Objective Malnutrition Diagnosis and Personalised Nutrition Delivery in the ICU

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Poor ICU nutrition delivery remains a challenge worldwide. Objective malnutrition diagnosis and personalisation of nutrition delivery may be one way of addressing this problem.

Modern, and increasingly expensive ICU care now allows prolonged survival from illness and injury by providing life-sustaining support for extended periods of time, making previously nonsurvivable ICU insults, survivable. In fact, innovations in ICU care have resulted in yearly reductions in hospital mortality from sepsis (Kaukonen et al. 2014). However, these same data reveal many ICU "survivors" are not returning home to functional lives post-ICU; but instead to rehabilitation settings where it is unclear if they ever return to a meaningful quality of life (QoL) (Kress and Hall 2014). ICU acquired weakness (ICU-AW) is a common complication of critical illness. A hallmark of ICU-AW is reduced muscle mass and strength, which both are independent predictors of ICU survival (Weijs et al. 2014).

Muscle mass and quality derived by CT scans in mechanically ventilated patients, is associated with a 6-month higher mortality (Weijs et al. 2014; Looijaard et al. 2016; Looijaard et al. 2018). Tragically, an increasing number of patients who survive ICU suffer from severe, prolonged functional disabilities (Kress and Hall 2014; Hopkins et al. 2017; McNelly et al. 2016; da Silveira et al. 2018). Recent data shows ICU patients (mean age: 55) are likely to be discharged to post-acute care facilities and incur substantial costs of ~$3.5 million/functioning survivor (Herridge et al. 2016). Unfortunately, post-ICU functional disability is most common and most severe in survivors requiring time on a ventilator for respiratory failure, where recent data shows 2 out of 3 ICU survivors (65%) suffer significant functional limitations (Kress and Hall 2014). *Thus, it must be asked in modern ICU care, "are we creating survivors…or victims?"* This is a defining challenge for modern critical care all major ICU societies have recommended giving priority to research addressing post-ICU QoL outcomes in these survivors (Needham et al. 2017).

To improve functional and QoL outcomes in acute renal failure (ARF) survivors, one obvious low-cost therapeutic strategy that can be rapidly implemented is objective, data guided personalised nutrition delivery to attempt to maintain and allow recovery of muscle mass/function. This is particularly essential in patients with pre-existing and subsequent iatrogenic malnutrition that commonly occurs in ICU patients. In fact, despite increasing obesity rates in many countries, preexisting malnutrition is highly prevalent in ICU patients- with as many as 1 in 2 (30-50%) patients being malnourished at ICU admission(Normal et al. 2008). Unfortunately, unrecognised malnutrition in the hospital and ICU may be among the most pressing "silent epidemics" facing hospitalised patients in the world today. Although it is well known that greater then 1 in every 3 hospitalised patients is malnourished at hospital admission (Barker et al. 2011), limited older data estimates only 3% of malnourished U.S. hospitalised patients are being recognised and diagnosed (Corkins et al. 2014). Thus, only 1 in 10 malnourished patients are ever diagnosed and even fewer are treated. This silent epidemic of "the skeleton in the hospital closet" has been described for >40 years (Butterworth 2005), but this data shows it has yet to be addressed. This is tragic as mortality is 5 times greater (11.7% versus 2.4%) overall for hospitalised patients diagnosed with malnutrition versus well-nourished (Corkins et al. 2014). Further, the outcomes of ICU patients with pre-existing malnutrition and sarcopenia are further complicated by the fact that critical illness is characterised by an acute catabolic response leading to rapid loss of lean body mass (LBM) contributing to muscle wasting, weakness, and loss of function (Dinglas et al. 2017; Wischmeyer 2016; Wischmeyer 2018).

Poor ICU nutrition delivery remains a challenge worldwide. *Review of current practice demonstrates the actual amount*

Table 1. New Personalised Nutrition Care Monitoring Devices for Muscle/Body Composition and Energy Needs

Measure	Endpoint	Descrirption
Muscle Ultrasound	Muscle Mass	Ultrasound-based measurement of skeletal muscle mass as well as quality measures of intramuscular glycogen content (IMGC), intramuscular Adipose Tissue (IMAT), and muscle size (MS).
Lean Body Mass via CT Scan	Muscle Mass	Lean body mass obtained from admission abdominal CT scan. Hounsfield Unit boundaries analysed by SliceOmatic software to reflect whole-body muscle
Segmantal Bioelectrical Impedance Spectroscopy (S-BIS)	Muscle Quality/ Intracellular Water	Segmental BIS can distinguish intracellular water (ICW) and extracellular water (ECW). ICW reflects muscle cell mass, whereas ECW represents the sum of interstitial and ECW are only affected by segmental volume, so the ECW/ICW ratio could indicate the ratio of non-contractile tissue to contractile tissue regardless of assessed somatotype (age, gender, disease state).
Indirect calorimetry	Resting Metabolic Rate	Measures the oxygen consumption (V02) and the carbon dioxide (VCO2) production at the mouth (mask or ventilated hood) in a non-invasive way. V02 and VC02 corresponds to the whole-body cellular respiration and makes it possible to calculate the whole-body energy expenditure (EE) and resting metabolic rate (RMR).

of nutrition delivered primarily via enteral nutrition (EN) in ICU patients is <50% of the prescribed goal even in our most malnourished patients (Cahill et al. 2010). In an era of heightened concern about patient safety and medical error, we and others have consistently documented that critically ill patients receive, on average only 40-50% of their prescribed goal nutritional requirements for prolonged periods (>1 week) after ICU admission (Barr et al. 2004; Binnekade et al. 2005; De Jonghe et al. 2001; Heyland et al. 2003; Krishnan et al. 2003; Rubinson et al. 2004). This is particularly concerning as the average protein delivery (thought essential for muscle/functional recovery) for the first 12 days of an ICU stay is only 0.6 g/kg/d (Cahill et al. 2010), which is one-third of the guideline recommendations of 1.5-2.0 g/kg/d in ICU (Taylor et al. 2016). *This is an urgent patient safety crisis that must be addressed.* One of the major drivers of lack of emphasis on improved nutrition delivery in ICU and post-ICU patients is lack of objective data to guide "personalised ICU nutrition." Specifically, lack of objective tools to: 1) Diagnose nutrition risk objectively, 2) Determine accurate bedside energy requirement data which is known to change throughout the course of illness, and 3) Lack of quantitative assessment tools to evaluate effect of nutrition on patient. As ICU physicians would not deliver vasopressors without a continuous blood pressure measure; we believe the ICU community has not embraced a focus on nutrition delivery due to lack of objective data to guide personalised nutrition care.

> preexisting malnutrition is highly prevalent in ICU patients with as many as 1 in 2 patients being malnourished at ICU admission

Role of Muscle Mass, Body Composition, and Indirect Calorimetry Analysis in Malnutrition Diagnosis and Nutrition Delivery

The use of a quick non-invasive technique to evaluate skeletal muscle quantity and quality in ICU patients could have profound prognostic implications for how malnutrition is diagnosed. As stated in new Global Leadership Initiative on Malnutrition (GLIM) Guidelines (Cederholm et al. 2019), muscle mass is a new and innovative marker of malnutrition. A number of techniques are now available to assess muscle mass, lean body mass (LBM), or Fat-Free Mass (FFM) in ICU patients at bedside. Further, new and easy-to-use bedside indirect calorimetry devices have also recently been developed. Key new available techniques for ICU nutrition and metabolic analysis for the delivery of personalised nutrition are summarised in **Table 1**.

Muscle Ultrasound

Recently, we have assisted with development of a muscle-specific U/S-based technique to enable non-invasive measurement of skeletal muscle mass as well as quality measures of intramuscular glycogen content (IMGC), intramuscular Adipose Tissue (IMAT), and muscle size (MS) (Wischmeyer et al. 2017; Wischmeyer and San Millan 2015). Validation of muscle mass from U/S with gold standard techniques (such as MRI/CT scan) has been previously published (Arbeille et al. 2009). Specific to ICU, a very recent trial showed good inter-/intra-rater reliability for muscle mass U/S in acutely ill patients (Pardo et al. 2018). Further, recent data has shown increased U/S-muscle mass is correlated to improved functional handgrip strength following an a targeted ICU nutrition intervention (Ferrie et al. 2016). Thus, muscle U/S measures correlates with improved patient function and this is modifiable by improved nutrition delivery. The decline in muscle function both during and after critical illness is the result of not only a change/reduction of skeletal muscle mass but also as a result of changes in muscle quality such as muscle composition, histology and morphology (Looijaard et al. 2016; Correa-de-Araujo

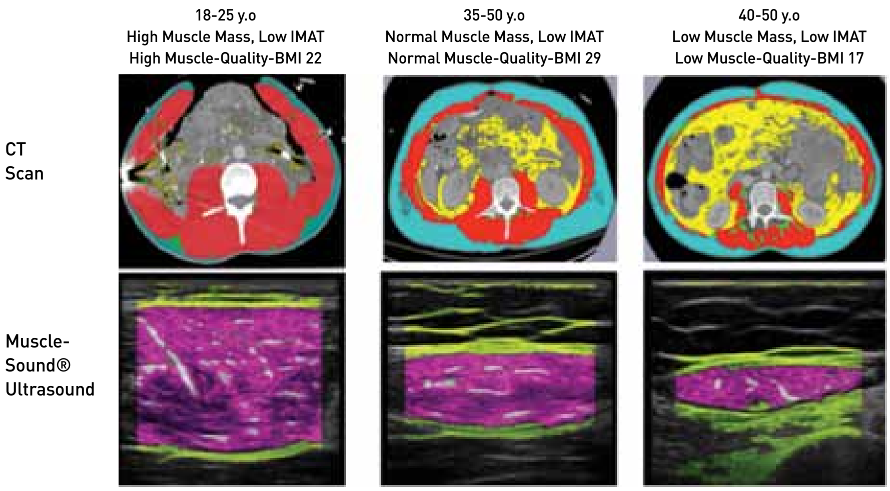
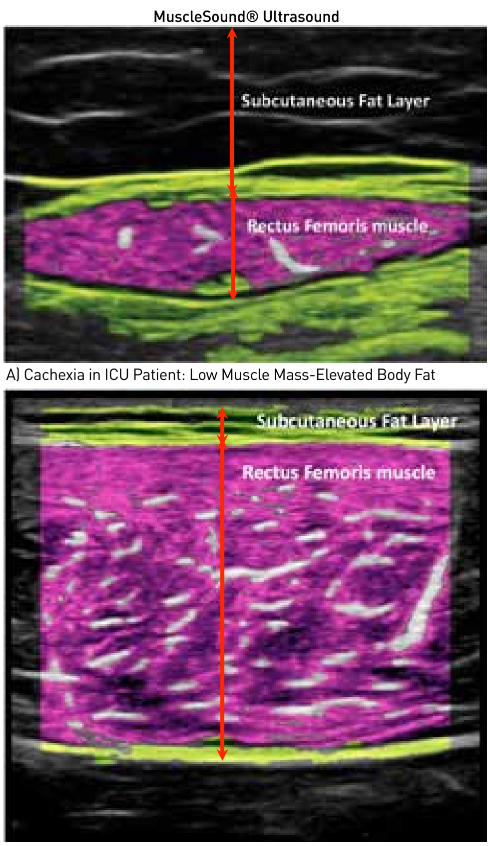


Figure 1. Examples of Muscle Quality and Mass evaluation via CT Scan (level L3) and MuscleSound® analyses (short-axis rectus femoris muscle) assessed at the same time.



Bioimpedance Spectroscopy Body Composition Analysis

Intracellular Water	12.8L
Extracelluler Water	8.8L
Dry Lean Mass	7.8kg
Lean Body Mass	29.4kg
Body Fat Mass	20.0kg

Muscle-Fat Analysis

Weight	49.4kg
Skeletal Muscle Mass	14.7kg
Body Fat Mass	20.0kg

Obesity Analysis

BMI	17.6kg/m²
PBF	40.5%

Body Composition Analysis

Intracellular Water	47.1L
Extracelluler Water	31.9L
Dry Lean Mass	27.6kg
Lean Body Mass	106.6kg
Body Fat Mass	10.4kg

Muscle-Fat Analysis

Weight	117.0kg
Skeletal Muscle Mass	59.5kg
Body Fat Mass	10.4kg

Obesity Analysis

BMI	29.3kg/m²
PBF	8.9%

B): Professional Athlete: High Muscle Mass-Low Body Fat

Figure 2: Examples of Muscle Ultrasound of the rectus femoris muscle- and Total Body Composition analyses using MuscleSound® ultrasound analysis (muscle quality and size) and Segmental Bioelectrical Impedance Spectroscopy (S-BIS) measurements (InBody S10).

et al. 2017; Fragala et al. 2015). Skeletal muscle quality is already recognised as a marker of function in healthy individuals (Watanabe et al. 2013) and critically ill patients (Wischmeyer et al. 2017; Parry et al. 2015; Puthucheary et al. 2013; Bear et al. 2017) and has been emerging as a means to describe the changes associated with altered muscle functioning (Fragala et al. 2015; Watanabe et al. 2013; Sieber 2017; Kelley and Kelley 2017). Assessing muscle mass and quality in clinical populations at the bedside is of key importance due to the emerging associations between low muscle quality with low muscle mass and poor functional status (da Silveira et al. 2018). This allows for an increased understanding of the relationship between skeletal muscle quantity and quality, and malnutrition/outcome risk (McNelly et al. 2016; da Silveira et al. 2018). Our group has initial validation data for muscle quality from U/S versus gold-standard CT scan muscle quality and have an R2 value of 0.989 (unpublished data). Finally, Puthucheary et al reported an increase in IMAT observed in muscle biopsies during ICU stay (Puthucheary et al. 2018). They described the existence of a compromised muscle bioenergetic status as a result of a dysregulated lipid oxidation (Puthucheary et al. 2013; Puthucheary et al. 2018).

The ease of adoption of muscle U/S at the ICU bedside has been markedly improved by the availability of a muscle specific U/S device (Musclesound Inc, Colorado, USA) This handheld U/S device is easy to carry and can be connected to a portable tablet device. The device is focused on allowing rapid, accurate measures of LBM at the bedside, with built-in guidance to ensure reproducible measurements. This new device is a significant improvement in LBM U/S technology. Unique measures of muscle glycogen and muscle quality can now be ascertained at the bedside in study subjects using the Musclesound U/S. As described. muscle quality has recently been correlated to muscle strength (Akazawa et al. 2018). Muscle glycogen U/S measures have been validated via muscle biopsy (Hill and Millan 2014) and we have shown ICU patients have significant muscle glycogen deficits (Wischmeyer et al. 2017; Wischmeyer and San Millan 2015). Muscle glycogen is known to change daily based on adequacy of nutrition intake, muscle uptake of substrate and "physical stress." Thus, it could prove useful in monitoring of nutrition delivery and

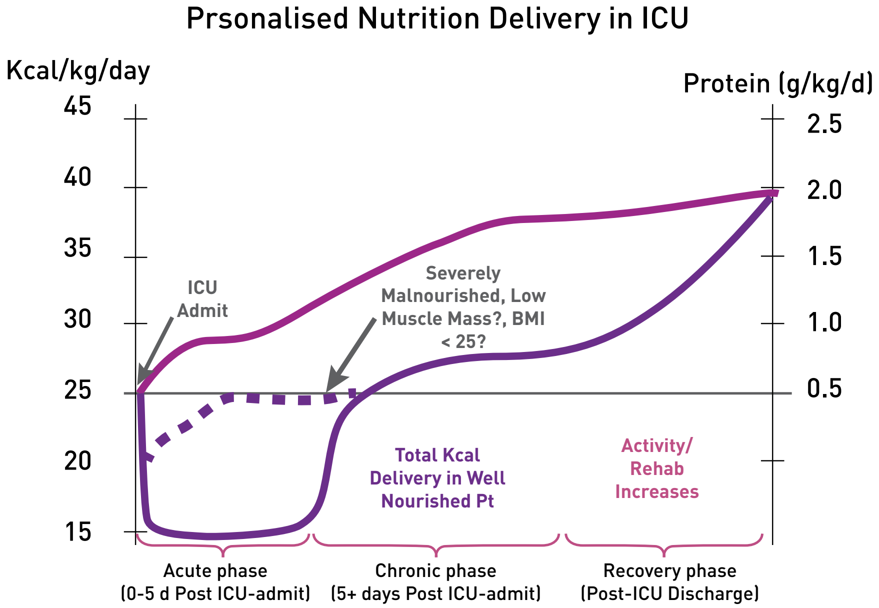


Figure 3. Hypothesised Personalised Nutritional Needs Over Time in ICU (adapted from Wischmeyer 2018)

utilisation in ICU patients. See **Figure 1** for example comparisons of muscle measures via MuscleSound and CT Scan.

Segmental Bioelectrical Impedance Spectroscopy (SBIS)

Segmental bioelectrical impedance spectroscopy (SBIS) is another non-invasive approach of muscle quality assessment via bioelectrical impedance (BIA). SBIS or BIA equipment does not measure muscle mass directly, but instead derives an estimate of muscle mass based on whole-body electrical conductivity (Cruz-Jentoft et al. 2019; Kaido et al. 2012). Skeletal muscle has a large amount of water, and SBIS can separately assess intracellular water (ICW) and extracellular water (ECW), which are divided by the muscle cell membrane. SBIS can distinguish ICW and ECW from the total water in a particular segment. Segmental BIS is advantageous for assessments of a localised (left/right) region (arm, leg and trunk) instead of only the whole-body ICW reflects muscle cell mass, whereas ECW represents the sum of interstitial fluid and blood plasma in extracellular space. The calculations of ICW and ECW are only affected by segmental volume, so the

> **unrecognised malnutrition in the hospital and ICU may be among the most pressing silent epidemics facing hospitalised patients in the world today**

ECW/ICW ratio could indicate the ratio of non-contractile tissue to contractile tissue regardless of assessed somatotype (age, gender, disease state). The phase angle and an estimation of energy expenditure are also reported in the SBIS measurement in modern devices.

One limitation of SBIS and BIA measurements has been the concern for the effect of hydration status on measurements in the ICU (Looijaard et al. 2018). Recent research in critical illness has focused on the prognostic values of SBIS measurements such as the phase angle which are directly measured, and are not as sensitive to changes in hydration status. A multinational trial in a diverse population of 931 critically ill patients demonstrated a low phase angle at admission (day 1) was associated with increased 28-day mortality (Thibault et al. 2016). This was further validated in a recent study of 196 heterogenous ICU patients. This study showed a low phase angle at ICU admission was associated with increased 90-day mortality (Stapel et al. 2018). See **Figure 2** for example comparisons of body composition measures via SBIS (Inbody S10, Inbody Inc, California, USA) and muscle-specific U/S (Musclesound). The newly published GLIM criteria describes specific (Cederholm et al. 2019) Appendicular Skeletal Muscle Index (ASMI, kg/m2) and Fat Free Mass thresholds that may be obtained from BIA (or SBIS) for low muscle mass to objectively diagnose malnutrition.

A New Era of Indirect Calorimetry Devices for Measurement of Personalised Energy Expenditure

As shown in **Figure 3**, our research group has hypothesised that energy needs change throughout the course of illness and recovery (Wischmeyer 2018). However, this has not been validated with actual longitudinal resting energy expenditure (REE) measures, as is now possible with new metabolic cart devices (such as the Q-NRG, COSMED, Rome, Italy). As described, energy expenditure (EE) in ICU patients has been hypothesised to be highly variable based on a range of features including initial injury/illness, severity of illness (i.e. sepsis can dramatically decrease EE), nutritional status and other treatments (Wischmeyer 2018). It is also clear that clinicians ideally need to measure EE by indirect calorimetry (IC) to optimise nutritional support for better clinical outcome and to prevent over-/underfeeding (Heidegger et al. 2013; McClave et al. 2014). Difficulties in conduct, handling and interpretation of results often limit the use of IC in ICU patients. IC is the method utilised to measure EE in patients both during mechanical ventilation (MV) and can also now be routinely used in patients not requiring MV. The need for accurate determination of EE is increasing due to the rising prevalence of patients with clinical conditions making traditional equation-based estimation of EE unpredictable and plagued with variability. For example, elderly subjects with reduced lean body mass and increased fat mass have a reduced EE, not easily predicted with traditional equations for caloric need. In contrast, young patients, those with severe trauma, acute infection or significant obesity can have increased EE that is also difficult to estimate without IC (Heidegger et al. 2013; McClave et al. 2014). A number of studies have shown that predictive formula developed to calculate EE of such patients are not consistently clinically relevant (Fraipont and Preiser 2013; Guttormsen and Pichard 2014). Indeed, clinicians need to measure their patients' EE in order to optimise the prescription of nutritional support and the clinical outcome (Heidegger et al. 2013; McClave et al. 2014), and IC is considered to be the gold standard for determining EE in the ICU patients. This is now becoming a reality with the development and ongoing evaluation of new, easy-to-use indirect calorimeter technology.

Conclusion: An Exciting New Era for Objective Malnutrition Diagnosis and Personalisation of Nutrition Delivery

The advent of a range of novel and innovative technologies to allow objective diagnosis of malnutrition, accurate determination of nutrition needs, and evaluation of nutrition utilisation is a major advance in the nutritional and metabolic care of critically patients. We believe it is essential that some or all of these devices are utilised in all future critical care nutrition trials to assess and guide malnutrition diagnosis and nutrition therapy. All of these devices continue to require further research to better evaluate their optimal application in ICU outcomes and care. Many of these trials are planned or underway. It is our dream that one day the muscle-specific ultrasound, the SBIS, and the new generation of metabolic carts will become to the ICU dietitian what the pulse oximeter, blood pressure cuff, and stethoscope are to the ICU nurse. We believe this will finally usher in an era of truly personalised nutrition care.

Conflict of Interest

Paul Wischmeyer reported receiving grant funding related to this work from National Institutes of Health, Canadian Institutes of Health Research, Nutricia, Abbott, Baxter, Fresenius, and Takeda. Dr. Wischmeyer has served as a consultant to Abbott, Fresenius, Baxter, Cardinal Health, Nutricia, and Takeda for research related to this work. Dr. Wischmeyer has received unrestricted gift donation for nutrition research from Musclesound and Cosmed. Dr. Wischmeyer has received honoraria or travel expenses for CME lectures on improving nutrition care from Abbott, Baxter and Nutricia.

Jeroen Molinger has received grant funding related to this work from Nutricia and Baxter. He serves as consultant for Musclesound Inc. and Nutricia. ■

Key points

- ICU acquired weakness (ICU-AW) is a common complication of critical illness.
- An increasing number of patients who survive ICU suffer from severe, prolonged functional disabilities.
- Priority must be given to research addressing post-ICU QoL outcomes in survivors.
- One low-cost therapeutic strategy that can be rapidly implemented is objective, data guided personalised nutrition delivery to attempt to maintain and allow recovery of muscle mass/function.
- The use of a quick non-invasive technique to evaluate skeletal muscle quantity and quality in ICU patients could have profound prognostic implications for how malnutrition is diagnosed.

Abbreviations

ARF	Acute Renal Failure
ASMI	Appendicular Skeletal Muscle Index
BIA	Bioelectrical Impedance
ECW	Extracellular Water
EE	Energy Expenditure
FFM	Fat-Free Mass
GLIM	Global Leadership Initiative on Malnutrition
IC	Indirect Calorimetry
ICU	Intensive Care Unit
ICU-AW	ICU Acquired Weakness
ICW	Intracellular Water
IMAT	Intramuscular Adipose Tissue
IMGC	Intramuscular Glycogen Content
LBM	Lean Body Mass
MS	Muscle Size
MV	Mechanical Ventilation
REE	Resting Energy Expenditure
SBIS	Segmental Bioelectrical Impedence Spectroscopy
U/S	Ultrasound
QoL	Quality of Life

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INFOGRAPHIC

NUTRITION IN THE ICU

NUTRITION – KEY FACTS

At least **one third** of patients in developed countries have some degree of malnutrition upon admission to the hospital.

If left untreated, approximately **two thirds** of those patients will experience a further decline in their nutrition status.

Among patients who are not malnourished upon admission, nearly **one third** may become malnourished while in the hospital.

According to the NutritionDay ICU Audit, it takes **1 week** to reach 1500kcal intake in most ICUs in the world.

Undernutrition is associated with **prolonged length** of stay, mechanical ventilation, infection and mortality.

Overnutrition is associated with **prolonged** mechanical ventilation and infection, and increased morbidity.

Source: Tappenden et al. (2013) Jrnl of the Acad. of Nutr. and Dietitics, 113(9); Singer (2019) Critical Care 23(1).

OBJECTIVES OF NUTRITION THERAPY IN THE ICU

- Preserve lead body mass
- Maintain immune function
- Avert metabolic complications

Source: VanBlarcom and McCoy (2018) Crit. Care Nurse, 38(3):46-52.

NUTRITION DISORDERS AND RELATED CONDITIONS

- Malnutrition/Undernutrition
- Sarcopenia/Frailty
- Overweight/Obesity
- Micronutrient abnormalities
- Refeeding syndrome

Source: Singer et al. (2019) Clinical Nutrition, 38:48-79.

NUTRITION CARE PROCESS

1 Nutrition Assessment

2 Nutrition Diagnosis

3 Nutrition Intervention

4 Nutrition Monitoring and Evaluation

Source: Cederholm T et al. (2017) Clin. Nutrition, 36:40-64.

KEY PRINCIPLES TO IMPROVE NUTRITION FOR THE CRITICALLY ILL

- Create a culture where all stakeholders value nutrition
- Redefine clinicians' roles to include nutrition care
- Recognise and diagnose malnourished patients and those at risk
- Implement comprehensive nutrition interventions and monitor continuously
- Communicate nutrition care plans
- Develop a discharge nutrition care and education plan

Source: Tappenden et al. (2013) Jrnl of the Acad. of Nutr. and Dietitics, 113(9).