Review Article

Energy expenditure in critically ill children

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Abstract: In critically ill children, optimal nutritional intake can improve recovery. During stay in the pediatric intensive care unit (PICU), both underfeeding and overfeeding have to be avoided. The assessment of energy requirements is difficult during critical illness because of lack of devices to measure it. In addition, energy requirements vary during the different phases of critical illness; i.e. the acute, stable and recovery phase. Energy expenditure is affected by the illness itself, but also by the conditions of the PICU such as mechanical ventilation, sedation, fever and the lack of physical activity. During the acute phase, energy intake has to be increased gradually while not exceeding resting energy expenditure (REE). The latter may be estimated using the Schofield equation or ideally be measured using a validated indirect calorimeter. After the acute phase, energy intake has to be increased to enable recovery and growth. The aim of this review is to give an overview of the current knowledge concerning REE in critically ill children and factors that may affect REE. The principles of measurement or calculation of REE will be described. The available evidence will be synthesized and practical recommendations will be provided for guiding energy intake during the different phases of illness.

Keywords: Critical care; pediatrics; energy expenditure; indirect calorimetry (IC); nutrition

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Introduction

In critically ill children, adequate energy intake is associated with improved clinical outcome (1-3). The determination of energy requirements throughout stay in the pediatric intensive care unit (PICU) is challenging and both underfeeding and overfeeding have to be avoided. Energy requirements are depending on the different phases of illness (i.e., the acute, stable and recovery phase) and may be affected by the severity of illness and by factors such as sedation, muscle relaxants, mechanical ventilation and fever. To determine the energy requirements of critically ill children, resting energy expenditure (REE) is measured with indirect calorimetry (IC) or otherwise calculated using a predictive equation, and if needed, disease and activity factors are considered.

Measurements of REE by IC in critically ill children

Components of total energy expenditure (TEE) in healthy children

In healthy children, the TEE expended by children over 24 hours is made up by the basal metabolic rate (BMR), the thermic effect of food, physical activity, growth and, rarely, cold-induced thermogenesis (4). The BMR is the main component of TEE, and can be considered as the sum of the energy expenditure of the various organs and tissues of the body (4,5). BMR—expressed in kcal/kg of body weight per day—is high in infants and young children due to their body composition with a relatively large proportion of organs with high metabolic rate. The energy needed for growth results from energy expenditure of protein and lipid synthesis and energy deposition in newly formed tissues (4).

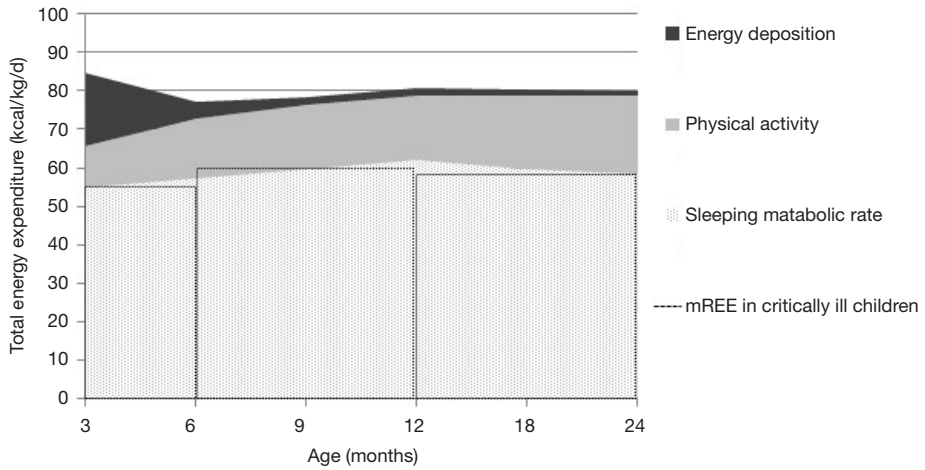

Figure 1 Total energy expenditure in children aged 3–24 months [data from Butte *et al.* (6)] and REE in critically ill children on mechanical ventilation measured by indirect calorimetry [mREE; data from Jotterand Chaparro *et al.* (7)]. Adapted from Jotterand Chaparro 2016. REE, resting energy expenditure.

Table 1 Respiratory quotient (RQ) and calorimetric values associated with oxidation of common macronutrients (for 1 gram of macronutrient) (8)

Substrate	RQ	Caloric value (kcal/g)	O_2 consumption (L/g)	CO_2 production (L/g)
Glucose	1.00	4.18	0.829	0.829
Protein	0.81	4.32	0.966	0.782
Fat	0.71	9.46	2.019	1.427

This expenditure is particularly important in rapidly growing infants (approximately up to the age of 12 months) and during puberty (6). As a result, TEE is high in young children in comparison to older children and adults, as illustrated in *Figure 1*.

Precise measurement of BMR requires very strict conditions i.e. fasting for at least 12–14 hours, being awake, supine, resting comfortably, not having done strenuous exercise in the preceding day, etc. (4). These conditions are rarely achieved. Therefore, most studies measure the REE—the energy expended when the body is at rest, with no extra energy used for muscular effort (4). REE is usually slightly higher (up to 10%) than BMR and is often used as a proxy for BMR.

Main principles of measurement of REE with IC

For measurement of the REE in clinical practice, IC remains the reference method. The principle of IC is that energy production by substrate oxidation in the body is coupled to oxygen consumption (VO_2) and carbon dioxide production (VCO_2) (8). The ratio between VCO_2 and VO_2 associated with metabolic processes at the cellular level is called the respiratory quotient (RQ): RQ = VCO_2/VO_2 (8). The RQ and the energy released depend on the particular substrate that is oxidized, as described in *Table 1*. For instance, the stoichiometric equation for the oxidation of 100 gram of glucose is as follows (8):

$$C_6H_{12}O_6 + 6O_2 = 6CO_2 + 6H_2O + 673\ kcal\ (RQ = 1) \quad [1]$$

To calculate REE from VO2 and VCO2, various formulas have been developed. The Weir formula is the most commonly used (9):

$$REE\ (kcal/d) = 5.50\ VO_2\ (mL/min) + 1.76\ VCO_2\ (mL/min) - 1.99\ total\ urinary\ nitrogen\ (g/d) \quad [2]$$

IC measures REE over a brief period (30 minutes–two hours) under strict conditions, and this value is mostly used for the REE over 24 hours.

Practical use of IC measurement in PICU

To determine energy expenditure in critically ill children and guide nutritional support, the European Society of Pediatric and Neonatal Intensive Care (ESPNIC) and the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N) recommend to measure REE, using a validated indirect calorimeter, after the acute phase of critical illness (10,11). For targeting patients who could be a candidate

Table 2 Criteria proposed by the A.S.P.E.N to identify patients who are suggested candidates for IC measurement during the PICU stay (12)

Underweight (BMI <5th percentile for age), at risk of overweight (BMI >85th percentile for age) or overweight (BMI >95th percentile for age)
Children with >10% weight gain or loss during ICU stay
Failure to consistently meet prescribed caloric goals
Failure to wean, or need to escalate respiratory support
Need for muscle relaxants for >7 days
Neurologic trauma (traumatic, hypoxic and/or ischemic) with evidence of dysautonomia
Oncologic diagnoses (including children with stem cell or bone marrow transplant)
Children with thermal injury
Children requiring mechanical ventilator support for >7 days
Children suspected to be severely hypermetabolic (status epilepticus, hyperthermia, systemic inflammatory response syndrome, dysautonomic storms, etc.) or hypometabolic (hypothermia, hypothyroidism, pentobarbital or midazolam coma, etc.)
Any patient with ICU LOS >4 weeks may benefit from IC to assess adequacy of nutrient intake

IC, indirect calorimetry; PICU, pediatric intensive care unit.

Table 3 Predictive equations of Schofield using weight (21)

Age (years)	Girls	Boys
<3	58.317 × W – 31.1	59.512 × W – 30.4
3–10	20.315 × W + 485.9	22.706 × W + 504.3
10–18	13.384 × W + 692.6	17.686 × W + 658.2

W = weight in kg.

for IC measurement, a list of 11 criteria has been proposed (*Table 2*) (12). It has been shown that according to these criteria, more than 70% of children admitted to the PICU would require IC measurement (13).

Measuring REE with IC requires financial, technical and human resources, which may explain why only a small minority of PICUs make use of an indirect calorimeter (10–17% of PICUs worldwide) (1,14-16). In ventilated patients, some conditions such as high inspired oxygen concentrations, potential leaks around the endotracheal tube or humidity may lead to inaccurate measurements. Clinicians must ensure that conditions for accurate calibration of the device and valid measurement at bedside are achieved. Until recently, the majority of PICUs used the Deltatrac II, (Datex-Ohmeda, Helsinki, Finland), which has been validated in critically ill adults and children (17-19). However, this device is no longer being manufactured. Currently, among the available indirect calorimeters used in adults (M-COVX, Datex-Ohmeda, Finland; Quark RMR and Q-NRG+, Cosmed, Italy, and CCM Express, Medical Graphics Corp, UK), none has been validated in ventilated critically ill children. Thus, a validated calorimeter is urgently needed for the pediatric population including new-born and infants and those with high inspired oxygen concentrations (up to 60–70%).

Estimation of REE by predictive equations in critically ill children

Available predictive equations in healthy children

As an alternative for REE measurement with IC, predictive equations can be used to estimate REE. Various equations exist and most of them are based on age, sex, body weight and height. To estimate REE in critically ill children, international nutritional guidelines (10,11,20) recommend to estimate REE using the Schofield equation, with an accurate weight (21). *Table 3* shows the Schofield equation for boys and girls, divided by different age categories.

Validity of the commonly used predictive equations of REE in critically ill children

According to a worldwide survey (15), most PICUs estimate REE using the common predictive equations of Schofield (25%) (21), the equation of the World Health Organization (25%) (5) and, more surprisingly, the equation of Harris-Benedict (17%) (22).

The validity of Schofield equations (21) has been evaluated in a number of studies in critically ill children (23).

The findings showed that the two Schofield equations [along with Talbot tables (24)] compared with many other equations were the least inaccurate (23). However, prediction of REE within ±10% compared to REE measured by IC (mREE) was only noticed in about 35% of children. These equations may underestimate REE in young children and overestimate it in older children (25).

Nutritional guidelines (10,11) recommend not using the Harris-Benedict equation (22) in critically ill children, as there is strong evidence that this equation, developed for healthy adults, overestimates REE in the large majority of children and leads to a risk of overfeeding.

Validity of specific equations developed to estimate REE in ventilated critically ill children

Some equations have been designed for populations with specific diseases or conditions including ventilated critically ill children; namely the equations of White *et al.* in 2000 (26), Meyer *et al.* in 2012 (27) and Mehta *et al.* in 2015 (28). A few studies have assessed the validity of the equations of White (26) and Meyer (27), and showed that these equations were inaccurate (23,25,29). The equation developed by Mehta *et al.* (28) in 2015 seems promising. This equation is not a traditional equation, as it requires measurement of VCO_2 and it uses a fixed RQ of 0.89 in the Weir formula (9). A recent study conducted in children after cardiopulmonary bypass showed that the most important determinant of its bias was the RQ (30). Another group demonstrated that estimating REE with this equation, using VCO_2 measured by the Servo-I® with the Capnostat-III sensor, was accurate for children weighing more than 15 kg, but not for smaller children (31). The main problem in children weighing less than 15 kg was that the used sensor did not measure the VCO_2 accurately enough. Thus, future studies need to assess the validity of this equation, and in parallel, a sensor for children weighing less than 15 kg needs to be developed.

Influence of critical care conditions on REE in critically ill children

Energy expenditure in critically ill children

Critically ill patients are lying in bed in a thermoneutral environment, are not physically active, sedated and regularly mechanically ventilated. Therefore, energy expenditure is lower than in healthy children (*Figure 1*) and it is often assumed that TEE is equal to REE in the acute phase of disease. Several studies, with the large majority conducted in children on mechanical ventilation, have investigated which factors during intensive care treatment might influence individual energy expenditure (*Table 4*).

Day-to-day variability of REE in mechanically ventilated children

In mechanically ventilated children with various medical and surgical diagnoses, no clinically significant day-to-day changes in mREE were observed in the first week after PICU admission (7,37,38,50,51,64). This implies that intra-individually, mREE does not change significantly during this period on mechanical ventilation.

Body temperature

Body temperature has been found to be the most important factor to influence mREE within the individual patient (26). In a study of 74 critically ill, mechanically ventilated children, every increment of degree Celsius increased mREE by 8% (7). Other studies have also shown this positive correlation with factors per degree Celsius ranging from 6% to 8% (29,33,34).

Drugs

Sedatives and vasoactive drugs are frequently used in critically ill children and have been reported to influence mREE (29,37). In a study of 57 mechanically ventilated children aged 9 months to 15.8 years, mREE was lower than REE estimated by predictive equation in 82% of children when sedation was used (29). However, these results were not reported in other studies (35,36). In a few studies of mechanically ventilated children, the use of muscle relaxants decreased mREE from 6% to 10% (7,29,39) and in one study even up to 36% (35). In some other studies, the use of muscle relaxants did not influence mREE (37,38,40).

Diet induced thermogenesis

It has been postulated that the amount and manner of nutritional support influences energy expenditure in critically ill patients, however no effect has been shown in studies so far (29,35). This might be due to the use of continuous nutritional support in many studies.

Table 4 The effect of several factors on mREE (only percentages given if studies showed consistent results)

Factor	Increase or decrease	Percentage change in relation to mREE	References
Physical activity	↑	20%	(32)
Body temperature, per ℃	↑	Up to 8%	(7,29,33,34)
Sedatives	↓/–	–	(29,35,36)
Muscle relaxants	↓/–	–	(7,29,35,37-40)
Specific diseases			
Surgery	–	–	(41-46)
	↑	Up to 15%, post-admission in infants	(47-49)
Sepsis	–	–	(32,36,50-52)
	↑	Up to 40% during the recovery phase in neonates	(52,53)
Traumatic brain injury	↑/–	–	(34,54-56)
Trauma	↑/↓	–	(54,57,58)
Burns, acute phase	↑	Up to 80%	(59-63)
Burns, recovery phase	↑	Up to 15%	(59,62,63)

↑ increase, ↓ decrease, – no change. REE, resting energy expenditure.

Physical activity

In one study of seven critically ill children, TEE was measured with the double labeled water method during six days at the PICU (32). TEE was 20% higher than REE. This increased energy expenditure was related with activity recorded with accelerometry (32). This means that physical activity levels should be accounted for in calculating total energy requirements in critically ill children who stay at least one week at the PICU.

Specific diseases

Surgery

In infants admitted in PICU after surgery, a few studies have found an increase in mREE immediately after surgery with a peak at 4 hours for up to 15% (47-49). This increase was only temporarily (47-49) and mREE returned rapidly to levels comparable to preoperatively (41-43). In studies including older children, mREE did not increase after surgery (44-46).

Sepsis

In a study of ten spontaneously breathing septic neonates, an increase of 20% in mREE (mean value of 57±3 kcal/kg per day) was found on days 1–3 after the onset of sepsis compared with healthy controls and 15% on day 4 (53). In another study of 19 septic neonates, mREE increased from 49±13 kcal/kg per day during the acute phase to 68±11 kcal/kg per day during the recovery phase of sepsis (52). According to the authors, this was probably due to the resumption of growth. In older children with sepsis, mREE was not different compared to critically ill children with other diagnoses or healthy controls (32,36,50,51).

Traumatic brain injury

Although two studies in the eighties have found increased mREE of up to two times predicted REE in children after severe traumatic brain injury (54,55), more recent studies did not show such hypermetabolic state (34,56). The authors of the latter studies suggested that this might be due to differences in treatment, as guidelines have evolved over the years concerning sedation, paralysis and temperate control of these patients. In this group, REE might be dependent on the phase of disease and the neurologic state of the individual patient.

Trauma

Only a few studies have measured REE in children after severe trauma in different populations and found both decreased and increased mREE (54,57,58).

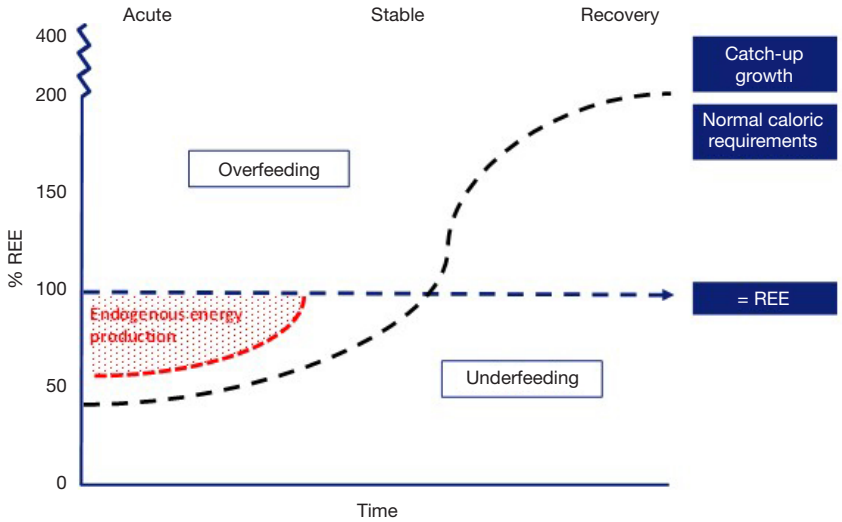

Figure 2 Energy requirements during different phases of critical illness; % of REE. Acute phase: first phase after event, characterized by requirement of (escalating) vital organ support. Stable phase: stabilization or weaning of vital organ support, while the different aspects of the stress response are not (completely) resolved. Recovery phase: clinical mobilization with normalization of neuro-endocrine, immunologic and metabolic alterations. Adapted from Joosten *et al*. (70). REE, resting energy expenditure.

Burns

A recent systematic review in critically ill adults and children has concluded that percentage of body surface area burn and post burn day were both associated with mREE (65). Some studies observed an increase of mREE in children with burns for up to 180% compared to predicted REE in the acute phase (59-63). Moreover, although REE decreased upon recovery, mREE remained significantly higher (up to 15%) compared to predicted REE up to months and even years postburn (59,62,63). This hypermetabolic state is considered to be mediated by increased pro-inflammatory cytokines (61,66,67), catecholamines and stress hormones (61,62) in burn patients.

In conclusion, these studies show that the main factors that may influence REE in critically ill children are body temperature and physical activity. Moreover, burns may have a significant clinical impact on energy expenditure.

Optimal energy intake in different phases of disease using REE

Energy requirements in the acute and stable phases of critical illness

The acute phase is characterized by the requirement of vital organ support and is accompanied by a stress response, resulting in hypercatabolism (68). The pathways of energy production during the acute phase of critical illness are altered and alternative substrates are used as a result of the loss of control of energy substrate utilization by their availability. Traditionally, overfeeding and underfeeding were defined as the percentage of energy delivery related to the mREE; an intake of >110% mREE indicated overfeeding and an intake of <90% mREE indicated underfeeding (69). However, during the acute phase of critical illness, endogenous production of energy provides the majority of energy requirements (up to 75%), irrespective of the exogenous provided amount of energy (*Figure 2*) (71). This results in a considerable risk for an energy imbalance, which is associated with poor outcome.

In a recent retrospective study, patients that were overfed (>110% mREE) had a significant longer PICU and hospital stays compared to those who were adequately fed (90–110% mREE) (72). Moreover, in a large multicenter randomized controlled trial it was shown that withholding parenteral nutrition (PN) until day 8 of admission, as compared with starting PN early (<24 hours) when enteral nutrition (EN) was insufficient, and thereby accepting significantly lower energy intakes compared to predicted REE, significantly decreased nosocomial infection and accelerated recovery (2).

New PICU guidelines advocate that in the acute phase of critical illness energy intake should not exceed REE (10,11). Furthermore, it is recommended to increase EN

Table 5 Prescribing nutrition in different phases of disease

Phase	Enteral nutrition	Parenteral nutrition	Energy target
Acute phase	Increase EN in stepwise manner	No PN	Do not exceed 100% REE
Stable phase	Increase EN further, if possible	Start PN >1 week after PICU admission, if energy targets are not met	Increase of %REE depending on age and disease
Recovery phase	Increase EN further, if possible	Continue PN if necessary to achieve energy targets	Up to 200% REE (and occasionally up to 400% REE). Target for (catch-up) growth

EN, enteral nutrition; PN, parenteral nutrition; REE, resting energy expenditure.

in a stepwise fashion until delivery goal is achieved using a feeding protocol or guideline and to target an energy intake by the end of the first week in the PICU of at least two-thirds of the daily energy requirements (*Table 5*) (10,11). These guidelines are based on observational studies that showed better clinical outcomes in patients who received adequate nutritional intake (1,3,72). However, not all of these studies measured REE. At this stage, no interventional studies determined the precise energy intake related to improved outcomes in critically ill children. In a systematic review (73), followed by an observational study (7), it was observed that a minimum intake of 57 kcal/kg per day (and 1.5 g/kg per day of protein) was associated with positive nitrogen balance.

Energy requirements during the recovery phase of critical illness

The recovery phase starts when the patient is mobilized and the stress response is resolving and normalized. This phase could last up to several months. During this phase, the body shifts further from catabolism to anabolism with protein synthesis exceeding protein breakdown, which results in tissue repair and (catch-up) growth (68). Thereby, energy requirements may rise considerably, even exceeding normal energy requirements of healthy children (*Figure 2*) (70,74). Recent guidelines state that, after the acute phase, energy intake should account for energy debt, physical activity, rehabilitation and growth (*Table 5*) (10). Only a few studies have investigated the energy requirements in the recovery phase, mostly in children with heart disease and burns. Recently, it was shown in critically ill infants mainly with heart disease and with a mean PICU stay of 50 days that weight gain was achieved comparable with healthy children by following a nutritional protocol with energy target set at 2× predicted REE (75). In infants recovering from surgical repair of congenital heart disease, caloric goals of 2–3× REE (120–150 kcal/kg/day) are presumed to be necessary for weight gain and even up to 4× REE (200 kcal/kg/day) for infants with remained hemodynamically significant lesions (76,77). In burned patients, a hypermetabolic state with increased nutritional demands has been shown even up to two years after injury (59,62,78). One study, published in 1988, showed that energy intake should be approximately 1.6× REE to maintain weight in this group (79).

The use of the RQ

The RQ may help evaluate substrate utilization and/or nutritional support, and determine overfeeding and underfeeding. As shown in *Table 1*, fat oxidation results in an RQ of 0.7, whereas protein and carbohydrate oxidation result in RQs of 0.8 and 1.0, respectively. Carbohydrate intake higher than oxidative capacity may result in lipogenesis, leading to an RQ >1.0, which makes it a possible marker for detecting overfeeding (80). Moreover, the use of endogenous fat stores to meet energy requirements can decrease the RQ below 0.85 (59). However, cut-off values for the RQ (<0.85, 0.85–1.0, >1.0) correspond only moderately with the currently used criteria of under- and overfeeding (the ratio of intake and mREE) (81,82). Alternatively, the use of a difference between measured RQ and predicted RQ [using the proportions of carbohydrates and fats in nutritional intake (RQmacr)], of more than >0.05 has been proposed as a definition of overfeeding (83). This definition might be a more useful marker, as the RQ can alter during PICU admission due to change in phase of disease. Hence, the RQ can be used to determine under- and overfeeding and to monitor the tolerance of nutritional support. However, the RQ cannot be used to "fine-tune" nutritional therapy because each patient has his/her own metabolic "fingerprint" or "signature" inheriting a unique metabolic machinery capable of generating a particular, and not always predictable, response during the different phase

of the stress response.

Overall, measurements of REE and RQ after the acute phase of disease may be helpful to guide nutritional therapy and to increase nutritional intake in relation to REE until (catch-up) growth and tissue repair are achieved.

Conclusions

In critically ill children, clinicians have the complex role of prescribing an optimal energy intake, avoiding both underfeeding and overfeeding. During the acute phase, energy intake should be increased progressively according to the tolerance of the patients and not exceed REE, predicted by Schofield equation (21). Afterwards, energy intake may be increased considering the energy debt, physical activity, rehabilitation and growth. Usually this means that the target energy intake should be between 100% and 200% of REE. In some patients, measurement of REE using a validated calorimeter may be needed. In addition to measured REE, the RQ might be a helpful tool as well. The presence of a nutrition team including a dedicated dietitian is recommended to guide energy intake and nutritional support.

Future studies need to validate a new calorimeter for this specific population, including neonates and infants and patients on high inspired oxygen concentrations. In parallel, the development of more accurate predictive equations of REE or other methods to measure energy expenditure is needed.

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Footnote

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