICU length of stay ($p = 0.004$) and also independently to age and gender.

Table 1 Population characteristics

Characteristics	*N* = 685 (%)	Median (Q1–Q3)
Age (months)	685	18.8 (2.7–103.8)
Female gender	279 (40.7%)	
Underlying chronic disease[a]	324 (47.3%)	
Pelod score		11 (1–12)
PIM2 score		2 (1–6.2)
Surgical patients	236 (34.5%)	
Invasive ventilation	342 (49.9%)	
Days without ventilation		2 (1–3)
Sedation	289 (42.4%)	
Neuroblocking agents use	60 (8.8%)	
Enteral nutrition	370 (54%)	
Parenteral nutrition	48 (7%)	
Nutrition support (enteral or parenteral)	391 (57.1%)	
Length of stay (days)		4 (2–8)
Length of stay > 5 days	270 (39.4%)	
Acquired undernutrition[b] *n* = 270	97 (35.9%)	
Acquired infection	64 (9.3%)	
Death	32 (5%)	

PELOD pediatric logistic organ dysfunction, *PIM2* Pediatric Index of Mortality 2

[a] Underlying chronic disease consisted of cancer (*N* = 22), hematological disease (*N* = 24 of which 7 with hematological stem cell transplantation), chronic intestinal failure with parenteral nutrition (*N* = 8), cerebral palsy (*N* = 76), neuromuscular disease (*N* = 29), chronic respiratory failure (*N* = 97), tracheostomia (*N* = 54), non-invasive ventilation (*N* = 73), chronic liver or kidney disease requiring transplantation (*N* = 41), heart transplantation (*N* = 4). One patient could present with more than one chronic condition

[b] Analysis on population with length of stay > 5 days

Discussion

This study set out to establish the levels of "static undernutrition" and faltering growth and their association with outcome in critically ill children. We found that a total of 26.7% of children were either undernourished or had faltering growth, with almost equal percentages in each group. Patients with a history of underlying chronic disease were more likely to present faltering growth at PICU admission. Children with

Table 2 Nutritional status profile at admission in PICU

Patient's characteristics	*N* (%)	Median (Q1–Q3)
"Static" undernutrition or faltering growth $n = 683$	162 (23.7%)	
Faltering growth $n = 592$	81 (13.7%)	
« Static » undernutrition $n = 683$	89 (13.0%)	
Weight (kg)	669	10.6 (4.9–24)
Z score weight for age	669	− 0.37 (− 1.39–+ 0.83)
Height (cm)	640	81 (56–125)
Z score height for age	640	0.5 (− 0.79–+ 1.80)
Mid upper arm circumference[a] (cm)	438	13.5 (11.0–16.0)
Z score MUAC[a]	438	0.36 (− 0.62–+ 1.50)
BMI (kg/m^2)[b]	640	15.4 (13.9–17.5)
Z score BMI-for-age[b]	640	− 0.24 (− 1.32–+ 0.88)
Severe undernutrition: *z* score BMI < − 3SD	41 (6.4%)	
Undernutrition: *z* score BMI < − 2SD	89 (13.9%)	
− 2SD < *z* score BMI < + 2SD	493 (77.0%)	
Z score BMI > + 2SD	58 (9.1%)	

« Static undernutrition » is defined as per BMI-for-age *z* score < − 2SD

MUAC mid upper arm circumference, *HC* head circumference, *BMI* body mass index, *UN-FG* undernutrition and/or faltering growth

[a] Analysis on population under 4 years of age

[b] In 45 patients (6.6%), BMI was not calculated due to the absence of weight or height accurate measurements; subjective assessment was performed by the nutrition support team

faltering growth had a higher risk for longer length of PICU stay, which was significant and independent from other covariate.

Nutritional status is not frequently assessed in PICUs. According to a recent international survey conducted by the NutriSIP (French-speaking PICU nutrition group), only 10/34 (29%) PICU performed this routinely [28]. PICU nursing teams face difficulties to accurately weigh and measure bed ridden children who are often unstable and sensitive to weighing maneuvers. However, it has been shown that a teaching program dedicated to the nursing team is feasible and can improve PICU nutritional status assessment. The teaching program initiated in our unit prior to the study [27] allowed for systematic, safe, and accurate anthropometric measurements: 97.7 and 93.4% of the children had respectively weight and height measured at admission, allowing for BMI calculation and malnutrition diagnosis in a vast majority of patients. Computerization and automatization of anthropometric data collection and nutritional indices calculation belonged to routine practice in our unit. This should be envisioned to allow for implementation in clinical practices in other units [6]. Faltering growth assessment is even more rarely performed, as it requires the assessment of children's previous growth data. In our study, the plotting of growth curves was made possible because almost all parents brought their child's personal medical files that contained their previous growth parameters performed by local doctors, nurses, schools, etc., which is standard French medical practice.

We found a relatively low rate of children presenting with "static" undernutrition (13%), defined as BMI-for-age *z* score, compared to the literature (> 20%) [2, 13, 18, 23, 24]. This can be due to the fact that our unit does not admit patients with cardiac disease who have a particular high risk for undernutrition approaching up to 50% [3, 17]. However, this PICU also has a nutrition support team and a nutritional assessment protocol in place, which may have impacted our measurement accuracy and undernutrition rate [1, 19], compared to other studies who based analysis on data collected from registers [24]. The nutrition support team intends to prevent nutritional status deterioration during PICU admission, but unfortunately has limited impact prior to PICU admission.

In our pediatric institution, undernutrition was more frequent (25 to 30%) in the overall pediatric population [6], but no data was available about faltering growth. However, our pediatric high dependency care unit population [12](where children presenting with organ failure but with no need for organ replacement therapy are admitted for continuous monitoring) had a similar prevalence of undernutrition and faltering growth at admission. In our study, we found that 13.7% had faltering growth, matching the number of children with undernutrition. Grimberg et al. [10] found in a general pediatric practice that 9% of children had faltering growth. Our data from PICU therefore indicates a higher level.

This is, to the authors' knowledge, the first study reporting on faltering growth on PICU. There is currently no known data on the prevalence of faltering growth at PICU admission

Table 3 Factors associated with "static" undernutrition and/or Faltering Growth at admission to pediatric intensive care; each group is compared to the well-nourished group

Static undernutrition or faltering growth $N = 683$	Yes $N = 162$	No $N = 521$	OR	95%CI	p
Age in months	20.2 (4.6–83.0)	17.3 (2.3–106.8)	0.999	0.996–1.002	0.54
PELOD score	11.0 (1.0–11.0)	11.0 (1.0–12.0)	0.931	0.780–1.111	0.43
PIM2 score	2.9 (1.0–6.8)	1.9 (1.0–5.7)	1.083	0.972–1.206	0.15
Surgical patients	61 (37.0%)	173 (33.2%)	1.22	0.84–1.75	0.30
Male gender	82 (50.6%)	323 (62.0%)	0.63	0.44–0.90	0.01
Chronic underlying disease	118 (72.8%)	204 (39.2%)	4.17	2.83–6.15	< 0.0001
Static undernutrition $N = 610$	Yes $N = 89$	No N = 521	OR	95%CI	p
Age in months	20.0 (6.6–101.4)	19.5 (2.3–104.4)	1.000	0.997–1.004	0.92
PELOD score	11.0 (1.0–11.0)	11.0 (1.0–11.0)	0.822	0.623–1.085	0.17
PIM2 score	1.5 (0.9–7.1)	2.0 (1.0–5.8)	1.018	0.859–1.208	0.83
Surgical patients	35 (39.3%)	173 (33.2%)	1.56	0.94–2.58	0.08
Male gender	47 (52.8%)	323 (62.0%)	0.63	0.38–1.04	0.07
Chronic underlying disease	66 (74.2%)	204 (39.2%)	5.34	2.98–9.58	< 0.0001
Faltering growth $N = 602$	Yes $N = 81$	No N = 521	OR	95%CI	p
Age in months	11.2 (3.9–37.8)	20.0 (2.6–108.8)	0.995	0.991–0.999	0.02
PELOD score	11.0 (1.0–11.5)	11.0 (1.0–11.0)	0.932	0.735–1.18	0.56
PIM2 score	3.5 (1.1–9.7)	1.9 (1.0–5.8)	1.100	0.962–1.258	0.16
Surgical patients	21 (25.9%)	173 (33.2%)	0.70	0.41–1.20	0.19
Male gender	39 (48.1%)	323 (62.0%)	0.60	0.37–0.96	0.003
Chronic underlying disease	68 (84.0%)	204 (39.2%)	3.48	2.10–5.76	< 0.0001

Malnourished children were compared to well-nourished children (the faltering growth group was compared to the well-nourished group, excluding children with isolated static undernutrition. The static undernutrition group was compared to the well-nourished group, excluding children with isolated faltering growth) Age, Pelod and PIM2 scores are presented in median (Q1–Q3); other variables are presented in numbers (%).« Static undernutrition » is defined as per BMI-for-age z score < − 2SD

PELOD pediatric logistic organ dysfunction, *PIM2* Pediatric Index of Mortality 2, *OR* odd ratio, *CI* confidence interval

Table 4 Outcome of critically ill children with "static" undernutrition and/or faltering growth at admission

Characteristics	"Static" undernutrition or faltering growth		Well-nourished		p[a]
	N	Median (Q1–Q3)	*N*	Median (Q1–Q3)	
Length of stay (in days)					
"Static" undernutrition/faltering growth	162	5 (2–9)	521	4 (2–8)	0.11
"Static" undernutrition	89	4 (2–9)	521	4 (2–8)	0.51
Faltering growth	81	7 (3–12)	521	4 (2–8)	0.001
Mechanical ventilation days (NIV+ IV)					
"Static" undernutrition/faltering growth	162	2 (0–6)	521	2 (0–5)	0.59
"Static" undernutrition	89	1 (0–4)	521	2 (0–5)	0.17
Faltering growth	81	2 (1–8)	521	2 (0–5)	0.12
Invasive mechanical ventilation days					
"Static" undernutrition/faltering growth	162	1 (0–3)	521	1 (0–2)	0.50
"Static" undernutrition	89	0 (0–2)	521	1 (0–2)	0.4
Faltering growth	81	1 (0–3)	521	1 (0–2)	0.41

« Static undernutrition » is defined as per BMI-for-age z score < − 2SD

IV invasive mechanical ventilation, *NIV* non-invasive mechanical ventilation

[a] Wilcoxon non-parametric test

Table 5 Outcome of children with undernutrition and/or faltering growth at admission

Population	Number	Number	OR	95%CI	*p*
Children with undernutrition and/or faltering growth	Acquired infection *N* = 64	No acquired infection *N* = 619			
	13	149	0.80	0.43–1.52	0.50
	Death *N* = 32	No death *N* = 649			
	11	150	1.74	0.82–3.68	0.15
	Acquired undernutrition *N* = 97	No acquired undernutrition *N* = 173			
	23	51	0.74	0.42–1.32	0.31

Undernutrition is defined as per BMI-for-age *z* score < − 2SD

OR odd ratio, *CI* confidence interval

and its negative impact on outcome (i.e., extended length of stay). The finding of this malnutrition dynamic feature impact on outcome is consistent with and complementary to previous studies that linked static malnutrition definition to poor PICU outcome, in terms of length of mechanical ventilation and mortality [4, 11, 24]. On the other hand, numerous studies have linked faltering growth in the non-PICU population to poor outcomes (e.g., cognitive development, school achievement, economic productivity in adulthood) [5, 16]. We also showed a trend toward suboptimal outcome in the static undernourished group which was however non-significant.

It is also remarkable that a large majority of children presenting with faltering growth had a *z* score BMI above the − 2SD cut-off point that usually defines undernutrition. We believe that faltering growth is an aspect of malnutrition that should not be neglected in the PICU setting and that children presenting with faltering growth are a high risk group in the PICU. Non-voluntary loss of weight prior to PICU admission worsen children outcome.

Faltering growth appeared to be significantly correlated to a history of underlying chronic disease, but a lot of children presenting with an underlying chronic disease did not suffer from faltering growth. In developed countries, malnutrition is not a result of limited access to food, but rather due to severity of illness [9, 20]. However, faltering growth negative impact on outcome was independent of underlying chronic disease in our multivariate analysis. In addition, we did not find any correlation between faltering growth and severity and organ dysfunction scores nor with patient profile (diagnosis on admission, surgery versus non-surgery).

Limitations Although the staff performing measurements in this study were fully trained, anthropometric measurements remain challenging and measurement bias due to errors cannot be excluded. The source of weight/length data from prior records used for faltering growth definition may have introduced variability due to operator and device measurement errors in different settings. The use of French growth charts to establish growth faltering does not allow for strict comparison to growth data from other countries. Future studies should use the WHO growth charts. Our study population may differ from other PICU as no cardiac patients were admitted; in units where children with congenital heart diseases are admitted worse undernutrition may be expected. Integrating types of underlying chronic condition would help to better describe the phenomenon, but the diversity of patient who were recruited did not allow us to perform such an analysis. More detailed data analysis regarding nutritional status prior to PICU admission would have strengthened our results (e.g., nutritional support and interventions, precise cause of undernutrition, detailed history of chronic underlying chronic disease). Such data should be prospectively collected in future studies. The power of our study design did not allow us to show an association with acquired infections or mortality, which rates are too low in the PICU setting; a larger cohort would be needed to explore the impact of faltering growth and static undernutrition on these specific outcomes. It remains difficult to determine if the severe disease that is responsible for PICU admission acts as a mediator or a confounder in between malnutrition and outcomes. Finally, fluid shifts may have impacted weight measurements, but results from other nutritional methods assessing body composition would also have been impacted.

To conclude, undernutrition and faltering growth are more commonly seen in children suffering from an underlying chronic disease. We have identified faltering growth being independently associated with suboptimal outcome. Nutritional status has to be assessed systematically at admission, using both static nutritional indices and dynamic assessment, to define malnutrition and adapt nutritional support. Further studies are needed to better assess if different regimens can succeed to enhance malnourished children's outcome.

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Authors' contributions FV Valla, B Gaillard-Le-Roux, F Cour-Andlauer, S Rooze, and T Ginhoux contributed to conception of the study. FV Valla and C Ford-Chessel contributed to the data collection. FV Valla, J Berthiller, E Javouhey, and R Meyer contributed to the analysis of the results. FV Valla and R Meyer drafted the manuscript. R Meyer revised the English version of the manuscript. All authors critically revised the manuscript, gave final approval, and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in our study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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2.2. Article n°2

Fréquente dégradation du statut nutritionnel en cours de séjour en réanimation pédiatrique

“Nutritional status deterioration occurs frequently during children’s ICU stay”

2.2. Article n°2

Fréquente dégradation du statut nutritionnel en cours de séjour en réanimation pédiatrique

"Nutritional status deterioration occurs frequently during children's ICU stay" (104)

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2.2.1. Introduction

L'objectif de cette étude était de décrire l'évolution du statut nutritionnel global des enfants admis en réanimation, de l'admission à la sortie de réanimation, et de suivre au décours de la sortie de réanimation ceux ayant développé une dénutrition en cours de séjour. Par ailleurs, nous avons recherché si des caractéristiques d'admission ou de séjour étaient associées à l'incidence de la dénutrition acquise en cours de séjour.

2.2.2. Matériel et méthode

Etude prospective observationnelle monocentrique (conduite dans une unité de réanimation pédiatrique non cardiologique, non néonatale, sur 26 mois entre 2013 et 2015).

Ont été inclus les enfants de plus de 36SA d'âge corrigé, de 0 à 18 ans, et dont les séjours étaient supérieurs à 5 jours (temps minimal considéré nécessaire pour développer une dénutrition).

Des mesures anthropométriques étaient réalisées à l'admission (poids et taille) et régulièrement au cours du séjour (poids quotidien, taille tous les 6 jours). La définition de la dénutrition acquise en cours de séjour s'appuyait sur l'évolution des indices nutritionnels (références OMS) suivants : z-scores de l'IMC (et z-score du RPA chez les moins de deux ans), ainsi que sur le pourcentage de perte de poids.

Les enfants recrutés sur la première année de l'étude et ayant présenté une dénutrition en cours de séjour en réanimation étaient suivis à 1, 2 et 3 mois pour une réévaluation nutritionnelle.

2.2.3. Résumé des résultats et discussion

579 séjours de plus de 5 jours sur 1732 séjours totaux (33,4%) ont été analysés.

15% des enfants admis présentaient une dénutrition à l'admission.

En cours de séjour, 10,2% des enfants se sont dénutris (baisse du z-score de l'IMC > 1DS), alors que 27,8% étaient à risque de dénutrition (baisse du z-score de l'IMC >0,5DS).

La gravité à l'admission (score de mortalité PIM2) et la durée de séjour étaient indépendamment associées à la dénutrition acquise en cours de séjour. Dans le sous-groupe des moins de deux ans, la dénutrition à l'admission était inversement associée à la dénutrition acquise.

Au décours du séjour en réanimation, seulement 3 enfants dénutris sur les 70 suivis n'avaient pas normalisé leur statut nutritionnel à 3 mois.

La dénutrition acquise est donc fréquente et précoce en réanimation pédiatrique, et associée à la gravité de l'affection sous-jacente et à la durée de séjour.

Il est difficile de déterminer précisément dans quelle mesure la dénutrition acquise en cours de séjour est une cause ou une conséquence de l'allongement de la durée de séjour.

Le pronostic après la sortie de réanimation semble néanmoins favorable.

Les limites de cette étude tiennent à con caractère monocentrique, à l'absence de collecte des données d'apport nutritionnels, et au facteur confondant qu'est la variation du statut hydrique dans ce contexte.

Cette étude évaluait le statut nutritionnel global, sans discrimination quant à la composition corporelle.

2.2.4. article publié

Nutritional Status Deterioration Occurs Frequently During Children's ICU Stay*

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Objectives: Malnutrition and faltering growth at 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: Twenty-three-bed general PICU, Lyon, France.

Patients: All critically ill children 0–18 years old 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 *z* score. Faltering growth was defined as body mass index *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 body mass index *z* score decline greater than 1 SD 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.

Conclusions: 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. (*Pediatr Crit Care Med* 2019; 20:714–721)

Key Words: failure to thrive; faltering growth; malnutrition; pediatric intensive care

Recent recommendations published by a North American 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 are 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 (WAz), body mass index (BMI) for age *z* scores, or weight-for-height/-length *z* scores (WHz).

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 0–18 years old (preterm infants and cardiac patients are admitted in other units and were 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, and onset of parenteral support at day 2–4 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 4–28 d old 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 1 m), 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); that is, *z* scores of BMI for age, WAz, height-/length-for-age (HAz), and WHz. Undernutrition was considered if WHO BMI *z* score was below –2 SD.

PICU faltering growth was defined, as per Mehta et al (1) and Bouma et al (13), as a *z* score decline of nutritional variables 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 1 SD and above 1 SD, 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 cutoff 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 variables, that is, gender, age, Pediatric Logistic Organ Dysfunction (PELOD) score, Pediatric Index of Mortality (PIM) 2, chronic medical condition (onset of chronic condition at least 3 mo prior to PICU admission), surgical admission, and admission diagnosis (i.e., trauma, respiratory failure, metabolic/kidney failure, gastrointestinal/liver failure, sepsis, shock, neurologic failure, other). These further included PICU variables, that is, nutritional support type (enteral vs 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 postdischarge 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 (1, 2, and 3 mo after PICU discharge) and asked to report the most recent weight measured by a healthcare professional or by themselves.

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 the 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 the Kruskal-Wallis nonparametric test, and linear variables 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 analysis of variance (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).

RESULTS

Out of the 1,732 admissions recorded during the conduct of the study, 579 (33.4%) admissions that spent longer than 5 days on PICU were analyzed (see patient flowchart in **Fig. 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 mo) and weight 9.0 kg (4.1–23.0 kg); 60% were males. Patients' nutritional status data are presented in **Table 2**, **Figure 2**, and **Supplemental Table 1** (Supplemental Digital Content 1, http://links.lww.com/PCC/A963). At admission, undernutrition (WHO BMI *z* score < – 2 SD) was diagnosed in 15%. Respiratory failure was the predominant admission diagnosis, followed by neurologic failure (status epilepticus, brain injury, encephalitis, meningitis, and neurosurgery).

The lowest PICU BMI *z* score was encountered at 4.9 days (IQR, 0.0–6.4 d) from admission in the overall population, and 6.0 days (IQR, 4.2–10.4 d) 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 1 SD (faltering growth) and 27.8% presented a decline greater than 0.5 SD (risk of faltering growth). Similarly, in the subgroup of children younger than 2 years, WAz decline was greater than 0.5 SD in 26.8%.

Overall Population Analysis

In the overall population (**Supplemental Table 2**, Supplemental Digital Content 2, http://links.lww.com/PCC/A964), 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 PIM 2) and in children with neurologic failure or sepsis.

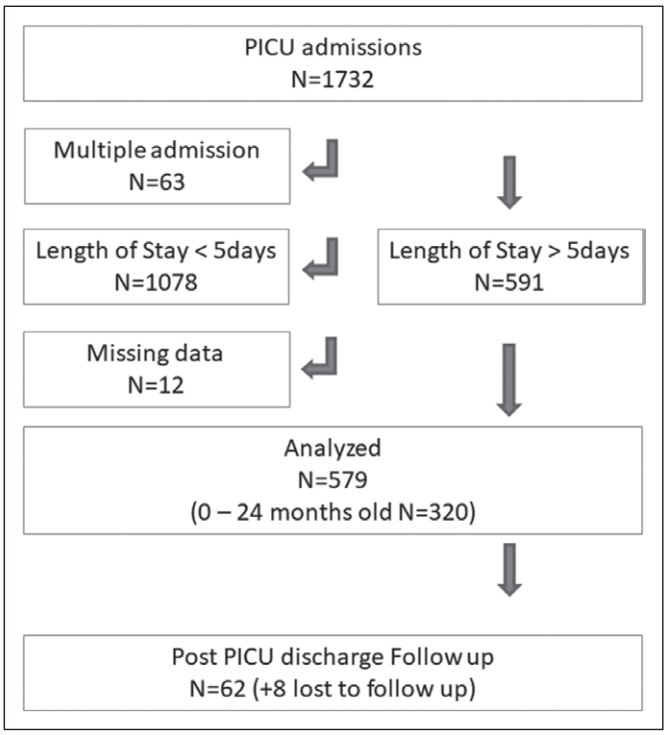

Figure 1. Patient flowchart. PICU admissions were recorded between September 2013 and December 2015. Post-PICU discharge follow-up was conducted in patients admitted in the first year of the study only.

These children presented with significantly longer ventilation duration and length of stay and more frequent acquired infections. In the multivariable linear regression model, PIM 2 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 Table 3**, Supplemental Digital Content 3, http://links.lww.com/PCC/A965), 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 with the overall group, as shown in **Supplemental Table 4** (Supplemental Digital Content 4, http://links.lww.com/PCC/A966). Out of the 62 children followed up, four died prior to hospital discharge without BMI recovery. BMI caught up with PICU admission values prior to PICU discharge in two children and in 31, 17, and three children within 1, 2, and 3 months post PICU discharge, respectively. Only five children (8%) did

TABLE 1. Patients'Characteristics in Overall Cohort (0–18 yr Old) and Young Age Subgroup (0–24 mo Old): Characteristics and Outcomes

Characteristics	*n* = 579	0–18 yr Old	*n* = 320	0–24 mo Old
Admission demographics				
Age (mo)		13.6 (1.9–96.1)		2.1 (0.9–5.6)
Male gender		349 (60.3%)		192 (60.0%)
Admission weight (kg)		9.0 (4.1–23.0)		4.3 (3.5–6.0)
Pediatric Logistic Organ Dysfunction score		11.0 (10.0–13.0)		11.0 (11.0–12.0)
Pediatric Index of Mortality 2 score		4.5 (1.5–8.5)		4.5 (1.4–7.9)
Chronic medical condition		322 (55.6%)		136 (42.5%)
Surgical admission		147 (25.4%)		39 (12.2%)
Bronchiolitis		136 (23.4%)		136 (42.5%)
Admission diagnosis				
Trauma		33 (5.7%)		2 (0.6%)
Respiratory failure		308 (53.2%)		227 (70.9%)
Metabolic/kidney failure		29 (5.0%)		9 (2.8%)
Gastrointestinal/liver failure		68 (11.7%)		28 (8.8%)
Sepsis		31 (5.4%)		13 (4.1%)
Shock		24 (4.1%)		6 (1.9%)
Neurologic failure		72 (12.4%)		35 (10.9%)
Other		12 (2.2%)		0 (0.0%)
PICU stay interventions				
Enteral nutrition support		449 (77.5%)		282 (88.1%)
Parenteral nutrition support		95 (16.4%)		33 (10.3%)
Neuroblocking agent use		120 (20.7%)		63 (19.7%)
Mechanical ventilation support		441 (76.2%)		236 (73.8%)
Invasive ventilation		331 (57.2%)		155 (48.4%)
Noninvasive ventilation		193 (33.3%)		139 (43.4%)
Mechanical ventilation duration (d)		5.0 (1.0–9.0)		5.0 (0.0–10.0)
Invasive ventilation duration (d)		2.0 (2.0–7.0)		0.0 (0.0–6.0)
Noninvasive ventilation duration (d)		0.0 (0.0–4.0)		0.0 (0.0–4.0)
PICU stay outcomes				
Length of stay (d)		9.0 (6.8–14.5)		9.3 (6.8–14.6)
Death		31 (5.4%)		14 (4.4%)
Acquired infection		182 (31.4%)		106 (33.1%)
Respiratory		119 (20.6%)		70 (21.9%)
Urinary		10 (1.7%)		7 (2.2%)
Septicemia		43 (7.4%)		23 (7.2%)
Other		10 (1.7%)		6 (1.9%)

Results are presented as median (interquartile range, 25–75) or *n* (%).

TABLE 2. Patients' Nutritional Status in Overall Cohort and Young Age Subgroup (0–24 mo Old)

Characteristics	*n* = 579	0–18 yr Old	*n* = 320	0–24 mo Old
Admission characteristics				
Admission weight (kg)		9.0 (4.1–23.0)		4.3 (3.5–6.0)
Admission length/height (cm)		75.0 (52.5–125.0)		54.0 (51.0–60.9)
Admission BMI (kg/m^2)		15.4 (13.8–17.7)		14.6 (13.3–15.9)
Admission WHO BMI *z* score (SD)		−0.4 (−1.5 to 0.8)		−0.9 (−1.7 to 0.1)
BMI *z* score < − 2 SD		87 (15%)		62 (19.4%)
−2 SD < BMI *z* score < + 2 SD		447 (77.2%)		249 (77.8%)
BMI *z* score > + 2 SD		45 (7.8%)		9 (2.8%)
Admission WHO WAz (SD)	472	−0.9 (−2.2 to 0.1)		−1.5 (−2.9 to −0.3)
Admission WHO weight-for-height *z* score (SD)	395	0.0 (−1.2 to 1.0)		−0.1 (−1.3 to 0.8)
Admission WHO height-for-age *z* score (SD)		−0.9 (−2.4 to 0.2)		−1.7 (−3.4 to −0.1)
Nutritional status evolution over PICU stay				
Day from admission of lowest PICU BMI *z* score (d)		4.9 (0–6.4)		5.2 (2.0–5.9)
PICU stay lowest weight (kg)		8.8 (4.0–22.2)		4.1 (3.4–5.8)
PICU lowest WHO BMI *z* score (SD)		−0.8 (−1.9 to 0.4)		−1.1 (−2.0 to −0.2)
PICU lowest WHO WAz (SD)	472	−1.2 (−2.6 to −0.2)		−1.8 (−3.2 to −0.6)
Maximum delta of WHO BMI *z* score (SD)		−0.14 (−0.57 to 0.00)		−0.12 (−0.53 to 0.00)
BMI *z* score delta 0 SD		244 (42.1%)		147 (45.9%)
BMI *z* score delta 0; −0.5 SD		174 (30.1%)		89 (27.8%)
BMI *z* score delta −0.5; −1 SD		102 (17.6%)		64 (20.0%)
BMI *z* score delta −1; −1.5 SD		33 (5.7%)		10 (3.1%)
BMI *z* score delta −1.5; −2 SD		16 (2.8%)		9 (2.8%)
BMI *z* score delta < − 2 SD		10 (1.7%)		1 (0.3%)
Maximum delta of WHO WAz (SD)	472	−0.16 (−0.53 to 0.00)		−0.16 (−0.53 to 0.00)
WAz delta 0 SD		198 (34.2%)		145 (45.3%)
WAz delta 0; −0.5 SD		150 (25.9%)		89 (27.8%)
WAz delta −0.5; −1 SD		94 (16.2%)		73 (22.8%)
WAz delta −1; −1.5 SD		17 (2.9%)		9 (2.8%)
WAz delta −1.5; −2 SD		8 (1.4%)		1 (0.3%)
WAz delta < − 2 SD		4 (0.7%)		3 (0.9%)
Day 6 BMI *z* score (SD)		−0.8 (−1.7 to 0.4)		−1.0 (−2.0 to −0.1)
Day 6 WAz (SD)	472	−1.1 (−2.5 to −0.1)		−1.7 (−3.2 to −0.5)

BMI = body mass index for age, WAz = weight-for-age *z* score, WHO = World Health Organization.

Results are presented as median (interquartile range, 25–75) or *n* (%). Lowest nutritional indices values and delta are not based on discharge values but on the difference between admission values and lowest ones encountered during PICU stay.

BMI *z* score and height-for-age *z* score WHO references are available from 0 to 18 yr old; WAz is available from 0 to 10 yr old; and weight-for-height *z* score is available from 0 to 5 yr old.

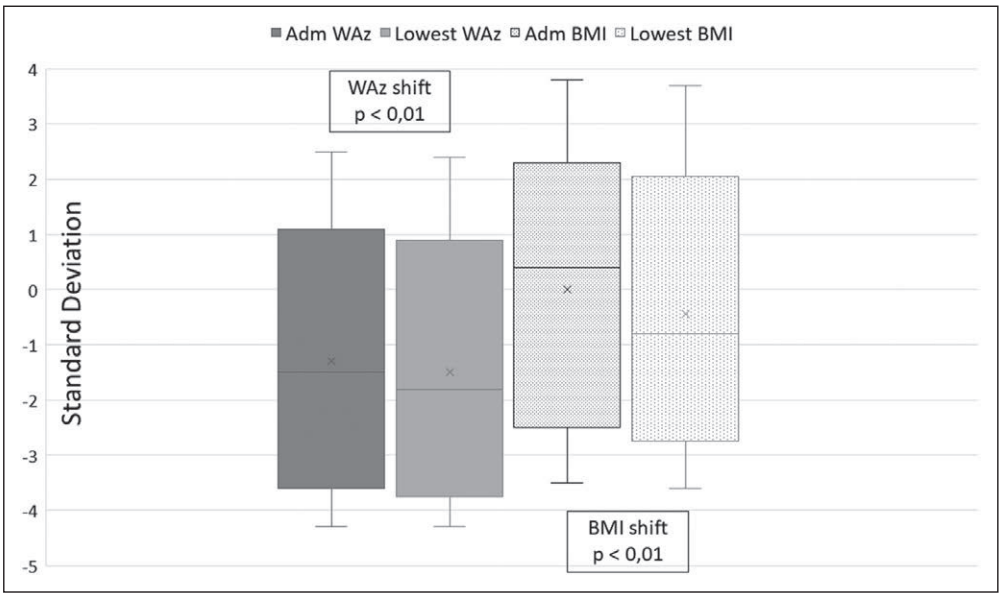

Figure 2. Nutritional status deterioration over PICU stay. Weight-for-age *z* score (WAz) and body mass index (BMI) *z* score decrease significantly during PICU admission in children under 24 mo and in the overall population, respectively. Adm = PICU admission.

not catch up at 3 months. Four of these five 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. Furthermore, 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 to the results of Hulst et al (7), 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.

TABLE 3. Linear Model of Predictors of Body Mass Index *z* Score Delta During PICU Stay

Step	B (95% CI)	SE B	Standardized Coefficient Beta	*p*
1				
Constant	−0.27 (−0.33 to −0.21)	0.03		0.000
Length of stay (d)	−0.01 (−0.01 to −0.00)	0.00	0.11	0.000
2				
Constant	−0.25 (−0.31 to −0.18)	0.03		0.000
Length of stay (d)	−0.01 (−0.1 to −0.00)	0.00	−1.17	0.000
Pediatric Index of Mortality 2 score	−0.003 (−0.006 to 0.000)	0.001	−0.9	0.03

$R^2 = 0.036$ or step 1; delta $R^2 = 0.007$ for step 2 (all $p < 0.001$).

Age, admission weight, acquired infection, neuroblocking agent use, and invasive ventilation were entered in the model and excluded during the linear regression analysis.

In the regression model, body mass index *z* score delta during PICU stay is significantly correlated (0.00) to length of stay and Pediatric Index of Mortality 2 score, which accounts in 4% in its variability.

TABLE 4. Linear Model of Predictors of Weight-for-Age *z* Score Delta During PICU Stay in Children Under 2 Years Old

Step	B (95% CI)	SE B	Standardized Coefficient Beta	*p*
1				
Constant	−0.39 (−0.45 to −0.32)	0.03		0.000
Admission weight-for-age *z* score	−0.47 (−0.7 to −0.2)	0.01	−0.19	0.001

$R^2 = 0.036$ for step 1 (all $p < 0.001$).

Age, length of stay, and Pediatric Logistic Organ Dysfunction score were entered in the model and excluded during the linear regression analysis.

In the regression model, weight-for-age *z* score (WAz) delta during PICU stay is significantly correlated (0.00) to admission WAz, which accounts in 4% in its variability.

Kelleher et al (9) 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 d); this group did present with faltering growth, as they are normally expected to grow fast in the first month of life. 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 with suboptimal outcomes (2, 6, 17, 26). PICU healthcare 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 that 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, undernourished patients were identified and received optimized nutritional care, compared with 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 the study by Briassoulis et al (27), which has shown a contrasting combination of hypometabolism and overfeeding 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.

Following BMI *z* score or WAz does not allow for differentiating overall faltering growth and fat mass/lean mass loss. Other variables 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 hypometabolism 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 hypometabolism, 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 variables 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 3 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 with 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 does 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. Second, 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 subgroups based on admission diagnosis.

CONCLUSIONS

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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Supplemental Table 1: Additional nutritional data in overall cohort and young age subgroup (0-24 months old).

Characteristics	N= 579	0 – 18 years old	N= 320	0 – 24 months old
Admission characteristics				
Admission WHO WHz (SD)	395	0.0 (-1.2 ; +1.0)		-0.1 (-1.3 ; +0.8)
Admission WHO HAz (SD)		-0.9 (-2.4 ; +0.2)		-1.7 (-3.4 ; -0.1)
Nutritional status evolution over PICU stay				
PICU Lowest WHO WHz (SD)	395	-0.3 (-1.5 ; +0.7)		-0.4 (-1.5 ; +0.6)
PICU Lowest WHO HAz (SD)		-1.1 (-2.5 ; +0.1)		-1.9 (-3.5 ; -0.3)
Max delta of WHO WHz (SD)	395	-0.11 (-0.49 ; 0.00)		-0.05 (-0.44 ; 0.00)
Max delta of WHO HAz (SD)		-0.01 (-0.11 ; 0.00)		-0.05 (-0.29 ; 0.00)
PICU maximal weight loss (% of admission weight)		1.0 (0.0 ; 4.8)		0.4 (0.0 ; 3.8)
PICU weight loss 0%		253 (43.7%)		152 (47.5%)
PICU weight loss 0-5%		185 (32.0%)		111 (34.7%)
PICU weight loss 5-10%		94 (16.2%)		45 (14.1%)
PICU weight loss >10%		47 (8.1%)		12 (3.8%)

WHO: World Health Organization; SD: Standard deviation; HAz: Height for Age z-score; WHz: Weight for Height z-score; PICU: pediatric Intensive Care Unit; Results are presented as median (IQR 25 ; 75) or number (%). Lowest nutritional indices values and delta are not based on discharge values, but on the difference between admission values and lowest ones encountered during PICU stay.

HAz WHO references are available from 0 to 18 years old; WHz is available from 0 to 5 years old.

HAz decline is predominant in young infants who normally experience rapid growth.

Supplemental Table 2: Association between maximal WHO BMI z-score decrease during PICU stay and patients' characteristics and outcomes.

Characteristics	BMI z-score delta : 0 ; -0.5 SD	BMI z-score delta : -0.5 ; -1 SD	BMI z-score delta : > -1 SD	p[a]	Pearson correlation	
N=579	418	102	59		R (95CI)	p
Admission demographics						
Age (months)	11.5 (1.5 ; 99.9)	7.8 (1.9 ; 60.5)	36.7 (4.0 ; 101.0)	**0.04**		0.7
Male gender	243 (58.1%)	71 (69.6%)	35 (59.3%)	0.1		
Admission Weight (kg)	8.6 (3.9 ; 24.0)	6.9 (4.3 ; 18.0)	16.0 (6.0 ; 27.0)	**0.02**	-0.003 (-0.072 ; 0.063)	0.9
Admission WHO BMI z-score (SD)	-0.42 (-1.55 ; +0.79)	-0.38 (-1.26 ; +0.55)	+0.15 (-1.19 ; +1.23)	0.2	-0.92 (-1.173 ; -0.006)	**0.03**
BMI z-score <-2SD	70 (16.7%)	12 (11.8%)	5 (8.5%)	0.07		
-2SD < BMI z-score <+2 SD	310 (74.2%)	86 (84.3%)	51 (86.4%)			
BMI z-score >+2 SD	38 (9.1%)	4 (3.9%)	3 (5.1%)			
Admission WHO HAz (SD)	-0.96 (-2.34 ; +0.20)	-1.31 (-2.72 ; -0.06)	-0.34 (-1.38 ; +0.69)	**0.03**	-0.56 (-0.135 ; +0.025)	0.14
PELOD score	11.0 (10.0 ; 12.0)	11.0 (10.0 ; 20.0)	13.0 (11.0 ; 22.0)	**0.000**	-0.163 (-0.257 ; -0.069)	**0.000**
PIM2 score	4.7 (1.5 ; 8.1)	4.9 (1.4 ; 7.8)	7.4 (2.8 ; 14.7)	**0.005**	-0.122 (-0.221 ; -0.032)	**0.003**
Chronic medical condition	230 (55.0%)	56 (54.9%)	36 (61.0%)	0.7		
Surgical admission	102 (24.4%)	26 (25.5%)	19 (32.2%)	0.4		

Admission diagnosis				**0.007**		
Trauma	22 (5.3%)	5 (4.9%)	6 (10.3%)			
Respiratory failure	234 (56%)	59 (57.8%)	15 (25.9%)			
Metabolic/Kidney failure	21 (5.0%)	5 (4.9%)	3 (5.2%)			
GI/Liver failure	49 (11.7%)	11 (10.8%)	8 (13.8%)			
Sepsis	20 (4.8%)	3 (2.9%)	8 (13.8%)			
Shock	16 (3.8%)	2 (2.0%)	6 (10.3%)			
Neurologic failure	47 (11.2%)	14 (13.7%)	11 (19.0%)			
Other	9 (2.2%)	3 (2.9%)	1 (1.7%)			
PICU stay interventions						
Enteral nutrition support	317 (75.8%)	84 (82.4%)	48 (81.4%)	0.3		
Parenteral nutrition support	61 (14.6%)	19 (18.6%)	15(25.4%)	0.09		
Neuromuscular-blocking agent use	80 (19.1%)	20 (19.6%)	20 (33.9%)	**0.03**		
Mechanical ventilation use	310 (74.2%)	78 (76.5%)	53 (89.8%)	**0.03**		
Invasive ventilation use	227 (54.3%)	58 (56.9%)	46 (78.0%)	**0.003**		
Non-invasive ventilation use	135 (32.3%)	38 (37.3%)	20 (33.9%)	0.6		
Mechanical ventilation duration (days)	5.0 (0.0 ; 9.0)	6.0 (1.0 ; 12.0)	6.0 (3.0 ; 11.0)	0.06	-0.106 (-0.196 ; -0.025)	**0.01**

Invasive ventilation duration (days)	1.0 (0.0 ; 6.0)	2.0 (0.0 ; 7.0)	5.0 (1.0 ; 9.0)	**0.005**	-0.112 (-0.204 ; -0.033)	**0.007**
Non-invasive ventilation duration (days)	0.0 (0.0 ; 4.0)	0.0 (0.0 ; 4.0)	0.0 (0.0 ; 2.0)	0.6	-0.018 (-0.087 ; 0.044)	0.7
PICU stay outcomes						
Delay from admission of lowest BMI z-zcore (days)	4.0 (0.0 ; 5.6)	6.0 (4.6 ; 9.4)	8.2 (3.7 ; 15.3)	0.9	-0.002 (-0.431 ; 0.064)	0.9
Acquired infection	117 (28.0%)	41 (40.2%)	24 (40.7%)	**0.02**		
Respiratory	79 (18.9%)	24 (23.5%)	16 (27.1%)	0.1		
Urinary	6 (1.4%)	4 (3.9%)	0 (0.0%)			
Septicemia	26 (6.2%)	10 (9.8%)	7 (11.9%)			
Other	6 (1.4%)	3 (2.9%)	1 (1.7%)			
Length of stay (days)	8.6 (6.4 ; 13.5)	10.1 (7.0 ; 16.9)	12.0 (8.1 ; 22.7)	**0.000**	-0.189 (-0.283 ; -0.098)	**0.000**
Death	23 (5.5%)	4 (3.9%)	4 (6.8%)	0.7		

BMI: Body Mass Index for age; WHO: World Health Organization; SD: Standard deviation; WAz: Weight for Age z-score; HAz: Height for Age z-score; WHz: Weight for Height z-score; PICU: pediatric Intensive Care Unit; PELOD score: pediatric organ dysfunction score; PIM2 score: Paediatric Index of Mortality 2 score; GI: gastro-intestinal; CI: confidence interval

a: Chi2 test or Kruskal Wallis test when appropriate

Supplemental Table 3: Association between maximal WHO weight for age z-score decrease during PICU stay and patients' characteristics and outcomes: children under 2 years of age only.

Characteristics	WAz delta : 0 ; -0.5 SD	WAz delta : -0.5 ; -1 SD	WAz delta : > -1 SD	p[a]	Pearson correlation	
N=320	N=234	N=73	N=13		R (95CI)	p
Admission demographics						
Age (months)	2.1 (0.9 ; 5.3)	2.1 (1.0 ; 5.6)	2.7 (1.7 ; 7.4)	0.8	-0.056 (-0.160 ; 0.038)	0.3
Male gender	138 (59.0%)	45 (61.6%)	9 (69.2%)	0.7		
Admission Weight (kg)	4.1 (3.4 ; 6.0)	4.5 (3.7 ; 5.8)	5.0 (4.3 ; 7.6)	**0.03**	-0.179 (-0.281 ; -0.050)	**0.001**
Admission WHO BMI z-score (SD)	-0.97 (-1.79 ; +0.01)	-0.64 (-1.46 ; +0.10)	0.7 (-0.09 ; +1.50)	**0.004**	-0.226 (-0.321 ; -0.114)	**0.000**
BMI z-score <-2SD	49 (20.9%)	11 (15.1%)	2 (15.4%)	0.7		
-2SD < BMI z-score <+2 SD	179 (76.5%)	59 (80.8%)	11 (84.6%)			
BMI z-score >+2 SD	6 (2.6%)	3 (4.1%)	0 (0.0%)			
Admission WHO WAz (SD)	-1.71 (-3.18 ; -0.47)	-1.22 (-2.13 ; -0.06)	0.68 (-1.95 ; +1.32)	**0.01**	-0.189 (-0.281 ; -0.067)	**0.001**
Admission WHO HAz (SD)	-1.73 (-3.48 ; -0.16)	-1.18 (-2.50 ; -0.15)	-0.35 (-2.74 ; +0.21)	0.08	-0.088 (-0.170 ; +0.012)	0.084
PELOD score	11.0 (11.0 ; 12.0)	11.0 (10.0 ; 13.0)	14.0 (11.0 ; 21.0)	**0.04**	-0.100 (-0.189 ; 0.005)	0.07
PIM2 score	4.7 (1.5 ; 7.9)	3.1 (1.1 ; 6.8)	6.7 (1.7 ; 12.4)	0.1	-0.001 (-0.098 ; 0.081)	0.9

Chronic medical condition	103 (44.0%)	27 (37.0%)	6 (46.2%)	0.5		
Surgical admission	27 (11.5%)	12 (16.4%)	0 (0.0%)	0.2		
Bronchiolitis	102 (43.6%)	32 (43.8%)	2 (15.4%)	0.1		
Admission diagnosis				0.2		
Trauma	1 (0.4%)	1 (1.4%)	0 (0.0%)			
Respiratory failure	171 (73.1%)	52 (71.2%)	4 (30.8%)			
Metabolic/Kidney failure	6 (2.6%)	2 (2.7%)	1 (7.7%)			
GI/Liver failure	21 (9.0%)	5 (6.8%)	2 (15.4%)			
Sepsis	7 (3.0%)	4 (5.5%)	2 (15.4%)			
Shock	4 (1.7%)	1 (1.4%)	1 (7.7%)			
Neurologic failure	24 (10.3%)	8 (11.0%)	3 (23.1%)			
Other	0	0	0			
PICU stay interventions						
Enteral nutrition support	209 (89.3%)	60 (82.2%)	13 (100.0%)	0.1		
Parenteral nutrition support	22 (9.4%)	10 (13.7%)	1 (7.7%)	0.5		
Neuromuscular-blocking agent use	43 (18.4%)	17 (23.3%)	3 (23.1%)	0.6		
Mechanical ventilation use	171 (73.1%)	55 (75.3%)	10 (76.9%)	0.9		
Invasive ventilation	106 (45.3%)	40 (54.8%)	9 (69.2%)	0.1		

Non-invasive ventilation	101 (73.1%)	55 (75.3%)	10 (76.9%)	0.9		
Mechanical ventilation duration (days)	5.0 (0.0 ; 9.0)	5.0 (1.0 ; 11.0)	6.0 (4.0 ; 10.0)	0.8	-0.011 (-0.141 ; 0.088)	0.8
Invasive ventilation duration (days)	0.0 (0.0 ; 6.0)	2.0 (0.0 ; 6.0)	5.0 (0.0 ; 6.0)	0.2	-0.46 (-0.188 ; 0.054)	0.4
Non-invasive ventilation duration (days)	0.0 (0.0 ; 5.0)	0.0 (0.0 ; 5.0)	0.0 (0.0 ; 4.0)	0.9	0.037 (-0.049 ; 0.103)	0.5
PICU stay outcomes						
Delay from admission of lowest BMI z-score (days)	4.9 (0.0 ; 5.7)	5.4 (5.1 ; 7.5)	8.5 (6.0 ; 18.0)		-0.595 (-0.795 ; -0.403)	**0.000**
Acquired infection	73 (31.2%)	29 (39.7%)	4 (30.8%)	0.4		
Respiratory	48 (20.5%)	18 (24.7%)	4 (30.8%)	0.8		
Urinary	4 (1.7%)	3 (4.1%)	0 (0.0%)			
Septicemia	17 (7.3%)	6 (8.2%)	0 (0.0%)			
Other	4 (1.7%)	2 (2.7%)	0 (0.0%)			
Length of stay (days)	9.0 (6.7 ; 13.9)	9.0 (6.9 ; 14.7)	16.6 (10.8 ; 23.6)	**0.04**	-0.038 (-0.173 ; 0.064)	0.5
Death	12 (5.1%)	2 (2.7%)	0 (0.0%)	0.5		

BMI: Body Mass Index for age; WHO: World Health Organization; SD: Standard deviation; WAz: Weight for Age z-score; HAz: Height for Age z-zcore; WHz: Weight for Height z-score; PICU: pediatric Intensive Care Unit; PELOD score: pediatric organ dysfunction score; PIM2 score: Paediatric Index of Mortality 2 score; GI: gastro-intestinal; CI: confidence interval

a: Chi2 test or Kruskal Wallis test when appropriate

Supplemental digital content 4: Post PICU discharge follow up : comparison of patients' characteristics between the follow up cohort (first year of the study) and the overall cohort presenting with a BMI z-score decrease greater than -0.5 standard deviation (SD) during PICU stay.

	Follow up cohort N=62	Overall cohort with PICU BMI z-score decline greater than -0.5 SD N=161	p
Age (months)	10.0 (1.9 ; 57.7)	16.4 (2.3 ; 77.8)	0,09
Male gender	37 (60.0%)	106 (65.0%)	0.39
Admission Weight (kg)	7.9 (3.8 ; 18)	10.8 (4.5 ; 20.4)	0,21
Admission WHO BMI z-score (SD)	0.0 (-1.2 ; 0.9)	-0.3 (-1.2 ; 0.6)	0,45
PELOD score	11 (10 ; 20)	11 (10 ; 21)	0,81
PIM2 score	3.8 (1.3 ; 8.9)	5.1 (1.6 ; 10.2)	0,12
Chronic medical condition	40 (65.5%)	92 (57.1%)	0.32
Enteral nutrition support	56 (90.3%)	132 (82%)	0.13
Parenteral nutrition support	9 (14.5%)	34 (21%)	0.27
Neuromuscular-blocking agent use	12 (19.4%)	40 (24%)	0.38
Mechanical ventilation duration (days)	6.2 (2.0 ; 10.0)	5.0 (1.0 ; 10.7)	0.13
Acquired infection	17 (27.4%)	65 (40.4%)	0.68
Length of stay (days)	10.0 (8.1 ; 18.2)	10.2 (6.9 ; 17.5)	0.84
Age < 24 months	40 (64.5%)	86 (53.4%)	0.13

Results are presented as median (IQR 25 ; 75) or number (%)

2.3. Article n°3

Une diminution de l'épaisseur du quadriceps femoris est fréquemment observée par ultrasonographie en cours de séjour en réanimation pédiatrique

"Thigh ultrasound monitoring identifies decreases in quadriceps femoris thickness as a frequent observation in critically ill children"

2.3. Article n°3

Une diminution de l'épaisseur du quadriceps femoris est fréquemment observée par ultrasonographie en cours de séjour en réanimation pédiatrique

"Thigh ultrasound monitoring identifies decreases in quadriceps femoris thickness as a frequent observation in critically ill children" (105)

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2.3.1. Introduction

L'évaluation globale du statut nutritionnel présente des limites intrinsèques d'interprétation, car elle ne distingue pas la masse grasse de la masse maigre, dont l'importance est pourtant cruciale en contexte de réanimation. L'étude de la composition corporelle en complèterait la compréhension. Les outils habituels permettant de déterminer la composition corporelle ne sont pas applicables à l'enfant sévèrement agressé, si bien que nous avons cherché à valider l'utilisation de l'échographie de l'épaisseur du quadriceps femoris comme outil diagnostique d'évaluation de la masse musculaire ; cet outil permettrait alors de suivre l'évolution de la masse musculaire en cours de séjour en réanimation pédiatrique.

2.3.2. Matériel et méthode

Etude prospective observationnelle bi-centrique internationale (conduite dans deux unités de réanimation pédiatrique non cardiologiques, non néonatales, sur 6 mois entre 2015 et 2016).

Ont été inclus des enfants de plus de 36SA d'âge corrigé, de 0 à 15 ans.

Une technique de mesure de l'épaisseur du quadriceps femoris a été développée sur la base de l'expérience adulte ; la moyenne de 4 mesures (2 transverses et 2 longitudinales) était calculée pour limiter les erreurs de mesure.

L'évaluation de la reproductibilité intra- et inter-opérateur a été étudiée.

Cette technique a ensuite été utilisée pour suivre l'évolution de l'épaisseur du quadriceps femoris en cours de séjour chez des enfants sévèrement malades, sous sédation et ventilés.

2.3.3. Résumé des résultats et discussion

Dans une population de 73 enfants inclus, les reproductibilités intra-opérateur (n=37) et inter-opérateur (n=36) de la technique étaient satisfaisantes, assurant une fiabilité des mesures permettant de détecter des variations de l'épaisseur musculaire de plus de 5%.

Le suivi ultérieur d'une cohorte de 17 enfants a montré une diminution rapide, conséquente et fréquente de l'épaisseur du quadriceps femoris. Cinq jours après l'admission, cette diminution était de −9.8% (−13.3 à +0.0) p<0,01, et elle était maximale à −13.3% (−23.6 à −8.9) p<0,01.

Cette étude a donc permis de valider une technique de monitorage de la masse musculaire en réanimation pédiatrique et confirmé les données adultes de fonte musculaire chez le patient sévèrement agressé.

La puissance de cette étude n'a pas permis d'identifier des facteurs de risque de fonte musculaire, ni dans le profil patient à l'admission, ni sur les données-patient d'évolution en cours de séjour ou à distance.

Le lien avec la faiblesse acquise en réanimation pédiatrique reste à démontrer.

Les limites de cette étude tiennent à la puissance de l'effectif de la cohorte suivie ; par ailleurs, une fois encore, le statut hydrique (œdème musculaire ?) très difficile à caractériser, a pu influencer les mesures et l'interprétation des résultats.

2.3.4. article publié

Thigh Ultrasound Monitoring Identifies Decreases in Quadriceps Femoris Thickness as a Frequent Observation in Critically Ill Children

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Drs. Valla, Portefaix, Meyer, Javouhey, and Pathan designed the study, collected and participated to interpretation of data. Drs. Young, Periasami, John, Baudin, White, and Ridout helped to collect data. Rabilloud analyzed and interpreted the data. Drs. Vuillerot and Gaillard Le Roux participated to literature search and data interpretation. All authors were involved in writing the article and had final approval of the submitted and published versions.

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Objectives: Significant muscle wasting develops in critically ill adults, with subsequent worse outcomes. In the pediatric setting, occurrence and effects of muscle wasting are undescribed; this is in part due to a lack of validated, objective methods for assessing muscle wasting. A single measurement of quadriceps femoris thickness has failed to show consistent reproducibility. We hypothesized that averaging repeated measurements could afford good reproducibility to allow for quadriceps femoris thickness decline detection and monitoring.

Design: A prospective bedside observational study.

Setting: Two PICUs.

Patients: Mechanically ventilated critically ill children were 15 years and younger.

Interventions: Transverse and longitudinal axis measurements of quadriceps femoris anterior thickness were undertaken using bedside ultrasound. The average of four measurement values was recorded. The location of measurement was marked for consistency within subsequent measurements by the same or another trained operator, to assess intra- and interoperator repeatability and reproducibility of the technique. Where feasible, serial measurements were undertaken until the time of extubation in a group of children with prolonged PICU stay (> 5 d).

Measurements and Main Results: Seventy-three children were enrolled to assess intra- and interoperator ultrasound reliability. Their median (25–75 interquartile range) age and weight were 30 months (4.5–96) and 10 kg (5–23.5). In the intraoperator repeatability study, mean relative difference in quadriceps femoris muscle thickness was 0.36% ± 2.5% (lower and upper limits of agreement: −4.5/+5.2%). In the interoperator reproducibility study, intraclass correlation coefficient was 0.998. In the 17 children monitored over their PICU stay, quadriceps femoris thick-

ness significantly decreased at day 5 by 9.8% ($p = 0.006$) and by 13.3% (< 0.001) at the last performed measurement.

Conclusions: Quadriceps femoris thickness decrease, proposed as a surrogate for muscle mass, is an early, frequent, and intense phenomenon in PICU. Quadriceps femoris ultrasonography is a reliable technique to monitor this process and in future could help to guide rehabilitation and nutrition interventions. (*Pediatr Crit Care Med* 2017; XX:00–00)

Key Words: body composition; muscle wasting; rectus femoris; reproducibility of results; vastus intermedius

In critically ill patients, ICU-acquired weakness (ICU-AW) corresponds to an acquired neuromuscular disease that is potentially reversible. The pathophysiology of ICU-AW is multifactorial. It involves peripheral nerves alteration (neuropathy) that can lead to muscle wasting. It also involves myopathic features, characterized by muscle alteration and muscle wasting (1, 2). First, muscle organ failure (resulting from hypoxia, compromised perfusion, and direct muscle injury) will induce the so-called "acute muscle wasting." This leads to muscle turnover metabolism alteration (including increased catabolism and decreased anabolism) and resultant increased muscle breakdown. In addition, disuse atrophy occurs in the comatose bedridden patient, under sedation or neuro-blocking agents. Furthermore, undernutrition is a constant challenge in the care of critical illness. This may be due to fluid restriction, intolerance to enteral feeding, and elective suspension of enteral feeds prior to specific procedures or extubation. These are likely to increase muscle wasting from fasting. Finally, in patients who remain ill for extended periods, chronic cachexia also contributes to muscle wasting, as seen in noncritical chronic inflammatory diseases and patients with malignancies (1, 3, 4).

In the adult setting, ICU-AW has been documented as a frequent, rapid, and early phenomenon, especially in multiple organ failures (1). It prolongs ICU and hospital stay, as well as post-ICU rehabilitation, resulting in increased healthcare costs (5, 6).

In contrast, PICU-AW is not well studied. The medium- to long-term effects of muscle wasting in children are almost completely undescribed (7–11). This is in part due to a lack of validated, objective methods for screening and assessing muscle wasting in children admitted to PICU (12).

Defining and validating accurate tools to assess PICU-muscle wasting are therefore essential to enable an accurate description of its occurrence rate in the clinical setting. Furthermore, this will aid understanding of the underlying biological processes and functional implications, while also helping to develop future therapeutic approaches to prevent and minimize PICU-muscle wasting (with the inclusion of feeding regimens, pharmaconutrition, early rehabilitation, etc). Classic methods for the assessment of muscle mass changes are neither accurate nor validated in the critically ill child (13). First, bioimpedance analysis of body composition is impacted by major fluid shifts and is not validated in critically ill infants and young children. In addition, other methods such as dual energy x-ray absorptiometry or CT imaging are challenging to perform in an unstable child because of the requirement for specific equipment (13). MRI, considered the gold standard for the assessment of body composition, is also technically difficult to perform in the PICU setting and is not practical for use as a daily bedside muscle mass assessment tool (13).

We aimed in this study to assess PICU muscle wasting over PICU stay, based on quadriceps femoris (QF) muscle thickness repeated measurements, as a surrogate for changes in muscle mass. Muscle mass assessment using anterior thigh ultrasonography has been shown to be reliable in adults, but single measurements of QF muscle thickness have thus far failed to be reproducible in children (12). We hypothesized that by designing a detailed measurement protocol using anterior thigh ultrasonography, coupled with the use of multiple measurements of QF muscle thickness across different axes, we could improve the accuracy and reproducibility of the technique. Thus allowing for the accurate assessment and serial monitoring of PICU muscle wasting over the course of critical illness.

MATERIAL AND METHODS

We conducted a prospective observational study across two PICUs (Lyon, France and Cambridge, United Kingdom) between November 2015 and April 2016. Intra- and interoperator repeatability and reproducibility of QF muscle thickness measurement using anterior thigh ultrasonography were assessed. Within each aspect of the study (intra- and interoperator repeatability and reproducibility), we intended to enroll 35 PICU children between 0 and 15 years old, with the aim of reliably detecting a 5% change in QF thickness. A sample size of 35 critically ill children was calculated based on previous literature and expected measurement variability within patients (12, 14). The study was approved by each of the institutional research ethics committees (France ANSM: 2015-A01158-41; United Kingdom: 13/LO/0974).

Measurement of QF Thickness

Ultrasonographic examination was performed using B-mode ultrasonography with either the Vivid S6 (GE Healthcare, Little Chalfont, United Kingdom) or the SonoSite EDGE (Fujifilm sonosite, Bothell, WA) in Lyon and Cambridge. We used a linear transducer which frequency was adapted according to the accumulative thickness of thigh muscle and fat, ranging from 9 to 13 Hz. The measurements were performed strictly perpendicularly to the skin plane to limit oblique scanning-related measurement errors and with an excessive amount of gel (to ensure no direct transducer-skin contact, thus avoiding any inadvertent compression of the thigh by the operator). QF muscle is composed of four heads, two of which (rectus femoris and vastus intermedius muscles) are located anteriorly. QF thickness was defined as the sum of the anterior thickness of these two heads (**Fig. 1**).

Measurements were obtained while recruited children were either sedated or fully cooperative to obtain muscle relaxation, therefore avoiding the confounding effects of muscle contraction on measured QF thickness. To obtain the most accurate QF thickness and maintain consistency for all children, each patient

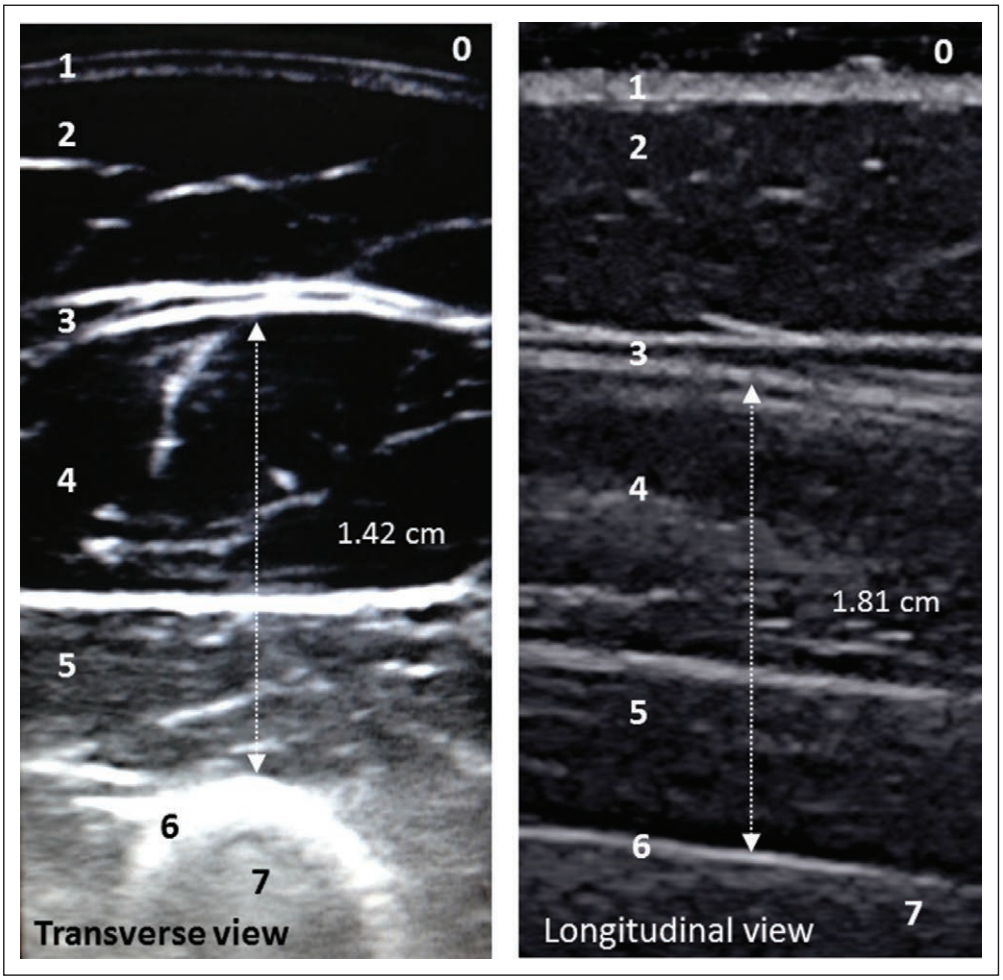

Figure 1. Thigh ultrasonography in transverse and longitudinal views in two different patients (0: layer of gel, no contact between the transducer and the skin is accepted, to confirm the absence of pressure of the transducer on the thigh; 1: skin; 2: fat; 3: quadriceps femoris fascia; 4: rectus femoris head of quadriceps femoris; 5: vastus intermedius head of quadriceps femoris; 6: outer cortex of the femur; 7: femur). On the transverse view, the femur is easily identified as a hyperechogenic semicircle, which has to be in the center of the image; quadriceps femoris thickness is measured vertically from the upper border of femur cortex to the under border of quadriceps femoris fascia. On the longitudinal view, the femur is identified as a roughly horizontal hyperechogenic row; the same measurement technique is followed, the center of the image corresponding to the center of the transducer that has to be located on the adequate marked skin location. The transducer has to be strictly perpendicular to the skin.

was positioned in a supine position and measurements of only one leg were taken. On each occasion, the leg was fully extended and positioned in a neutral rotation while external compression of the muscle was avoided to limit artefactual deformation of the muscle shape (this included removal of positioning aids and pillows). To overcome the progressive increase in thickness of the anterior QF muscle, we used a measuring tape to identify the widest portion of the thigh and recorded the distance of this point from the superior tip of the patella (identified to be the most accessible and consistent landmark in this population). Using an indelible marker, we then marked this point to ensure that all subsequent measurements were taken at exactly the same location.

Operators

Within the intraoperator repeatability study that was conducted in Lyon, France, one single reference operator (F.V.V.) performed all measurement sets twice consecutively for each patient (procedure detailed below); paired results were then compared. The reference operator had previously been trained by a pediatric radiologist, outside of this study.

Prior to the commencement of the interoperator reproducibility study, all operators (D.K.Y., U.P., M.J., F.B., N.P., A.P.) were first trained outside of the study by the reference operator. The additional operator's involvement in the study was deemed suitable once the reference operator had supervised four accurate measurement sessions.

Within the interoperator reproducibility study, conducted in both Lyon and Cambridge, the reference operator performed the first set of measurements, which was immediately followed by a second set of measurements completed by another operator. This procedure was repeated for all patients to ensure that consistency was maintained throughout. In both intra- and interoperator studies, the second set of measurements was done blind to the results of the first set.

Procedure

Each operator performed a set of four measurements of QF muscle anterior thickness. First, a transverse measurement was performed (transducer placed perpendicularly to thigh axis) and then a longitudinal one (transducer placed parallel to thigh axis); both measurements were repeated once. QF thickness was measured vertically on the image, from the outer cortex of the femur to the internal border of the QF fascia, as shown in Figure 1. Measurements of reference and additional operators were compared. Averages of two measurements (obtained in the same angle and in different angles) and of the four measurements were then calculated to account for operator-related error and compared with averages of the measurement set performed by the second operator (following the same protocol).

Further to the inter- and intraoperator repeatability studies, we also designed a QF measurement protocol that would enable

the accurate detection of a 5% change in QF muscle thickness during the course of a patient stay on PICU. We used a prospective observational study of 17 children enrolled between April and May 2016 from one PICU (Cambridge, United Kingdom). These patients were prospectively recruited under the inclusion criteria previously described: children admitted to PICU were 15 years and younger, fully sedated or cooperative. Due to the short longitudinal nature of this observational study, patients were only recruited if it was anticipated that their stay on PICU would be longer than 4 days. QF thickness monitoring was discontinued when children were no longer sufficiently sedated or cooperative for accurate measurement to take place. Patients presenting with a known history of neuromuscular disease were excluded from the study. Wherever possible, QF muscle thickness was measured on a daily basis, following the above-described protocol. Muscle wasting would be considered if QF thickness decreased by more than 5% over PICU stay (which would correspond to the limit of our ultrasound measurement protocol reliability). Our first endpoint aimed to compare admission values, named time point-a (TP-a) and obtained within the first 24 hours after PICU admission, to time point day 5 (TP-b) values (obtained between day 4 and day 5), and to time point-c (TP-c) values that corresponded to the final measurement considered accurate according to our protocol (namely when the patient was fully sedated or cooperative). We also compared indexed values of QF thickness measurement to admission body weight.

Certain characteristics were recorded for all patients, including age, gender, admission weight, height, body mass index (BMI) *z* score (World Health Organization [WHO] reference), and primary diagnosis. Potential risk factors for muscle wasting were also recorded, exploring each feature of muscle wasting physiopathology: disuse atrophy (length of ventilation, mechanical ventilation duration, use of sedation, and neuro-blocking agents), starvation (energy-protein intake deficits [15]), acute muscle wasting (Pediatric Logistic Organ Dysfunction 2 score, highest C reactive protein, length of PICU stay), and cachexia (underlying disease). No standardized physical therapy intervention was conducted for all patients during the study, but rather each patient is assessed and treated individually. The study protocol was approved by the respective U.K. and French Institutional Review Boards, who waived the need for informed consent.

Statistical Analysis

Pearson correlation coefficient was used to identify associated factors to QF thickness. Intraoperator repeatability was assessed using the Bland-Altman method. The bias was quantified as the mean relative difference between two repeated measurements carried out by the same operator. The lower and upper limits of variability were calculated as the values at two SDs below the mean relative difference and at two SDs over the mean relative difference, respectively. The analysis was carried out for each of the four measurements (two longitudinal and two transverse), but also for the mean of two measurements (longitudinal-longitudinal, transverse-transverse, or longitudinal-transverse) and the mean of four measurements. The intraoperator repeatability was quantified by the coefficient of variation with its 95% CI. The interoperator reproducibility of the mean of the four measurements was quantified using the intraclass correlation coefficient. A random-intercept linear model was used to estimate the interpatient variance and the intrapatient variance corresponding to the interoperator variance. The intraclass correlation coefficient was obtained as the ratio of the interpatient variance on the total variance (inter- plus intrapatient). The Bland-Altman method was also used to quantify the reproducibility between the reference operator and each of the six fully trained operators. Muscle wasting longitudinal study: the paired Wilcoxon signed rank test was used to compare TP-a values with TP-b and TP-c values. Pearson correlation coefficient was used to estimate and test the link between the cumulative energy or protein deficit and the QF thickness difference between two times. A linear mixed model with a random effect on intercept and slope was used to quantify the change of QF thickness over time adjusted for age, gender, BMI *z* score, PELOD2 score, and highest CRP value. All data analysis was carried out using the R software, version 3.1.3 (Lucent Technologies, Boulogne-Billancourt, France).

RESULTS

Intra- and Interoperator Repeatability and Reproducibility Studies

In total, 73 patients were enrolled: 37 children were included in the intraoperator repeatability study and 36 other children in the interoperator reproducibility study. The overall median (25–75 interquartile range [IQR]) age and weight were 13 months (3–98 mo) and 9.8 kg (4.6–23.5 kg), respectively, and 30 (41%) were girls (**Table 1**). The main reasons for PICU admission were respiratory failure, sepsis, trauma, and postoperative care. The overall median (25–75 IQR) QF thickness was 1.71 cm (1.40–2.26 cm). QF thickness was positively correlated ($p < 0.001$) with age ($r = 0.69$; CI 95%, 0.55–0.79), weight ($r = 0.80$; CI 95%, 0.70–0.87), and height ($r = 0.77$; CI 95%, 0.66–0.85) (**Fig. 2**). Seven operators participated to the interoperator reproducibility study (five pediatric intensivists and two pediatric physical therapists). The comparison of any single measurement or two measurement sets (longitudinal, transverse, or mixed) failed to be reproducible (the coefficient of variation of the four measurements within a set of four measurements was high in children < 40 kg, as shown in **Fig. 3**, ***A***). Comparison of four measurement sets is detailed below.

Intraoperator Repeatability Study

The mean (± SD) difference and relative difference between the two means of four measurement sets were 0.012 cm (±0.49) and 0.36% (±2.5), respectively, with a lower limit and upper limit estimated at −4.5% and +5.2%, respectively, as shown in Figure 3, ***B***. The coefficient of variation was 2.5% (95% CI, 2.0–3.2).

Interoperator Reproducibility Study

The intraclass correlation coefficient was 0.998 (close to 1). The mean (± SD) difference between the two means of four

TABLE 1. Intra- and Interoperator Reliability Study Population Characteristics

Characteristics	Intraoperator Group ($n = 37$)	Interoperator Group ($n = 36$)	Total ($n = 73$)
Age (mo)	30 (4.5/96)	8.5 (2/101.5)	13 (3/98)
Female (gender), %	18 (49)	12 (33)	30 (41)
Weight (kg)	10 (5/23.5)	9.7 (3.6/23.7)	9.8 (4.6/23.5)
Height (m)	0.85 (0.59/1.26)	0.65 (0.51/1.25)	0.77 (0.56/1.25)
z score body mass index (SD)	−0.5 (−2/+1)	0 (−0.5/+1.5)	0 (−1/+1.5)
Quadriceps femoris thickness: average of four measurements (cm)	1.74 (1.4/2.39)	1.7 (1.36/2.20)	1.71 (1.40/2.26)

Results are presented as medians (25–75 interquartile range) or n (%).

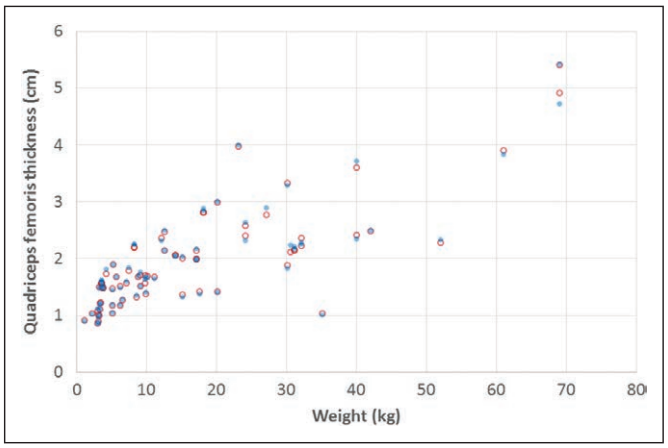

Figure 2. Average quadriceps femoris thickness according to patients' body weight (intra- and interoperator reproducibility study). Red circles and blue dots represent measurements performed by the reference operator and other operators, respectively.

measurement sets performed by the reference operator and the first operator was 0.006 cm (± 0.49). Their mean relative difference was 0.5% (±2.5), with a lower limit and upper limit estimated at –5.4% and +4.5%, respectively. Similar results were found for other operators.

QF Thickness Decrease in Acute Critical Illness

As we had found satisfying intra- and interoperator repeatability and reproducibility, QF thickness decrease was considered accurate and used as a surrogate to muscle wasting. Seventeen children were enrolled from Cambridge PICU in the muscle wasting monitoring study that followed. Their median (25–75 IQR) age and weight were 47 months (5–126 mo) and 20 kg (7.8–29.6 kg), respectively, and two (11.7%) were girls (**Table 2**). Respiratory failure, sepsis, and brain injury were the most common admission diagnoses. The median (25–75 IQR) PICU length of stay of 10 days (7–13.5 d) allowed for a median of five (4–6) measurements per patient. The reference operator performed 84% of the 104 QF measurement sets, and 16% were performed by three different fully trained operators who had previously taken part in the interoperator reproducibility study.

The median (25–75 IQR) QF thickness was 2.25 cm (1.72–2.79 cm) at admission (TP-a). At TP-b, QF thickness measurement showed a significant ($p = 0.008$) decrease of −9.8% (−13.3 to +0.0). At TP-c, QF thickness had shown further significant ($p < 0.001$) decrease by −13.3% (−23.6 to −8.9) as illustrated in **Figure 4**. When considering TP-b and TP-c, respectively, 12 (71%) and 15 (88%) children had more than 5% QF thickness decrease, while seven (41%) and 10 (59%) had more than 10% QF thickness decrease, and three (18%) and six (35%) had more than 20% QF thickness decrease, as shown in **Figure 5**. Additionally, after indexing QF thickness values to admission body weight, we also found a significant decrease between TP-a and TP-b ($p = 0.01$) and between TP-a and TP-c ($p = 0.0005$).

The mean change of QF thickness over time was estimated at −0.05 cm per day (95% CI, −0.07 to −0.03; $p < 0.001$). The mean QF thickness increased significantly with age (0.013 cm per supplementary month; 95% CI, 0.01–0.015; $p < 0.001$) and BMI *z* score (0.02 cm for an increase of 0.1 U of *z* score; 95% CI, 0.01–0.03; $p = 0.004$). It decreased significantly with the highest value of CRP (−0.002 cm for an increase of 1 U of CRP; 95% CI, −0.003 to −0.001; $p = 0.004$). Gender and PELOD2 score were not significantly linked to the mean QF thickness ($p = 0.34$ and 0.91, respectively). No factor was significantly linked to QF thickness change over time. Correlation between cumulative energy or protein deficit and QF thickness decrease was not statistically significant.

DISCUSSION

In a short longitudinal study, monitoring of QF thickness over PICU stay showed an early, statistically significant, and clinically important decrease, concerning the vast majority of children of all admission weight ranges. This was made possible by the development of a reliable QF thickness measurement protocol, which demonstrated both sufficient intra- and interoperator repeatability and reproducibility, using average scores for repeated ultrasound measurements in different axes.

Fivez et al (12) previously failed to design a measurement protocol offering sufficient intraoperator reliability in children on PICU. They were unable to accurately detect a change in QF thickness of less than 30%, which unfortunately is not beneficial in clinical practice. Indeed, early and precise recognition of muscle mass change is mandatory for future epidemiological and treatment studies. Based on our pilot study, in conjunction with adult literature, a technique that allows for accurate detection of a 5% change in muscle mass is recommended (1).

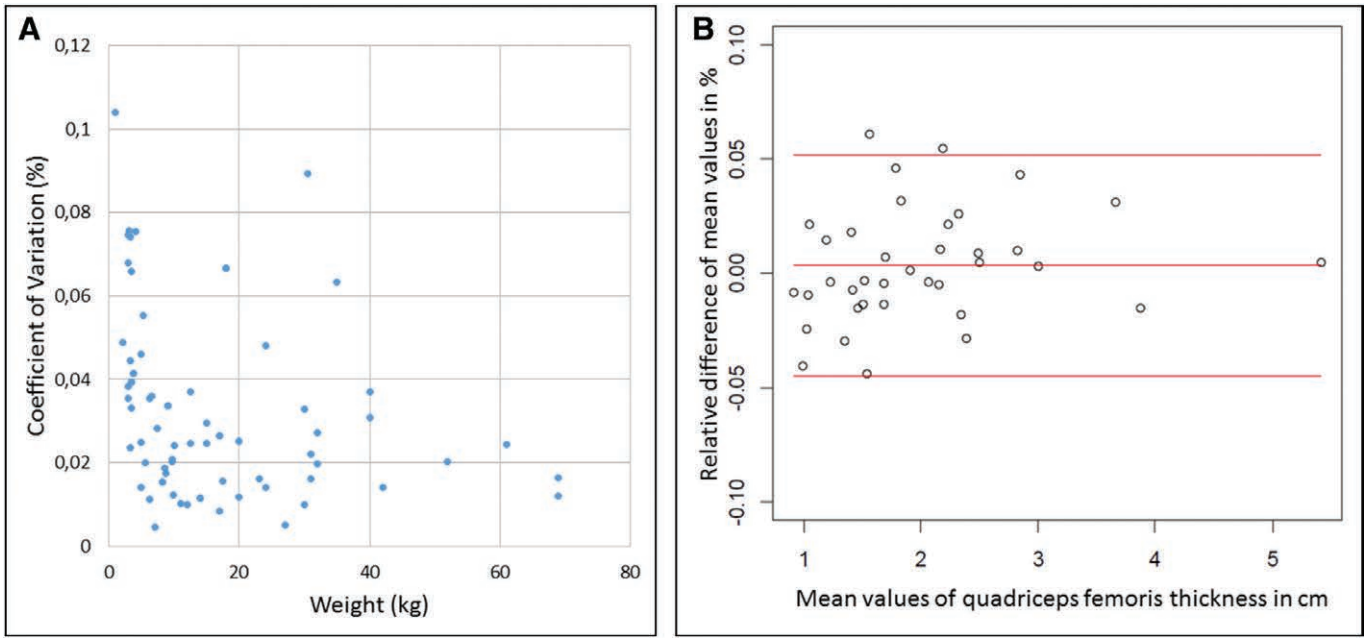

Figure 3. A, Coefficient of variation of quadriceps femoris thickness measurement, within a set of four measurements, according to patient's weight. **B**, Bland-Altman plots: intraoperator repeatability of quadriceps femoris measurement (sets of four measurements).

One explanation for the negative results seen in Fivez et al (12) study may be that eight of 30 patients were sedated but not intubated. Though the authors state that their patients were adequately sedated for the examination, subtle contractions of muscles in sedated but moving patients may transiently increase muscle thickness measurements. Similarly, McLeod et al (14) found a high coefficient of variation while measuring different muscle groups in preterm babies. The operator-related risk of error may be diminished using the average of subsequently repeated measurements, according to a detailed measurement protocol.

The measurement of the area of rectus femoris or vastus intermedius has been proposed as another way to estimate muscle mass. During our pilot training, we faced difficulties in accurately capturing the entire cross-section of these muscles within one single ultrasound image, especially in infants and children with a low level of fat mass. As a result, this technique was not selected for the study.

Ultrasonography is a core skill within the PICU intensivist's daily practice and care. Additionally, the learning curve for both experienced and nonexperienced team members was quite rapid. This is a noninvasive technique, available at the bedside, which requires only a few minutes, in comparison to other muscle mass assessment techniques like CT imaging or MRI. This method may therefore be used in future research and eventually enable muscle mass assessment integration into the systematic recommended nutritional status assessment in PICU.

We did not compare QF thickness ultrasonographic measurement with MRI measurement, which is the gold standard. In fact, MRI is technically difficult to perform in a critically ill child. Our primary outcome was to develop a technique that would allow for the accurate measurement and reliable monitoring of change in muscle thickness rather than examine absolute value measurement of muscle thickness (12). Similarly, anthropometric measurements, including thigh circumference and weight for example, were not compared with ultrasonographic measurements as they may be sensitive to fluid shift and fat mass change within this clinical setting. No healthy control group was recruited as full cooperation of infants and toddlers, which is essential for good reliability of the technique, was not possible. QF was chosen over other muscle groups because of its large thickness and ease of accessibility, allowing for more accurate assessment (14). However, it remains an indirect estimation of the overall muscle mass. In adults, muscle echogenicity shifts over intensive care stay (using gray scale assessment software) have been correlated to muscle wasting and outcomes (16) and have been proposed to assess and monitor muscle quality. It was also correlated to histological necrosis findings (17). No such data are available in the pediatric setting as it remains difficult to obtain parental consent for muscle biopsies. Extrapolation of adult results should be tested and their utility in muscle quality monitoring should also be further investigated.

The degree of muscle mass change over the course of a PICU admission can be easily and reliably estimated using ultrasound measurement of QF thickness. Implementation of this method may allow for the early detection and monitoring of muscle wasting over PICU stay in sedated or cooperative children.

PICU-AW is, however, a type of reversible neuromuscular disease and its assessment should comply with the neuromuscular assessment recommendations. A holistic overview of muscle function in relation to patient activity and participation, as described by the disability creation process model or the WHO International Classification of Functioning (18, 19),

TABLE 2. PICU Muscle Wasting Monitoring Study

Characteristics	*n* = 17
Patient characteristics	
Age (mo)	47 (5/126)
Female (gender)	2 (11.8%)
Weight (kg)	20 (7.8/29.6)
Height (cm)	101 (65/135)
z score body mass index (SD)	0 (−0.75/0.7)
Pediatric Logistic Organ Dysfunction 2 score (organ dysfunction score ranging, 0–33)	5 (3.5/6)
PICU length of stay (d)	10 (7/13.5)
Maximal C reactive protein over PICU stay (mg/dL)	86 (34/181)
Use of sedative drugs (d)	8 (6/10.5)
Use of neuro-blocking agent (d)	6 (4/9)
Mechanical ventilation duration (d)	9 (6/11)
Nutritional data	
Cumulative energy intake deficit at TP-b (kcal/kg/d)[a]	−23.4 (−30.0/−4.9)
Cumulative energy intake deficit at TP-b (%)[a]	−55.3 (−64.0/−16.5)
Cumulative energy intake deficit at TP-c (kcal/kg/d)[a]	−13.6 (−31.0/−2.5)
Cumulative energy intake deficit at TP-c (%)[a]	−31.4 (−64.0/−6.5)
Cumulative protein intake deficit at TP-b (g/kg/d)[b]	−1.0 (−1.1/−0.5)
Cumulative protein intake deficit at TP-b (%)[b]	−58.9 (−74.7/−28.0)
Cumulative protein intake deficit at TP-c (g/kg/d)[b]	−0.9 (−1.1/−0.3)
Cumulative protein intake deficit at TP-c (%)[b]	−58.7 (−71.5/−17.9)
Quadriceps femoris measurements	
QF thickness at admission TP-a (cm)	2.25 (1.72/2.79)
QF thickness at TP-b (cm)	2.11 (1.36/2.43)
QF thickness at TP-c (cm)	1.75 (1.36/2.33)
QF thickness shift from admission to day 5 (TP-a to TP-b) (%)	−9.8 (−13.7/+0.5)
QF thickness shift from admission to last measurement (TP-a to TP-c) (%)	−13.3 (−25.4/−8.7)
No. of QF measurements over PICU stay	5 (4/6)

QF = quadriceps femoris, TP-a = time point admission, TP-b = time point day 5, TP-c = time point corresponding to the last measurement performed.
[a]Comparison to energy requirements estimated by the weight-height Schofield equation.
[b]Comparison to protein requirements estimated by Jotterand et al (15) or American Society of Parenteral and Enteral Nutrition recommendations.
Results are presented as medians (25–75 interquartile range) or n (%) or absolute values.

is required rather than simply assessing for degree of muscle wasting in isolation. This would result in an assessment of muscle wasting and PICU-AW with an overall approach, focusing not only on muscle mass but also on muscle strength and muscle function, as well as on its consequences on daily life. This will allow for further investigation of the correlation between early ultrasonography recognition of muscle wasting during PICU stay and its functional outcome. This may additionally enable researchers to examine the extent to which adjuncts such as nutritional optimization and rehabilitation can minimize muscle wasting and its consequences.

Our PICU muscle mass monitoring study demonstrates that muscle mass decline is an early and extended phenomenon that occurs in most critically ill children. In critically ill adults, Parry et al (16) similarly found a large decrease (30%) of thigh muscle thickness, whereas Puthucheary et al (1) found that rectus femoris cross-sectional area decreased significantly at day 7 of ICU stay (−12.5% [95% CI, −35.4% to 24.1%]; $p = 0.002$) and continued to decrease at day 10 (−17.7% [95% CI, −25.9% to 8.1%]; $p < 0.001$). However, muscle wasting is not synonymous with muscle weakness, as shown by the higher incidence of ICU muscle weakness or ICU-AW, ranging from 25% to 100%

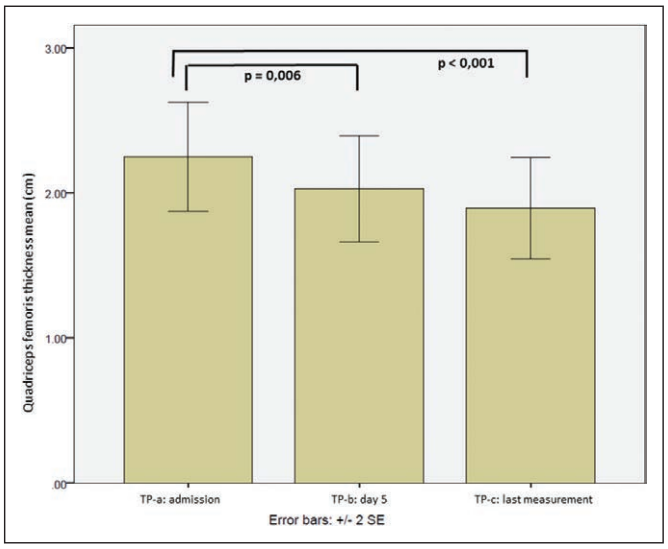

Figure 4. Quadriceps femoris thickness (in cm) monitoring at admission (TP-a), day 5 (TP-b), and at last measurement performed (TP-c). Data are presented in cm ± 2 SEs.

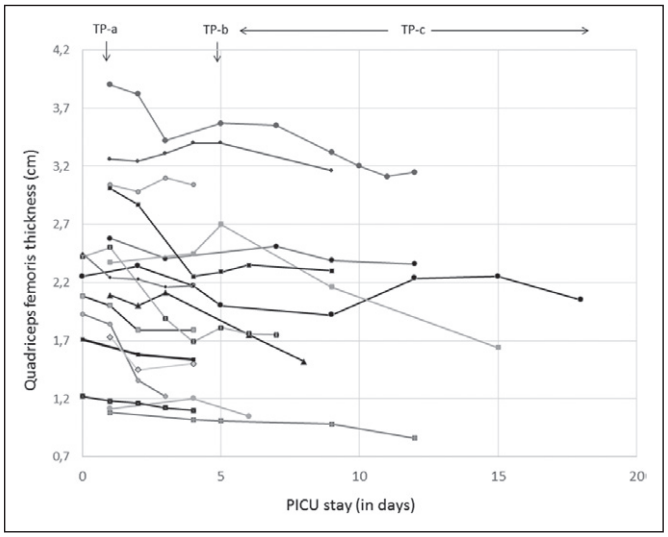

Figure 5. Monitoring over PICU stay of quadriceps femoris thickness (cm), assessed by thigh ultrasonography. Each of 17 lines represents one of the 17 children enrolled in the PICU muscle wasting longitudinal study. It is noticeable that the decrease of muscle thickness over stay is almost constant but not linear and subject to fluctuations. These fluctuations are related to errors of measurement (within the 5% change reliability of the technique) and eventually to patients' specific conditions (e.g., severe overhydration). TP-a = admission, TP-b = day 5, TP-c = last measurement performed.

in various studies. This also emphasizes the fact that validation of accurate assessment tools and standardization of diagnostic protocols are mandatory in this field. Field-Ridley et al (7) recently published a large analysis of PICU-AW, using the data collected in a U.S. register (Virtual PICU System, a clinical database with nationally participating PICUs). Incidence of critical illness myopathy was 0.02%, based on the International Classification of Diseases coding. PICU-AW independent risk factors were identified (including age, respiratory and infectious primary diagnosis, mechanical ventilation, renal replacement therapy, and extracorporeal life support). In this study, PICU-AW was also associated with longer length of stay and an increased need for rehabilitation following discharge from PICU. However, this study was limited by the voluntary report of PICU-AW into the register without any clear overarching PICU-AW definition. This may have led to an underestimation of the extent of PICU-AW. Furthermore, the risk factors that were identified should ideally be analyzed within the spectrum of other confounding factors, such as cumulative energy and protein deficit, cumulative doses of neuro-blocking agents and sedative drugs, for example. The extent of inflammation may also impact muscle metabolism shift in critical illness. In 2003, Banwell et al (8) reported an incidence of PICU-AW of 1.7%, based on prospective neurological examination of 830 children, assessing muscle weakness. Electromyography and muscle biopsy performed on seven and three patients, respectively, confirmed myopathy features, in a majority of them. Banwell et al (8) identified the length of stay and posttransplantation admission as risk factors for muscle weakness. In addition, the children in their sample were found to have prolonged muscle weakness three months after discharge.

Our intra- and interoperator reliability study enrolled a large number of children with an extended age range and a wide variety of clinical conditions, thus optimizing potential for wide extrapolation of results into other PICUs. When considering clinical application, the results identified in the current research, together with those of Fivez et al (12), emphasize the importance of adherence to a strict protocol that includes multiple measurements and excludes noncooperative children. This will limit per se its use in noncooperative children especially in the youngest with withdrawn sedation. However, our technique should be able to be used in the early hypermetabolic phase.

Our research findings suggest that ultrasonography used for the assessment of QF muscle thickness has good intrarater reliability. The findings also support the hypothesis that this technique has good interrater reproducibility among pediatric intensivists and physical therapists following appropriate training. In this study, only the reference operator received initial training from a pediatric radiologist; however, he was then able to train additional operators in the clinical setting where ultrasonography belongs to intensivists' daily practice; as replication of the technique was good, this approach of dissemination may be implemented in future research and clinical practice.

The power of the muscle mass monitoring study did not allow for independent risk factor recognition. In consequence, it does not yet allow the identification of a specific feature of interest that would particularly induce muscle wasting (such as disuse atrophy, fasting, severity of the disease, and/or inflammation). Future studies should seek to identify these risk factors and to correlate the degree of muscle wasting with various outcomes including length and cost of stay, mechanical ventilation weaning, muscle function, rehabilitation needs, and quality of life.

Hydration surely impacts on muscle mass and compromises the muscle wasting assessment accuracy of our technique. We did

not perform muscle biopsies to distinguish the implication in QF thickness variations, of muscle wasting itself and of muscle hydration. Assessment of body fluid overload is also challenging in the critically ill child: weight is a poor indicator in this setting, as it is influenced by both fluid shifts and nutritional status changes, and accuracy of fluid balance between inputs and outputs is questionable. The extend of the impact of fluid overload may be balanced by the combination of both muscular cell dehydration and muscular extracellular overhydration, as described by Gamrin et al (20, 21) and Häussinger et al (22). In consequence, moderate fluid shifts, which are frequent in critically ill children, may not alter QF measurements significantly, as stated by Puthucheary et al (23). However, the use of QF thickness as a surrogate of muscle wasting may not be perfectly accurate.

Accuracy of the technique may be challenged by the magnitude of change of QF thickness in neonates or infants, which is expected to be small. Average of two measurements did not show sufficient repeatability nor reproducibility in our study. We may hypothesize that averaging more than two measurements performed in the same angle (longitudinal or transverse) would have allowed for sufficient repeatability and reproducibility and should be tested in a future study. Averaging measurements of the same structure from different angle is not commonly proposed in the literature. However, in our study, the combination of transverse and longitudinal measurements was the only successful technique that allowed for good repeatability and reproducibility.

Finally, QF thickness ultrasound measurement should also be validated against the gold standard measurement that is MRI.

To conclude, multiplane ultrasonography enables QF thickness assessment and monitoring (as a potential surrogate to muscle wasting) in the critically ill child. QF thickness decrease is an early intense phenomenon that occurs in the majority of critically ill children. Further research is required to better understand PICU muscle wasting, to define early biomarkers, and to assess its impact on long-term functional outcomes.

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2.4. Article n°4

Modifications des dosages plasmatiques à l'admission en réanimation pédiatrique, liées à l'intensité du stress oxydant

"Multiple micronutrient plasma level changes are related to oxidative stress intensity in critically ill children"

2.4. Article n°4

Modifications des dosages plasmatiques à l'admission en réanimation pédiatrique, liées à l'intensité du stress oxydant

"Multiple micronutrient plasma level changes are related to oxidative stress intensity in critically ill children" (106)

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Valla FV, Bost M, Roche S, Pitance M, Cuerq C, Ridout J, Ecochard R, Ginhoux T, Bellon A, Ford-Chessel C, Portefaix A, Javouhey E, Blond E.

Pediatr Crit Care Med J. 2018;19(9):e455-63.

2.4.1. Introduction

La carence en micronutriments dans le cadre de la dénutrition globale sévère et du syndrome de renutrition est bien documentée dans la littérature ; l'importance de la supplémentation en cas de pertes excessives l'est également, notamment en cas d'épuration extrarénale ou de brûlures. En revanche, l'impact du stress oxydant sur les réserves en micro-nutriments impliqués dans le stress oxydant a peu été décrit en réanimation pédiatrique. Ce serait le préalable à l'élaboration d'étude testant l'effet d'une supplémentation dirigée. C'est ce dernier aspect qui est décrit dans cette étude.

2.4.2. Matériel et méthode

Etude prospective observationnelle transversale monocentrique (conduite dans une unité de réanimation pédiatrique non cardiologique, non néonatale, sur 16 mois entre 2013 et 2014).

Ont été inclus des enfants de plus de 36SA d'âge corrigé, de 0 à 18 ans.

Trois groupes d'enfant non dénutris ont été inclus, selon leur gravité définie sur la base du nombre de défaillance d'organe :

- Un groupe témoin non malade (bloc opératoire programmé, sans affection chronique sous-jacente)
- Un groupe présentant une défaillance d'organe majeure
- Un groupe présentant plus d'une défaillance d'organe majeure

Chez chacun des participants était réalisé, dans les 48 heures suivant l'admission, un dosage plasmatique de 7 micro-nutriments impliqués dans le stress oxydant : Sélénium, Cuivre, Zinc, Vitamines C, A, E et bêta-carotène. Parallèlement, un dosage des marqueurs plasmatiques de stress oxydant était réalisé (glutathion et glutathion peroxydase).

2.4.3. Résumé des résultats et discussion

51 enfants ont été recrutés dans le groupe présentant plus d'une défaillance d'organe, 48 dans le groupe présentant une seule défaillance d'organe, et 102 dans le groupe témoin.

Le stress oxydant plasmatique mesuré augmentait bien avec le nombre identifié de défaillance d'organe, confirmant la classification clinique par groupe de sévérité.

L'augmentation de l'intensité du stress oxydant s'accompagnait d'une diminution significative de tous les micronutriments dosés, à l'exception de la vitamine A qui ne montrait qu'une tendance.

La revue de la littérature réalisée retrouve des résultats discordants en ce qui concerne le statut en sélénium, zinc et cuivre à l'admission en réanimation pédiatrique ; néanmoins, ces études ont inclus des patients avec peu ou pas de défaillance d'organe donc avec peu de stress oxydant ; par ailleurs, le statut nutritionnel global, mal décrit, pouvait être un facteur confondant. En effet, il est primordial de bien identifier les sources de carence possibles (dénutrition préalable, mobilisation aiguë, ou pertes excessives), pour bien appréhender les enjeux futurs d'une éventuelle supplémentation efficace.

Les limites de cette étude tenaient à son caractère monocentrique et l'absence de monitorage en cours de séjour. Par ailleurs, l'état d'inflation hydrique a pu influencer les résultats et leur interprétation.

2.4.4. article publié

Multiple Micronutrient Plasma Level Changes Are Related to Oxidative Stress Intensity in Critically Ill Children

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Objectives: Micronutrient supplementation in critically ill adults remains controversial. In the pediatric setting, the impact of oxidative stress on the overall micronutrient status has been poorly explored, due to the limited number of studies and to confounding factors (i.e., malnutrition or extra losses). In order to better understand this phenomenon, we aim to describe micronutrient status, focusing on seven micronutrients, in well-nourished critically ill children presenting with severe oxidative stress.

Design: Prospective, transversal, observational, single-center study.

Setting: PICU, and anesthesiology department, Lyon, France.

Patients: Three groups of patients were clinically defined: severe oxidative stress PICU group (at least two organ dysfunctions), moderate oxidative stress PICU group (single organ dysfunction), and healthy control group (prior to elective surgery); oxidative stress intensity was controlled by measuring plasma levels of glutathione peroxidase and glutathione. Children presenting any former condition leading to micronutrient deficiency were excluded (malnutrition, external losses).

Interventions: Plasma levels of selenium, zinc, copper, vitamin A, vitamin E, vitamin C, and β-carotene were measured in PICU oxidative stress conditions and compared with those of healthy children.

Measurements and Main Results: Two hundred one patients were enrolled (51, 48, and 102 in severe, moderate, and healthy control groups, respectively). Median age was 7.1 years (interquartile range, 2.1–13.8 yr). There was a significant trend ($p < 0.02$) toward plasma level decrease of six micronutrients (selenium, zinc, copper, vitamin E, vitamin C, and β-carotene) while oxidative stress intensity increased. Biological markers of oxidative stress (glutathione peroxidase and glutathione) were in accordance with the clinical definition of the three groups.

Conclusions: A multiple micronutrient deficiency or redistribution occurs in critically ill children presenting with severe oxidative stress. These findings will help to better identify children who might benefit from micronutrient supplementation and to design

adapted supplementation trials in this particular setting. (*Pediatr Crit Care Med* 2018; XX:00–00)
Key Words: β-carotene; copper; selenium; vitamin C; vitamin E; zinc

Micronutrient deficiencies (i.e., trace element and vitamin deficiencies) can occur in case of low intakes due to chronic malnutrition or in case of gut, skin, or renal losses, or in case of unusual store consumption in certain pathologic conditions such as oxidative stress. In healthy beings, there is a balance between prooxidative and antioxidant pathways, in order to maintain cell functions (e.g., cell metabolism, reactive oxygen species-mediated intracellular signalization, nitric oxide-mediated vasodilation, reactive oxygen/nitric species-mediated phagocyte pathogen lysis). When disrupted, this balance will lead to pathologic consequences like cell quiescence or apoptotic pathways induction. Some micronutrients play a major role (as enzyme cofactors or direct antioxidant agents) in the antioxidant response, that is, selenium (Se), zinc (Zn), copper (Cu), iron, manganese, β-carotene, vitamin A, vitamin C, and vitamin E. Their quantitative deficiency during intense antioxidant response conditions can disrupt the pro/antioxidant balance and lead to a relative immune deficiency and favors infections (1).

In both adults and children, systemic inflammatory response syndrome (SIRS) triggers oxidative stress (2), as seen during septic shock (3), severe trauma, or acute respiratory distress syndrome (ARDS) (4).

In adults in whom micronutrient deficiency associated with severe oxidative stress is well described (5), recent randomized controlled studies (6–9) and meta-analysis (10–12) failed to confirm that IV micronutrient supplementation in such conditions reduced mortality, intensive care length of stay, or nosocomial infection rate, especially with Se supplementation. Indications and exact supplementation modalities adapted to each clinical situation remain unclear, and most recent guidelines do not recommend such supplementation any longer (13).

Pediatric intensive care and nutrition societies have not proposed such guidelines yet, due to lack of data (14). To date, there is no existing study in the literature that has explored overall micronutrient status in severe oxidative stress conditions in children who are not affected by former deficiencies (malnutrition or skin, gut, or renal chronic losses). Two pediatric randomized controlled trials (15, 16) conducted in PICUs did not prove any benefit of Zn and Se supplementation on outcome and nosocomial infection occurrence. However, baseline micronutrient status and clinical severity were very heterogeneous.

The aim of our study was to describe seven micronutrient plasma levels (i.e., Se, Zn, Cu, vitamin A, vitamin E, vitamin C, and β-carotene) in critically ill children (not affected by former micronutrient deficiency) presenting with various organ dysfunction (OD) intensities. We also aimed to review the existing literature on micronutrients involved in oxidative stress in the critically ill child, to analyze the data and studied populations, and comment the results for a better understanding of the phenomenon. This will hopefully help to design future supplementation trials.

MATERIAL AND METHODS

We conducted a prospective, transversal, observational single-center study, between May 2013 and September 2014. Children were recruited in the 23-bed PICU and the pediatric anesthesiology unit in Lyon university pediatric hospital (Hôpital Femme-Mère-Enfant), Lyon-Bron, France.

The study protocol was approved by the institutional review board (Comité de Protection des Personnes Lyon SUD-EST II, file number 2012–013) and was registered in France (French ID-RCB number: 2012-A00356-37).

All subjects (when appropriate) and their parents provided informed consent before enrollment.

Primary Outcome

The primary outcome was to describe the plasma concentrations of seven micronutrients (Se, Zn, Cu, vitamin A, vitamin E, vitamin C, and β-carotene) in severe oxidative stress conditions in critically ill children, compared with healthy control children.

Study Population

One-month to 18-year-old children, weighing above 4 kg, were consecutively included. Children presenting any former condition leading to a potential micronutrient deficiency were excluded. This concerned malnourished children with intake deficiency (malnutrition was defined as a *z* score body mass index [BMI] for age < –2 SD) or children under nonadapted feeding regimen (identified with a systematic dietary survey prior to inclusion), but also children presenting with excessive losses due to skin (burns), digestive (exudative enteropathy) or renal diseases, and renal replacement therapies. (These patients were excluded because our primary aim was to explore the specific impact of illness severity in relation to systemic inflammation, on the pathophysiology of micronutrient plasma level changes.)

Three groups of patients were set: severe oxidative stress group, moderate oxidative stress group, and healthy control group. Healthy children had to be recruited because normal French pediatric ranges are not established as for plasmatic levels of Se, Cu, Zn, vitamin C, β-carotene, and vitamin A. We chose a simple clinical definition, as oxidative stress biomarkers are usually not available in the first 48 hours of admission. We also aimed to select a useful classification for easy transposition into clinical practice in the future. These groups were clinically defined as follows:

1) Severe group: Fifty PICU children were planned to be recruited if presenting with at least two OD (> 1) (i.e., severe oxidative stress condition) resulting from severe sepsis/septic shock, ARDS, severe trauma, hemorrhagic shock.
2) Moderate group: Fifty PICU children were planned to be recruited. They should not present with any severe group condition described above and no more than one OD (= 1).

3) Healthy control group: We planned to recruit 100 healthy children (not subject to any chronic or acute illness) prior to elective minor surgical procedures (e.g., inguinal hernia, strabismus surgery, bone fixation device removal, meniscus surgery, etc.).

In each group, homogeneous repartition between age and sex was planned (20% < 2 yr old, 40% between 2 and 12 yr old, 50% of females).

The following baseline population characteristics were collected: Pediatric Index of Mortality (PIM) II score, Pediatric Risk of Mortality (PRISM) score, and Pediatric Logistic Organ Dysfunction (PELOD) II score and BMI-for-age *z* score. Fluid bolus and blood product administered prior to micronutrient sampling were also recorded.

Micronutrients Measurements

The plasma concentrations of the seven micronutrients were measured in the first 48 hours following PICU admission in the nonhealthy control children. Blood samples were taken immediately before surgery started in the healthy control group. Measurements were performed using atomic absorption spectroscopy for Se, inductively coupled plasma atomic emission spectrometry for Cu and Zn (total Cu was measured which includes both free Cu and ceruloplasmin-bound Cu). High performance liquid chromatography with ultraviolet detection was performed for vitamin A, vitamin E, and β-carotene, and high performance liquid chromatography with electrochemical detection for vitamin C (see detailed measurement techniques in the **supplemental text** [Supplemental Digital Content 1, http://links.lww.com/PCC/A664] and technique properties in **Supplemental Table 1** [Supplemental Digital Content 2, http://links.lww.com/PCC/A665]). In order to accurately interpret vitamin E and vitamin A values, vitamin E values were adapted to cholesterol and triglyceride plasma levels using the vitamin E/(cholesterol + triglyceride) ratio. Vitamin A values were adapted to vitamin A binding protein RBP4 (retinol binding protein 4) using the vitamin A/RBP4 ratio (17, 18).

Secondary Outcomes

In order to confirm oxidative stress severity in each group, plasma antioxidant activity was analyzed, using glutathione peroxidase (GPx) and glutathione plasma measurements as biomarkers. These measurements were made by enzymatic method for GPx and by high performance liquid chromatography coupled with mass spectroscopy for glutathione.

We also reviewed the literature to assess the available data on micronutritional status in critically ill children. We searched English papers in the the following electronic databases: MEDLINE, EMBASE, and the Cochrane Library (from the earliest available date up until December 2017). A combination of keywords and MeSH terms addressing oxidative stress ("antioxidant" or "oxidative stress"), micronutrients ("Se" or "Zn" or "Cu" or "vitamin A" or "vitamin C" or "vitamin E" or "β-carotene"), and critically ill children ("critically ill" or "PICU") were used, excluding in vitro and animal model, adult and preterm infant papers. Trials and observational studies were considered, including cohort studies, case-control studies, and case series.

Statistical Analysis

The characteristics of patients were described using the mean and SD or quartiles and range for quantitative characteristics and the absolute and relative frequencies in each category for qualitative ones.

The sample size was estimated using the appropriate formula in case of repeated measurements. Correlations between the measurements in a same patient and a between-patient variance were obtained from a previous pilot study.

To assess the relationship between each micronutrient or oxidative stress biomarker and the level (i.e., group) of oxidative stress, linear models that allow for sex and age were built after checking for their assumptions. The level of oxidative stress was introduced as an ordinal variable. A test for trends was used to check the equality to zero of the regression coefficient of the ordinal variable after adjustment on age and sex. The sign of the variable gives the direction of the trend. For vitamin A/RBP4, a patient had a very high value (16.55 μmol/mg), thus a sensitivity analysis was performed to determine whether this value influences the results (two trend tests with and without this value). As the number of comparisons was 11 (seven micronutrient + four oxidative stress biomarker), a compensation for multiple testing, thus *p* value correction, used Yekutieli method.

To illustrate the trends, boxplots of micronutrient values across clinical levels of oxidative stress were then produced. Missing data were supposed missing at random. The main statistical analyses (models and tests) used SAS software, Version 9.3 (SAS Institute, Cary, NC). Stata 13 software (StataCorp., College Station, TX) was used for other analyses and figures. All tests were two-tailed, and *p* value of less than 0.05 was considered for statistical significance.

RESULTS

Population Characteristics

As shown in patient flow chart (**Supplemental Fig. 1**, Supplemental Digital Content 3, http://links.lww.com/PCC/A666; **legend**, Supplemental Digital Content 1, http://links.lww.com/PCC/A664), 201 patients were enrolled (51 in the severe group, 48 in the moderate group, 102 in the healthy control group), of them 43.8% females. Median age was 7.1 years (interquartile range [IQR], 2.1–13.8 yr). In the severe group (OD > 1), patients presented with severe sepsis or septic shock (31.4%), ARDS (27.4%), major trauma (29.4%), and other (11.8%) severe condition (i.e., severe pancreatitis, hemorrhagic shock). In the moderate group (OD = 1), patients had been admitted after elective major surgery or presented with status epilepticus, status asthmaticus, viral infection, pneumonia (no criteria of ARDS), pneumothorax, sickle cell disease pneumonia, nonsevere trauma, local infections (cellulitis, appendicitis), or Guillain-Barre syndrome. Higher PELOD II, PRISM, and PIM

II scores were found in the severe group. In the moderate and severe combined group, median PELOD II score was 3 (IQR, 0–7) and median PIM II score was 2.6 (IQR, 0.9–8.3). None of the children were undernourished. Detailed population characteristics are shown in **Table 1**.

Measurement Issues

Seventeen percent (35/201) of vitamin C samples could not be analyzed because of delayed stabilization after blood sampling (supplemental text, Supplemental Digital Content 1, http://links.lww.com/PCC/A664). More than 95% of the samples underwent accurate measurement process for other micronutrients (**Table 2**).

Micronutrient Plasma Levels

Although oxidative stress intensity increased (as per group definition), we found a significant trend toward decrease of six micronutrient plasma levels ($p < 0.02$) for each of Se, Zn, Cu, vitamin C, vitamin E, and β-carotene (Table 2 and **Fig. 1**). Regarding plasma vitamin A, we found a close to significance ($p = 0.08$) trend toward decrease (Fig. 1). All these trends were adjusted on age and sex.

Oxidative Stress Biomarkers Plasma Levels

As shown in Table 2, GPx plasma concentrations increased ($p = 0.01$) and glutathione plasma concentrations decreased significantly ($p < 0.0001$), as oxidative stress intensity increased, as per clinical definition.

Review of the literature identified 11 relevant studies; their results are presented in **Table 3**. Se, Zn, and Cu were the most frequently studied micronutrients; vitamins were not studied in any. Se and Zn deficiencies were frequent. Oxidative stress biomarkers were measured in one of the studies. Most patients presented with moderate severity scores and sometimes with malnutrition. Information on nutritional status was available in a few studies only.

DISCUSSION

Our study showed that in PICU patients presenting with multiple OD, a significant plasma level depletion of six main micronutrients involved in oxidative stress (Se, Zn, Cu, vitamin C, vitamin E, and β-carotene) occurred, associated with a significant decrease trend while oxidative stress intensity increased. As it has been previously described (29), antioxidant biomarkers GPx and glutathione also significantly

TABLE 1. Population Characteristics

Characteristics	Total Population 201 (100%)	Healthy Controls 102 (51%)	OD = 1 48 (24%)	OD > 1 51 (25%)
Females, *n* (%)	88 (44)	48 (47)	18 (37)	22 (43)
Age, yr, median (25–75th percentile)	7.1 (2.1–13.8)	7.5 (2.4–14.5)	7.4 (1.1–13)	5.3 (1.5–13.3)
Age range, yr, *n* (%)				
< 2	49 (24)	21 (21)	14 (29)	14 (27.5)
2–12	88 (44)	44 (43)	21 (44)	23 (45)
> 12	64 (32)	37 (36)	13 (27)	14 (27.5)
Weight (kg), median (25–75th percentile)	23 (12–47)	23.5 (12–50)	24 (10–44)	20 (10.50–46)
Body mass index (kg/m^2), median (25–75th percentile)	17 (16–20)	18 (16–20)	17 (16–20)	17 (16–20)
Pediatric Logistic Organ Dysfunction II, median (25–75th percentile)	NA	NA	0 (0–2.5)	7 (4–10)
Pediatric Index of Mortality II, median (25–75th percentile)	NA	NA	0.9 (0.5–1.2)	8.1 (5–15.2)
Pediatric Risk of Mortality score, median (25–75th percentile)	NA	NA	6 (4–10)	27 (21–35)
Number of fluid bolus, median (25–75th percentile)	NA	NA	1 (0–2)	2 (1–4)
RBC, *n* (%)	NA	NA	10 (20.8)	7 (13.7)
Platelets, *n* (%)	NA	NA	0 (0)	4 (7.8)
Fresh frozen plasma, *n* (%)	NA	NA	1 (2.0)	5 (9.8)
Enteral nutrition/glucose perfusion, *n* (%)	NA	NA	6 (12.5)/42 (87.5)	17 (33)/34 (67)

NA = not applicable, OD = organ dysfunction.
OD > 1 indicates severe oxidative stress, and OD = 1 indicates moderate oxidative stress.

TABLE 2. Age- and Sex-Adjusted Micronutrient and Oxidative Stress Biomarker Plasma Levels

Micronutrient or Biomarker	Healthy Controls		OD = 1 (Moderate Oxidative Stress)		OD > 1 (Severe Oxidative Stress)		p
	n	Value, Median (25–75th percentile)	*n*	Value, Median (25–75th percentile)	*n*	Value, Median (25–75th percentile)	
Selenium, µmol/L	99	0.90 (0.80–1)	48	0.70 (0.50–0.80)	51	0.60 (0.40–0.60)	< 0.0001
Copper, µmol/L	102	15.60 (13.60–18.90)	48	15.10 (12.85–17.40)	51	13.60 (11.30–17)	0.0148
Zinc, µmol/L	102	11.50 (10.70–12.50)	48	7.15 (5.90–10.25)	51	7,20 (5.10–8.90)	< 0.0001
Vitamin A, µmol/L	100	1.10 (0.92–1.32)	44	0.77 (0.48–1.04)	44	0.45 (0.29–0.67)	
RBP4, mg/L	102	19.63 (16.97–22.87)	48	13.68 (8.85–17.87)	51	7.65 (4.80–11.28)	
Vitamin A/RBP4, µmol/mg[a]	100	5.60 (5.28–5.98)	44	5.53 (5.05–5.89)	44	5.35 (4.91–5.82)	0.0860
β-carotene, µmol/L	101	0.57 (0.35–0.94)	44	0.040 (0.28–0.73)	43	0.31 (0.23–0.45)	< 0.0001
Vitamin C, µmol/L	85	60 (45–74)	37	39 (23–50)	44	23.50 (14–31.50)	< 0.0001
Vitamin E, µmol/L	101	19.80 (17.90–22.40)	48	16.70 (13.80–21.12)	50	13.88 (10.42–17.70)	
Vitamin E/(cholesterol + triglycerides)	101	4.21 (3.73–4.76)	48	3.62 (2.88–4.58)	50	2.95 (2.26–3.86)	0.0006
Glutathione peroxidase, IU/L	100	545 (472–597)	47	585 (451–691)	50	567 (485–702)	0.0103
Glutathione, µmol/L	101	913 (827–1,024)	47	788 (666–917)	51	731 (594–815)	< 0.0001

OD = number of organ dysfunctions, RBP4 = retinol binding protein 4.
[a]The high value (16.55 µmol/mg) was excluded for the trend test.

increased and decreased respectively, in relation to critical illness intensity.

To our knowledge, our study is the first to prospectively assess oxidative stress association with critically ill children's overall micronutrient status, excluding patients with other conditions (i.e., malnutrition and abnormal losses) that interfere with micronutrient stores. It is also the first to describe vitamin C, vitamin E, vitamin A, and β-carotene status in PICU. It is of great importance to clearly describe the physiopathology of these micronutrients deficiencies, in order to distinguish the various conditions that impact micronutrient plasma levels. We have shown an association of oxidative stress with six micronutrients deficiency, independently from the overall nutritional and feeding status and from extra abnormal losses. This will further allow for appropriate identification of patients that may benefit more from micronutrient supplementation.

Se, Cu and Zn are mandatory in the oxidative stress response, as coenzymes of GPx and superoxide dismutase (30, 31). Their stores are mobilized and redistributed when the antioxidant enzymatic activity increases. Vitamin E, β-carotene, and vitamin C are antioxidative molecules per se and are directly consumed during intense oxidative stress response, potentially leading to their deficit. The lack of these micronutrients compromises the efficiency of the antioxidant response. So, micronutrient supplementation trials have been conducted in the last decade, mainly in adults, with controversial results. Various supplementation regimens (involving different doses and/or administration routes) have been tested on different patient populations (in terms of nutritional status, severity of illness, etc); such regimen impacts on outcome remain challenging to interpret (6–13). Carcillo et al (16) conducted in the United States a pediatric randomized controlled trial: a Se-Zn-metoclopramide-glutamine cocktail failed to improve critically ill children's outcomes. It is interesting to notice that the recruited children often presented with no Se deficit at admission and sometimes with no Zn deficit; some had extremely mild severity scores, which implies low oxidative stress. We

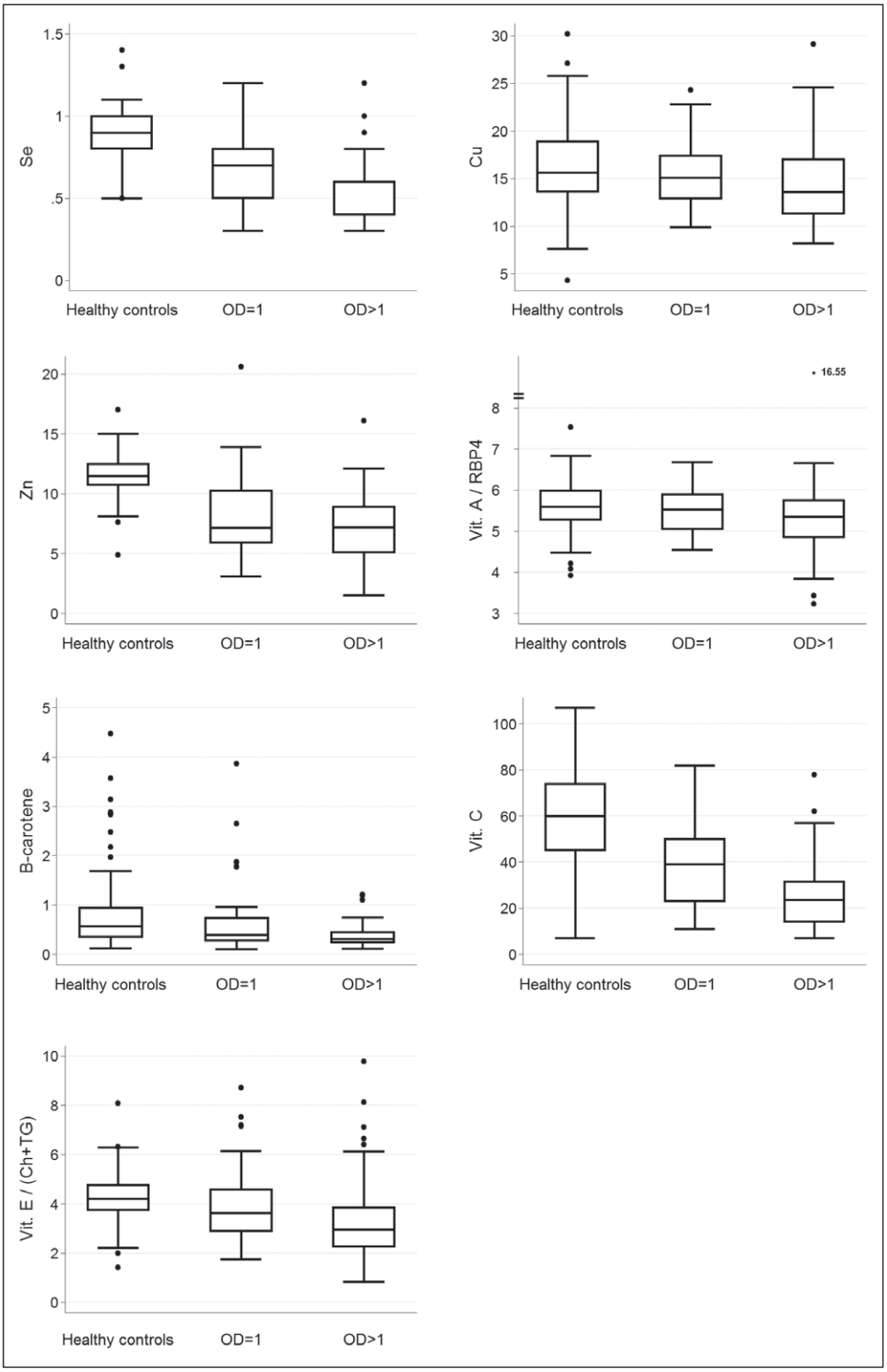

Figure 1. Micronutrient distributions according to the children groups. Total copper (Cu) (μmol/L) plasma levels were measured, which corresponded to the sum of free Cu and ceruloplasmin-bound Cu plasma levels. High ceruloplasmin plasma levels are common in critical illness inflammatory state and would normally lead to increased total Cu plasma levels. Our results showing a decrease of total Cu in the severe group are in favor of an even stronger redistribution of Cu in antioxidant enzyme complex. Glutathione peroxidase (GPx) plasma levels: even if the GPx median of the moderate group appears higher than the healthy controls' one, the decreasing trend with oxidative stress intensity remains statistically significant. Organ dysfunction (OD) > 1 indicates severe oxidative stress, and OD = 1 indicates moderate oxidative stress. β-carotene = beta-carotene (μmol/L), Se = selenium (μmol/L), Vit. A/RBP4 = vitamin A/retinol binding protein 4 (μmol/mg), Vit. C = vitamin C (μmol/L), Vit. E/(Ch + TG) = vitamin E/(cholesterol + triglycerides), Zn = zinc (μmol/L).

believe that the treated population has to be targeted perfectly, in order to be able to prove a benefit of micronutrient supplementation, and eventually to prevent them from potentially harmful or useless treatment.

In our study, the three groups were defined according to their supposed oxidative stress degree, based on their number of OD and clinical admission diagnosis. This definition was strengthened by the significant trend that was found with the biologic markers of oxidative stress (GPx and glutathione). This is rarely explored in the pediatric literature and compromises the interpretation of micronutrient deficiency results. Our results for micronutrient plasma levels in the healthy control group are matching with previously published ranges, in various other cohorts of healthy patients (Supplemental Table 1, Supplemental Digital Content 2, http://links.lww.com/PCC/A665). Measurement techniques used in our study are also described in Supplemental Table 1 (Supplemental Digital Content 2, http://links.lww.com/PCC/A665). Their low intra- and interassay coefficients of variation allowed for relevant accuracy of laboratory measurements.

The patient profile at admission should also be integrated in the interpretation of micronutrient plasma values. In our literature review, it was difficult to distinguish the respective role of malnutrition and oxidative stress on Se deficiency, like in the highly malnourished Brazilian PICU population described by Leite et al (24) and De Oliveira et al (25). Similarly, the absence of Cu deficiency in the study

TABLE 3. Studies Conducted in Critically Ill Children, Assessing Micronutrient Status

References, Country	No. of Patients (Age in Means ± SD or Median [IQR])	Healthy Controls	Micronutrients (Method Used)	Severity of Illness (Means ± SD or Median [IQR])	Malnutrition	Extra Losses of Micronutrients	Results (Means ± SD or Median [IQR])
Voruganti et al (19), United States	6 children (7–13 yr old)	No	Zinc, copper (FAAS)	Severe: burnt total body; surface area mean: 54% (± 9)	No	Major burns	Zinc deficiency (9.38 μmol/L ± 2.31); copper deficiency (5.62 μmol/L ± 3.28)
Broman et al (20), Sweden	100 children (5 mo [0.1–46 mo])	Yes	Selenium (ICP-MS)	Moderate to severe: PIM II score 14 (6–36), PELOD II score 9 (5–11)	10%	Continuous renal replacement therapy 35%; extra corporeal membrane oxygenation 50%	Selenium deficiency at admission (40% lower than reference group) 0.38 μmol/L (0.29–0.47 μmol/L); improvement during ICU stay (+14% at day 5), correlated to number of organ dysfunction
Yuan et al (15), China	96 children (median: 2 mo)	No	Zinc (atomic absorption spectrophotometry)	Unclear: "severe pneumonia" according to Pediatric Infectious Disease Society and Infectious Disease Society of America 2011	MD	MD	Zinc deficiency in 76% compared with normal ranges (40.7 ± 17 μmol/L if younger than 3 mo, 58 ± 19.2 μmol/L between 4 and 12 mo)
Dylewski et al (21), United States	20 children (0–18 yr)	No	Selenium (gas chromatography)	Severe: burnt total body; surface area mean: 42% (± 21%)	No	Burnt total body surface area > 10%	Selenium deficiency/ status suboptimal (1,08 μmol/L ± 0.34)
Wang et al (22), China	31 children (1 mo to 5 yr old)	Yes	Zinc, copper, iron (ICP-MS)	Low to moderate: PRISM III score 13 (8–46), no invasive ventilation (3%), short LOS	No	MD	Zinc deficiency (20.88 μmol/L ± 8.34); iron deficiency (3.95 mmol/L ± 1.56); no copper deficiency (14.53 μmol/L ± 5.78)
Cvijanovitch et al (23), United States	20 children (2.9 yr [0.7–10.1] yr)	No	Zinc, copper (atomic absorption)	Moderate: PRISM III scores 9 (7–14), LOS: 5 d (3–13 d)	MD	MD	Zinc deficiency (6.62 μmol/L ± 1.84); no copper deficiency (> 10.16 μmol/L)
Leite et al (24), Brazil	99 children (34 mo [9–83] mo)	No	Selenium (GFAAS)	Moderate to severe: PELOD 11 (2–12), PIM II score 6.0 (2.6–12.3)	53% of children	No	Selenium deficiency (0.30 μmol/L [0.15–0.39 μmol/L])
De Oliveira Iglesias et al (25), Brazil	173 children (34 mo [9–90] mo)	No	Selenium (GFAAS)	Moderate: PELOD score 11 (2–12), PIM II 3.68 (1.32–8.78)	Yes, 46%	MD	Selenium deficiency (0.30 μmol/L [0.15–0.39] μmol/L)
Briassoulis et al (26), Greece	50 children (116 ± 9.6 mo)	No	Zinc and copper (FAAS)	Moderate: PRISM 12.5 ± 1.6	MD	MD	Admission copper 12.7 μmol/L ± 0.7; admission zinc 8.9 μmol/L ± 0.5; zinc negatively correlated to PRISM ($p = 0.00$)
Briassoulis et al (27), Greece	40 severe head injury children (127 ± 7.9 mo)	No	Zinc and copper (FAAS)	Moderate: PRISM 13.2 ± 1	MD	MD	Admission copper 10.7 μmol/L ± 0.7; admission zinc 9.4 μmol/L ± 0.3
Heideman et al (28) and Carcillo et al (16), United States	284 children (median, 7 yr old); two groups	No	Zinc (inductively coupled plasma optical emission spectrometry); selenium (ICP-MS)	Mild to moderate: PELOD 11 (0–40) and 11 (0–50), PRISM 8 (0–34) and 7 (0–31)	MD	MD	Zinc deficiency in 84% (median, 6.77 μmol/L); selenium deficiency in 56% (median, 0.94 μmol/L)

FAAS = flame atomic absorption spectrophotometry (5,100 PC; Perkin-Elmer, Shelton, CT) with an air-acetylene flame, GFAAS = graphite furnace atomic absorption spectrophotometry with Zeeman background correction, ICP-MS = inductively coupled plasma mass spectrometry, IQR = interquartile range, LOS = length of stay, MD = missing data, PELOD = Pediatric Logistic Organ Dysfunction, PIM = Pediatric Index of Mortality, PRISM = Pediatric Risk of Mortality.

PIM and PIM II indicates percentage of mortality risk, PRISM indicates scoring from 0 to 76, PRISM III indicates scoring from 0 to 71, PELOD indicates scoring from 0 to 71, and PELOD II indicates scoring from 0 to 30.

by Wang et al (22) and the normal Se status in the study by Heideman et al (28) could be explained by the low degree of severity upon admission or by the richness of North American soils in Se compared with European ones (32). Finally, abnormal extra losses are involved in micronutrient deficiencies as proven in children suffering severe burns (19, 21) or under renal replacement therapy. In summary, different mechanisms are involved in the pathophysiology of micronutrient deficiency (i.e., inflammation, undernutrition, abnormal losses) and should all be taken into consideration when predicting risk for micronutrient deficiency in critically ill children.

Micronutrient deficiency at admission has been linked to outcome in PICU: Wang et al (22) showed that Zn deficiency at admission was correlated to the PRISM III severity score that predicts mortality. Leite et al (24) found the increase of Se plasma level from admission to day 5 to be correlated with improved outcomes in terms of survival rate, mechanical ventilation duration, and ICU length of stay. Carcillo et al (16) found in the pediatric critical illness stress-induced immune suppression (CRISIS) trial that children receiving high antioxidant dosing of a cocktail composed of Zn, Se, glutamine, and prolactine presented lower 7-day deficiency rates in Se and Zn, compared with children receiving a placebo. Broman et al (20) performed monitoring of Se plasma levels over 5 days in critically ill children and showed a significant increase in these levels over time, with normal nutritional intakes of micronutrients; however, children who did not increase Se plasma levels were also the one who remained the sickest. Pediatric literature remains scarce, and no data are available about Cu or vitamin evolution over PICU stay. It is mandatory to properly explore the impact of micronutrient supplementation in critically ill children.

Severity groups were defined by the number of OD. Admission main diagnosis in the severe group (OD > 1) gathered septic patients and ARDS patients or severely traumatized patients presenting with SIRS. Recent studies have highlighted the differences found in metabolic, innate immunity, and adipokine profiles while comparing sepsis and SIRS in both critically ill adults and children (33, 34). The number of patients included in our study did not allow for subgroup analysis, but we may hypothesize that children PICU admission profile may also affect micronutrient deficiency degree. However, this was not confirmed in the study by Broman et al (20) in which respiratory failure patients had similar Se shift than patients with other primary diagnosis. Previous studies performed by Briassoulis et al (26, 27, 35) research group tested in three subsequent trials different enteral formulas (standard vs immune enhanced formula with higher amounts of glutamine, arginine, ω-3 fatty acids, antioxidants like vitamin E, β-carotene, Se, and Cu). The immune enhanced formula treated group showed favorable effects on nutritional indices and antioxidant catalysts (with high increase in Zn and Cu plasma levels). Zn was also negatively and significantly correlated to PRISM score. A subgroup of head trauma children did not show similar significant improvement in Cu and Zn levels but cytokine profile improved; in a septic shock subgroup, cytokine profile was also improved without any short-term outcome influence.

Our study has some limitations, first because being single centered, but patient selection was sharp, and the two controls for one case design are powerful. Patient classification based on number of ODs and diagnosis may limit external validity of the study but may still be relevant in clinical practice. The vitamin A decrease was close to significance probably because of a lack of power in study design. Measurement bias affects vitamin C results with lack of data due to its molecular instability and technical measurement issues. Fluid balance and intravascular compartment fluid shift could not be accurately measured in this setting, which may have impacted micronutrient plasma levels especially in the severe group. Similarly, protein, albumin, and inflammation markers such as C-reactive protein (CRP) were not measured, and as a consequence, impact of inflammation on micronutrient transporters could not be evaluated properly. No monitoring of micronutrient plasma level was performed during PICU stay, which did not allow describing the evolution over time of the micronutrient deficiency observed at admission. Finally, normal ranges of micronutrients could not be set from our healthy children group as this would need a larger cohort. As a consequence, deficiency cut off values could not be determined, and comparison to this control group should remain cautious.

At this stage, it is too early to recommend any systematic micronutrient cocktail supplementation in critically ill children. Our results identified micronutrients of interest and will hopefully be able to guide future trial design assessing the impact of different micronutrient supplementation cocktails that may influence outcome. We believe that the supplementation approach should test regimens including different combinations of these six micronutrients, as the supplementation of one single nutrient may not be efficient. To prevent overtreatment, it is mandatory to accurately screen the children, taking into consideration their nutritional status, their current intakes (especially regarding Se and geographical variations of soil composition), their abnormal losses, and their presumed oxidative stress intensity. Future trials will need to focus on children presenting with high risk of micronutrient deficiency, according to the criteria described above. Their design should include plasma level close monitoring at admission but also during PICU stay and recovery phase. Overhydration and capillary leak impact on nutrient plasma levels should also be considered, integrating strict fluid balance assessment, fluid bolus, and blood product administration collection, in combination with inflammation assessment based on simple biomarkers monitoring (e.g., CRP, albuminemia). Finally, micronutrient loss assessment (through urinary output, wounds, renal replacement therapy, and drains) during PICU stay would also help describing the micronutrient shift pathophysiology.

CONCLUSIONS

In the critically ill child, a significant decrease in Se, Cu, Zn, vitamin C, vitamin E, and β-carotene plasma levels tends to occur as oxidative stress intensity increases. We can speculate that this micronutrient deficiency would be even stronger in case of malnutrition or pathologic losses of macronutrients,

which are common conditions in PICU. Our simple clinical definition of oxidative stress exposure severity was designed to easily screen children at PICU admission.

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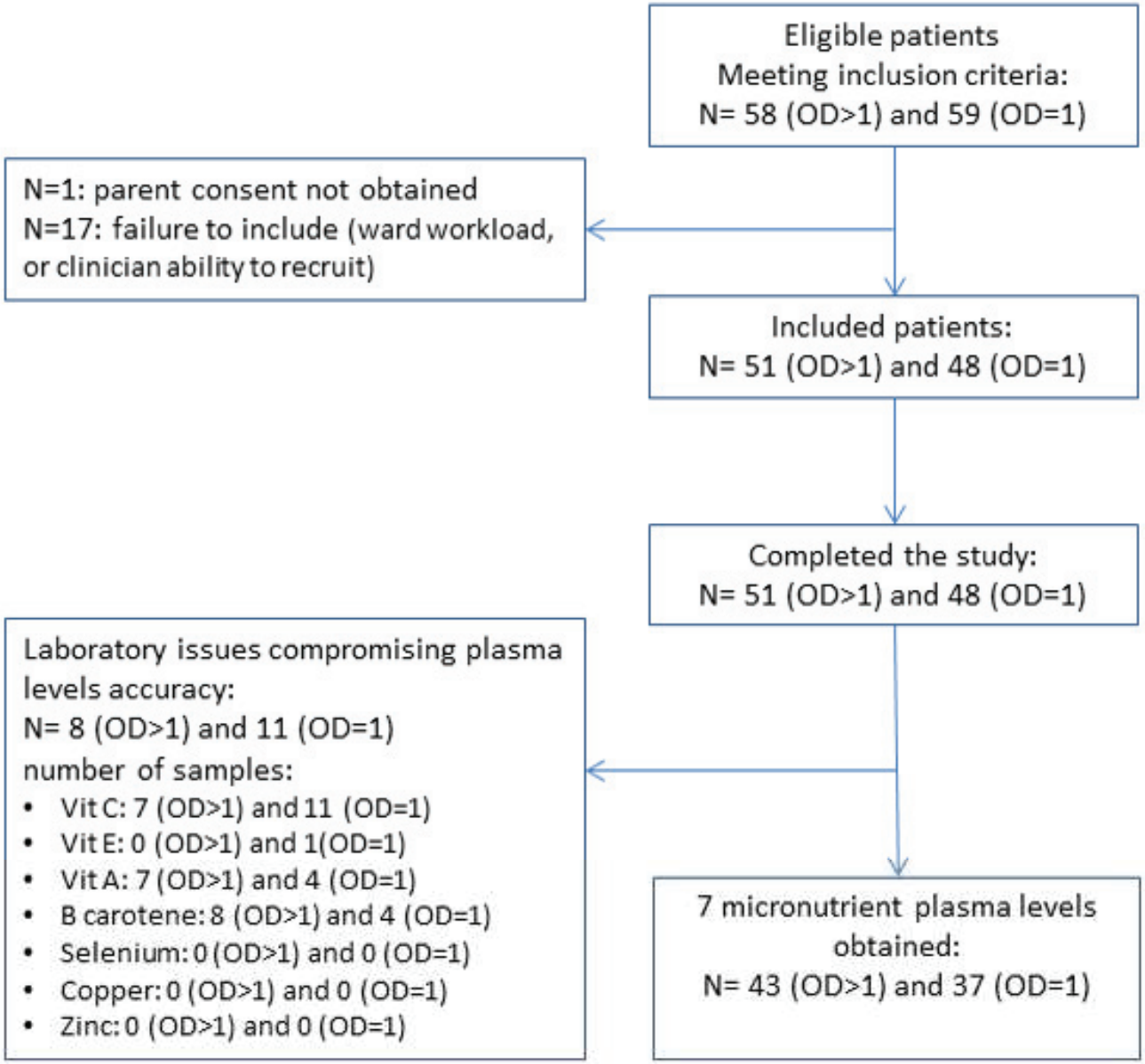
Eligible patients
Meeting inclusion criteria:
N= 58 (OD>1) and 59 (OD=1)
N=1: parent consent not obtained
N=17: failure to include (ward workload, or clinician ability to recruit)
Included patients:
N= 51 (OD>1) and 48 (OD=1)
Completed the study:
N= 51 (OD>1) and 48 (OD=1)
Laboratory issues compromising plasma levels accuracy:
N= 8 (OD>1) and 11 (OD=1)
number of samples:
• Vit C: 7 (OD>1) and 11 (OD=1)
• Vit E: 0 (OD>1) and 1(OD=1)
• Vit A: 7 (OD>1) and 4 (OD=1)
• B carotene: 8 (OD>1) and 4 (OD=1)
• Selenium: 0 (OD>1) and 0 (OD=1)
• Copper: 0 (OD>1) and 0 (OD=1)
• Zinc: 0 (OD>1) and 0 (OD=1)
7 micronutrient plasma levels obtained:
N= 43 (OD>1) and 37 (OD=1)

supplemental text : Supplemental Digital Content 1

Detailed measurement techniques

Vitamins A, E and beta-carotene analysis: Vitamins A and E and beta-carotene concentrations were measured by high-pressure liquid chromatography (HPLC) with Summit Dionex system (ThermoFisher Scientific, Courtaboeuf, France) and Chromeleon software (version 6.80, Thermo FisherScientific). Briefly, after precipitation of plasma proteins by ethanol, these vitamins and beta-carotene were extracted into hexane, evaporated under nitrogen and the dried residue was dissolved in methanol/ethanol (85/15, v/v). The eluate was analyzed by HPLC at 292, 325 and 450 nm, respectively, for vitamins E, A and beta-carotene measurements. Separation was carried out on an Adsorbosphere HS C18 3 mm (Interchim,Montlucon, France) held at 37°C, using a gradient elution system starting with 100% methanol-acetonitrile (40/60, v/v) and ending with a 100% mixture of methanol-acetonitrile-dichloromethane (46/30/24, v/v). Two internal standards were used to correct losses during liquid/liquid extraction: tocol for measurement of vitamins A, E; echinenone for measurement of beta-carotene.

Steghens JP, van Kappel AL, Riboli E, Collombel C. Simultaneous measurement of seven carotenoids, retinol and alpha-tocopherol in serum by high-performance liquid chromatography. J Chromatogr B Biomed Sci Appl 1997;694:71-81

Vitamin C analysis: Vitamin C concentration was measured by HPLC coupled to electrochemical detection with Summit Dionex system (ThermoFisher Scientific, Courtaboeuf, France) and Chromeleon software (version 6.80, Thermo FisherScientific).

Briefly, after stabilization of vitamin C with N-ethymaleimide (NEM) which blocked vitamin C in his reduced form and acidification of plasma aliquots with sulfosalycic acid 6%, aliquots of acidified and stabilized vitamin C were diluted in the mobile phase and injected in the chromatographic system. Separation was accomplished using isocratic elution with 12.5% methanol in 12 mmol/L ammonium acetate and 100 mmol/L EDTA, pH 3.8 on a BS-C13 column (CIL Cluzeau, Sainte Foy, France) at

37°C. No internal standard was used. Neither liquid/liquid nor solid/liquid extractions of vitamin C were performed. Plasma for vitamin C determination was just diluted in mobile phase and acidification solution.

Flourié F, Steghens JP. Plasma ascorbic acid: preanalytical factors and new HPLC method. Ann Biol Clin 2004;62:305-9

Glutathione analysis: Glutathione concentration was measured by HPLC coupled with mass spectrometry (Agilent Technologies, Venissieux, France) in positive electrospray ionization mode after a chromatographic separation on a 150mm×2mm stability 100 BS-C17 column (CIL Cluzeau, Sainte Foy La Grande, France). Measurement of glutathione was realized in whole blood after stabilization of glutathione by the used of N-ethymaleimide (NEM) which blocks glutathione in its reduced form avoiding the generation of artifactual high levels of glutathione disulfide. Briefly, after removing proteins by sulfosalycic acid 6%, stabilization of glutathione by 20 mM of N-ethylmaleimide (NEM) and adding gamma glutamyl-glutamic acid as an internal standard, heparinized whole blood was centrifuged at 10.000g during 10 minutes. Supernatant was diluted in mobile phase and injected into the chromatographic system. Elution was performed using a mobile phase containing MeOH/acetate ammonium buffer (8mM) adjusted to pH 2.7 (63/37, v/v) in an isocratic mode. Chromatograms were recorded in single ion monitoring $(M+H)^+$ at m/z 277 for gamma glutamyl-glutamic acid, at 308 for GSH, at 433 for GSH-NEM and 613 for GSSG for 10 minutes and integrated with Chemstation software (Agilent Technologies (version B.01.01)).

Steghens JP, Flourié F, Arab K, Collombel C. Fast liquid chromatography-mass spectrometry glutathione measurement in whole blood: micromolar GSSG is a sample preparation artifact. J Chromatogr B Analyt Technol Biomed Life Sci. 2003 Dec 25;798(2):343-9.

GPx analysis: Plasma GPx activity was measured by automatized spectrophotometry on heparinized samples using Randox© Kit Ransel. This method is based on that of Paglia and Valentine. Briefly, glutathione peroxidase (GPx) catalysis the oxidation of glutathione (GSH) by cumene hydroperoxide.

In the presence of glutathione reductase and NADPH the oxidized glutathione (GSSG) is immediately converted in his reduced form with a concomitant oxidation of NADPH to NADP+ allowing measuring the decreased in absorbance at 340 nm of NADPH.

Supplemental digital content table 1: micronutrient characteristics and measurement technique validities. Foreign children references are also presented.

	International units and conversion factor	Technique	Detection	Intra-assay CV	Inter-assay CV	International References values in children
Vitamin A (Retinol)	µmol/L x 286 -> µg/L	In house	UV 325 nm	1.40 µmol/L : 2.4 %	1.46 µmol/L : 3.8 %	0 - 1 years : 0.3 à 1.9 µmol/L [a]
				36 µmol/L : 1.2 %	3.13 µmol/L : 3.1 %	1 - 11 years : 1.0 - 1.6 µmol/L [a]
						11 - 16 years : 0.9 - 1.9 µmol/L [a]
						16 - 18 years : 1.0 - 2.6 µmol/L [a]
						12.5 - 17.5 years : 1.24 +/- 0,38 µmol/L [b]
Vitamin E α-Tocopherol	µmol/L x 0,414 -> mg/L	In house	UV 292 nm	17.5 µmol/L : 2.4 %	16.7 µmol/L : 3.9 %	0 - 2 years: 22.1 µmol/L [c]
				40.4 µmol/L : 1,1 %	37.2 µmol/L : 3.9 %	2 - 12 years: 20 µmol/L [c]
						12 - 18 years: 19.8 µmol/L [c]
						0 - 1 year: 5 - 50 µmol/L [a]
						1 – 18 years: 14.5 - 33 µmol/L [a]
						10 - 15 years: 21 µmol/L [d]
						12.5 - 17.5 years: 23 µmol/L [b]
β-Carotene	µmol/L x 0,537 -> mg/L	In house	Visible 450 nm	0.30 µmol/L : 4.0 %	0.26 µmol/L : 7.3 %	12.5 - 17.5 years : 0,46 +/- 0,32 µmol/L [b]
				0.54 µmol/L : 5.1 %	0.53 µmol/L : 7.8 %	
Vitamin C (Ascorbic acid)	µmol/L x 0,176 -> mg/L	In house	Electrochemical	36 µmol/L : 4.6 %	36 µmol/L : 8.4 %	12.5 - 17.5 years : 58,5 +/- 18,7 µmol/L [b]

				132 µmol/L : 2.1 %	120 µmol/L : 6.7 %	
Sélénium	µmol/L x 78,96 -> µg/L	SAAET	Absorption spectroscopy	0.34 µmol/L : 5,1 % 0.82 µmol/L : 3,6 %	0.69 µmol/L : 8 % 1.38 µmol/L : 4,6 %	0 - 1 years: 0.5 +/- 0.15 µmol/L [e] 1 - 6 years: 0.7 +/- 0.2 µmol/L [e] 7 - 18 years: 0.7 +/- 0.2 µmol/L [e]
Copper	µmol/L x 0,064 -> mg/L	ICP-OES	Emission spectroscopy	21.67 µmol/L : 3.2 % 39.87 µmol/L : 5.1 %	17.3 µmol/L : 3.9 % 49.80 µmol/L : 4.4 %	0 - 1 years: 11 +/- 5.5 µmol/L [f] 1 - 18 years: 19 +/- 1.6 µmol/L [g]
Zinc	µmol/L x 0,065 -> mg/L	ICP-OES	Emission spectroscopy	10.11 µmol/L : 5.1 % 39.20 µmol/L : 4 %	10.11 µmol/L : 7.9 % 39.20 µmol/L : 4.5 %	4 - 10 years: 17.85 +/- 0.18 µmol/L [h] 10 - 14 years: 18.1 +/- 0.7 µmol/L [h] 14 - 18 years: 17.55 +/- 0.05 µmol/L [h]

Table legend:

CV: coefficient of variation; SAAET: Electrothermal Atomic Absorption Spectrometry; ICP-OES: Inductively Coupled Plasma Atomic Emission Spectrometry; UV: ultra violet

[a] : Raizman JE. Et al. Pediatric reference value distributions for vitamins A and E in the CALIPER cohort and establishment of age-stratified reference intervals. Clin Biochem. 2014;47:812–5.

[b] : Breidenassel C. et al. Antioxidant vitamin status (A, E, C, and beta-carotene) in European adolescents - the HELENA Study. Int J Vitam Nutr Res Int Z Vitam-Ernahrungsforschung J Int Vitaminol Nutr. 2011;81:245–55.

[c] : Cuerq C, Restier L, Drai J, Blond E, Roux A, Charriere S, et al. Establishment of reference values of α-tocopherol in plasma, red blood cells and adipose tissue in healthy children to improve the management of chylomicron retention disease, a rare genetic hypocholesterolemia. Orphanet J Rare Dis. 2016;11:114

[d] : Herbeth B. et al. Determinants of plasma retinol, beta-carotene, and alpha-tocopherol during adolescence. Am J Clin Nutr. 1991;54:884–9.

[e] : Broman M. et al. Low serum selenium is associated with the severity of organ failure in critically ill children. Clin Nutr [Internet]. 2017 Jun [cited 2018 Mar 17]; Available from: http://linkinghub.elsevier.com/retrieve/pii/S026156141730225X

[f] : Salmenperä L. et al. Cu nutrition in infants during prolonged exclusive breast-feeding: low intake but rising serum concentrations of Cu and ceruloplasmin. Am J Clin Nutr. 1986;43:251–7.

[g] : local laboratories data (unpublished)

[h] : Malvy DJ. et al. Reference values for serum zinc and selenium of French healthy children. Eur J Epidemiol. 1993;9:155–61.

3. Discussion

La malnutrition, sous toutes ses formes, globale ou compartimentale, statique ou dynamique, est une entité fréquente chez l'enfant sévèrement agressé. Par ailleurs, un statut nutritionnel altéré à l'admission est associé à un moins bon devenir. Enfin, la dénutrition acquise en cours de séjour en réanimation pédiatrique, globale ou musculaire, est un phénomène précoce, intense et presque constant.

3.1. L'évaluation nutritionnelle bien que complexe et imprécise reste nécessaire

La dénutrition est fréquente, quelle qu'en soit sa forme. Pourtant, son dépistage est rarement ou mal conduit dans les unités de réanimation pédiatrique. En effet, au-delà de la méconnaissance de la problématique nutritionnelle globale, les professionnels de santé font face à des difficultés pour réaliser les mesures anthropométriques nécessaires à cette évaluation nutritionnelle. La justification couramment avancée est celle de la mise en jeu de la sécurité du patient lors de sa mobilisation, pour la pesée notamment (34,55,56). Or, une étude a montré qu'un programme de formation dédié pouvait permettre une amélioration des connaissances relatives à la nutrition, mais aussi du pourcentage d'enfants bénéficiant d'une évaluation nutritionnelle complète, incluant ces mesures anthropométriques (35). Rappelons néanmoins que chacune des mesures anthropométriques a ses biais de mesure et ses limites d'analyse, qui obligent le clinicien à rester critique dans l'interprétation des valeurs recueillies. L'équipement optimisé du service (lits avec système de pesée intégré) pourrait aider ; définir la meilleure façon de mesurer, d'extrapoler ou d'estimer la taille devrait être étudié également. Enfin, nous ne disposons pas à ce jour de score de risque nutritionnel validé chez l'enfant en réanimation pédiatrique : en effet, ni les scores de réanimation adulte, comme le NUTRIC Score ou le NRS 2002 (1,107–109), ni les scores de pédiatrie générale ne sont applicables (Joosten 2014) : parmi eux, StrongKid, PYMS (Pediatric Yorkshire Malnutrition Score), STAMP (Screening Tool for the Assesment of Malnutrition in Pediatrics), SGNA (Subjective Global Nutritional Assesment for children), SRNP (Score de Risque Nutritionnel Pédiatrique), NRS (Nutrition Risk Score) (110–117). Ainsi, le SRNP classerait quasiment chaque enfant de réanimation pédiatrique comme à haut risque nutritionnel, et se révèle peu discriminant (116). Nous ne disposons pas plus de normes adaptées pour les outils paracliniques (Impédancemétrie, IRM, Scanner, DEXA) permettant une évaluation nutritionnelle simple, peu coûteuse et compatible avec les caractéristiques inhérentes au patient de réanimation. L'évaluation subjective est quant à elle peu précise, et la seule échelle validée s'avère finalement complexe à mettre en place (115,118,119).

3.2. Evolution de la masse musculaire et faiblesse acquise en réanimation pédiatrique

L'évaluation globale du statut nutritionnel ne peut être considérée comme suffisante, même si elle est déjà en elle-même associée au pronostic. En effet, le seul calcul des indices de dénutrition (IMC, RPA, RTA, RPT) différenciera mal les sujets présentant une masse musculaire importante ou faible. Ceci est particulièrement problématique dans les populations pédiatriques atteintes de pathologies chroniques invalidantes : les enfants atteints de paralysie cérébrale ou de maladies neuro-musculaires et non-marchants, qui constituent une part importante du recrutement de réanimation pédiatrique aujourd'hui, ont une masse musculaire réduite (120) ; or, les modifications métaboliques profondes du métabolisme, lors de l'agression sévère et qui caractérisent les patients de réanimation, puisent précisément leurs ressources dans le pool d'acides aminés musculaires, afin d'assurer la néosynthèse protéique et la production énergétique endogène (121). Chez l'adulte en réanimation, il a été montré que la masse musculaire mesurée à l'admission était inversement associée à la mortalité, alors que l'IMC ne l'était pas (85,122). Les études pédiatriques similaires font aujourd'hui défaut, mais la validation d'outils tels que l'échographie musculaire du quadriceps femoris présentée dans ce travail de thèse rendra possible leur développement futur.

3.3. Statut nutritionnel et devenir : cause, conséquence, ou simple association ?

L'impact de la malnutrition à l'admission en réanimation pédiatrique a également été montré chez l'enfant, en dehors du contexte de réanimation, avec une augmentation des durées de séjour, des coûts hospitaliers et des infections nosocomiales (43,123–125). L'association significative et indépendante retrouvée entre malnutrition à l'admission et pronostic péjoratif chez l'enfant en réanimation est étayée par la physiopathologie (ressources musculaires essentielles lors de l'agression) décrite précédemment et qui propose un rationnel permettant d'expliquer cette relation (notamment par déficit de masse maigre) (42,121,126–130). Néanmoins, concernant la dénutrition acquise en cours de séjour, globale et/ou musculaire, le lien décrit avec la durée de séjour tient probablement d'une relation à double sens : la sévérité de la pathologie responsable de l'admission en réanimation influence la durée de séjour et favorise la dénutrition, de la même façon que la dénutrition pourra prolonger la durée de recours à une ventilation mécanique et la durée de séjour.

3.4. Statut nutritionnel et coopération multidisciplinaire en amont de la réanimation

Le lien démontré entre la cassure des courbes de croissance avant l'admission et le pronostic péjoratif est également retrouvé dans la population pédiatrique en dehors du contexte de réanimation (43,125,131,132) ; cette donnée fait d'ailleurs partie des critères permettant le calcul de certains scores nutritionnels pédiatriques. En ce qui concerne les enfants de réanimation, cette association encourage à prendre en charge cet aspect de dénutrition en amont de l'admission en réanimation, lorsque cela est envisageable. Ainsi, il est

probablement préférable de décaler une chirurgie lourde non urgente, après instauration d'un support nutritionnel et/ou correction d'une dénutrition diagnostiquée, comme proposé dans les recommandations de nutrition péri opératoire adultes (133). Un syndrome de renutrition pourrait par ailleurs être évité. Il est donc indispensable de sensibiliser les acteurs de la prise en charge chronique des patients afin que l'évaluation nutritionnelle et la prise en charge de la dénutrition fassent partie intégrante du parcours de soin de l'enfant à l'hôpital, et avant son admission en réanimation.

3.5. Statut nutritionnel et coopération multidisciplinaire en aval de la réanimation

La dénutrition acquise en réanimation pédiatrique et plus encore la fonte musculaire aiguë de l'enfant sévèrement agressé, font partie intégrante du syndrome de faiblesse musculaire acquise en réanimation pédiatrique. Ce syndrome correspond à une maladie neuro-musculaire à part entière, acquise mais réversible (80,81). Elle associe une myopathie (bilatérale, prédominant aux racines des membres, flasque) à une neuropathie (avec atteinte des nerfs périphériques et diaphragmatique) (76,134). Elle retentit à court terme sur la durée de ventilation et de séjour hospitalier, à moyen terme sur le délai de rééducation et d'autonomisation, et à plus long terme sur la scolarisation, la socialisation, la qualité de vie et la vie familiale (92). Il est primordial de sensibiliser les équipes d'aval de réanimation pédiatrique afin de mettre en place une stratégie multidisciplinaire à même d'évaluer, suivre et prendre en charge la dénutrition et la faiblesse acquises en réanimation pédiatrique. Elle doit associer une stratégie nutritionnelle visant à rattraper la cassure des courbes de croissance (action conjointe du diététicien, du pédiatre, des puériculteurs), à une stratégie de rééducation fonctionnelle (kinésithérapeutes, pédiatres, médecins rééducateurs, orthophonistes, psychomotriciens, psychologues, etc.). Plus globalement, sa prise en charge devrait s'intégrer dans le suivi post réanimation et la prévention du syndrome de stress post traumatique.

3.6. Statut nutritionnel et prise en charge multidisciplinaire en réanimation

La malnutrition est une problématique fréquente de réanimation pédiatrique, à l'admission et en cours de séjour. Ses conséquences sont néfastes sur le pronostic. Cela incite donc à mettre en place dès le séjour en réanimation une prise en charge nutritionnelle adaptée, ayant pour objectif, plus que de corriger ou empêcher la dénutrition, d'en limiter l'intensité. La stratégie idéale n'est pas encore parfaitement définie, et les recommandations pédiatriques de 2017 de la société américaine de nutrition parentérale et entérale (ASPEN) et de la société de réanimation (SCCM) restent de très faible niveau de preuve (6). Il en ressort néanmoins que :

- Une évaluation nutritionnelle à l'admission et en cours de séjour est nécessaire
- Une nutrition entérale précoce est recommandée
- Une augmentation progressive de cette nutrition entérale sur 5 à 7 jours est préconisée pour atteindre la cible énergétique et limiter le déficit énergétique

- La cible énergétique est idéalement déterminée individuellement par calorimétrie indirecte, et à défaut en utilisant les équations validées en pédiatrie (équations de Schofield)
- La cible protéique est augmentée par rapport à celle de l'enfant sain (1,5 g/kg/j) et doit être atteinte précocement
- La nutrition entérale est l'approche à privilégier, en site gastrique en première intention
- La nutrition parentérale ne doit pas être débutée dans les 24 premières heures, mais au-delà, d'autant plus s'il s'agit d'une nutrition parentérale de complément
- L'utilisation de protocoles locaux et le recours à une équipe support de nutrition aide à atteindre les objectifs nutritionnels fixés
- La pharmaco-nutrition n'est pas recommandée

Certaines de ces stratégies pourraient améliorer les durées de séjour et la mortalité ; elles mériteraient des études de haut niveau de preuve, conduites sur de larges cohortes.

En ce qui concerne la supplémentation protéique, dont on attend une action sur la diminution du catabolisme musculaire, il a été montré que le fait d'apporter plus de 60% de l'objectif protéique améliorait la survie à J60. En revanche l'étude PEPaNIC a montré une augmentation de la mortalité chez les patients recevant une nutrition parentérale très précoce (J1) systématique, par rapport à une nutrition parentérale très tardive (J8) quelle que soit la nutrition entérale reçue (135–139). Il faut relever que le groupe « parentérale précoce » atteignait les objectifs énergétiques et protéiques totaux dès J3 pour les dépasser au-delà, alors que le groupe « parentérale tardive » atteignait les objectifs en respectant le délai proposé par les recommandations américaines récentes (6,140). Cette étude a donc davantage comparé normo-nutrition et sur-nutrition par adjonction de nutrition parentérale systématique. Cependant, l'analyse secondaire conduite pour tester le rôle respectif de chaque macro-nutriment a étonnamment révélé une absence d'effet délétère des lipides et des hydrates de carbone, l'effet sur le pronostic péjoratif étant à mettre sur le compte de l'administration précoce d'acides aminés (141). Les auteurs expliquent ces résultats par le concept d'inhibition par les acides aminés de l'autophagie intra-cellulaire (142–144). En somme, il est possible que la temporalité des apports en protéines ou acides aminés soit importante, de même qu'il est possible que l'amino-acidogramme des solutions de nutrition entérale et parentérale ait un impact différent. Peut être devrait on limiter les apports protéiques à la phase aiguë de l'agression, et les augmenter ensuite drastiquement au-delà des apports de l'enfant sain. L'étude de Koekkoek et al. a d'ailleurs montré un devenir meilleur dans un groupe de patients adultes traités avec des doses de protéines entérales faibles puis élevées, par rapport à un groupe recevant d'emblée des apports élevés ; le troisième groupe recevant des apports faibles présentait le moins bon pronostic (145).

En ce qui concerne la supplémentation en micro-nutriments, il faut probablement en apporter à doses physiologiques au quotidien, pour éviter l'apparition de carences (6). Le

syndrome de renutrition est bien entendu un cas à part où la carence préalable majeure est démasquée lors de la renutrition ; il justifie une supplémentation intensive (146–157). En revanche, aucune étude pédiatrique ne justifie l'utilisation des micro-nutriments à doses supra-physiologiques comme pharmaco-nutriments. Néanmoins, ceci mériterait d'être exploré au travers d'études mieux construites, sélectionnant des patients carencés en micronutriments ou suffisamment agressés pour présenter une mobilisation majeure de leur pool de micronutriments.

3.7. Le statut nutritionnel comme critère de jugement dans les études interventionnelles

Nous ne disposons pas à ce jour d'étude pédiatrique ayant évalué l'effet de ces stratégies nutritionnelles sur le pronostic en termes d'effet sur le statut nutritionnel, global ou musculaire, ni sur la faiblesse acquise en réanimation pédiatrique, ni sur le plus long terme (réhabilitation, qualité de vie, etc.). En effet, le statut nutritionnel fait rarement partie des éléments de pronostic étudiés dans les études conduites en réanimation pédiatrique.

3.8. Le support nutritionnel : importance de la temporalité et de l'intégration à une stratégie plus large.

La sous-nutrition est reconnue comme délétère, mais la sur-nutrition l'est également. Par ailleurs, le stress métabolique évolue en même temps que la gravité et le contrôle de la pathologie sous-jacente conduisant l'enfant en réanimation ; l'approche nutritionnelle devra probablement être adaptée à chacune des phases (aiguë, stable et récupération), précisément pour éviter ces ceux écueils (2,42,121).

Enfin, la nutrition ne peut opérer seule, et devrait être associée à une approche de mobilisation passive, et active dès que possible, dans une stratégie globale de réhabilitation précoce, associant l'ensemble des professionnels de santé impliqués en réanimation pédiatrique (kinésithérapeutes, infirmiers, médecins, etc.) (1). La littérature pédiatrique reste néanmoins très pauvre à ce sujet.

4. Conclusion

L'évaluation systémique du statut nutritionnel est recommandée en réanimation pédiatrique, la malnutrition, dans la plupart de ses formes, étant associée à un moins bon pronostic dans ce contexte particulier. Cette recommandation de l'ASPEN et de la SCCM (6) fera également partie des guidelines européennes de nutrition de l'ESPNIC (European Society of Paediatric and Neonatal Intensive Care) dont la publication est attendue prochainement. De même, la définition de l'état de dénutrition des recommandations HAS (publiées prochainement) évolue et inclura dorénavant une recherche étiologique.

Par ailleurs, l'homogénéisation des méthodes utilisées pour cette évaluation nutritionnelle nécessite de maitriser les techniques et outils décrits dans ce travail de thèse, validés et recommandés dans cette population, tout en intégrant les erreurs de mesure inhérentes à leur application chez l'enfant sévèrement agressé.

Cela permettra d'évaluer l'effet de stratégies nutritionnelles, idéalement couplées à des approches de mobilisation précoce, sur des critères prenant en compte le statut nutritionnel, à court, moyen et long terme. Notamment, la faiblesse acquise en réanimation pédiatrique pourrait être mieux décrite, de même que l'impact potentiel qu'auraient sur elle ces approches thérapeutiques. Bien entendu, il faudrait associer à l'évaluation du statut nutritionnel une évaluation fonctionnelle, testant la force musculaire, la fonction musculaire et le retentissement sur le cadre de vie élargi. Les outils de cette évaluation fonctionnelle restent à valider dans cette population hétérogène pédiatrique.

D'autres questions en lien direct avec le statut nutritionnel mériteraient qu'on leur consacre une démarche scientifique de recherche solide ; parmi elles, plusieurs seront conduites dans un futur proche par le NutriSIP, groupe francophone de nutrition en soins intensifs pédiatrique :

- Evaluation de l'impact de l'obésité sur le devenir ; « l'obesity paradox » de l'adulte s'applique-t-il chez l'enfant ? Une méta-analyse des études permettrait de mieux appréhender les résultats très différents retrouvés dans les différentes études publiées
- Quelle est la meilleure technique d'extrapolation/estimation de la taille chez l'enfant de réanimation pédiatrique ? Une étude multicentrique testant 15 modalités différentes doit commencer prochainement en France, Belgique, Suisse et Liban.
- Facteurs associés à la déplétion en micro-nutriments à l'admission en réanimation pédiatrique. Une analyse secondaire de la base de données de l'étude décrite dans ce travail de thèse est prévue.
- Evaluation de la dépense énergétique totale mesurée par eau doublement marquée chez les nourrissons atteints de bronchiolite aiguë et sous support ventilatoire non invasif.

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