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## Optimising nutrition for recovery after ICU

Optimising nutrition and metabolism post-ICU for recovery of functional lean body mass and quality of life.

In-hospital mortality following intensive care unit (ICU) care has consistently declined in recent years (Kaukonen et al. 2014). However, these data reveal many of these ICU “survivors” are not returning home to functional lives after the ICU, but instead to rehabilitation and nursing home settings where it is unclear if they ever returned to a meaningful quality of life (QoL). As in-hospital ICU mortality has declined, we have markedly increased the number of patients going to rehabilitation settings (Kaukonen et al. 2014). Once in rehabilitation, it is unclear if these ICU “survivors” ever return home as we know; ~40% of mortality within the first year of ICU stay occurs post-ICU discharge (Weycker et al. 2003). Unfortunately for those who do survive, nearly half the survivors will not return to work in the first year following discharge (Kamdar et al. 2017), often as a result of post-intensive care syndrome (PICS) and weakness post-ICU (Dinglas et al. 2017).

PICS is a multi-factorial syndrome; however, a significant component of PICS is often post-ICU weakness. This is unfortunately not surprising as we know critically ill burn patients lose as much as a kilogram of lean body mass (LBM) per day (Stanojcic et al. 2016). Other ICU patients also suffer significant LBM loss, much of it in the first 7-10 days of ICU stay (Wischmeyer 2016). Patients gain weight back following the ICU, but virtually all this regained weight is fat mass, not functional muscle and LBM (Herridge et al. 2003). This is not surprising, as data from the burned ICU patients demonstrates the catabolic/hypermetabolic state brought on by critical illness can persist for up to two years following hospital discharge and markedly hinders recovery of QoL, muscle mass and function in our ICU patients (Stanojcic et al. 2016).

To address this epidemic, we must ask ourselves in our ICU care, “Are we creating survivors or victims?” If we are going to begin creating more survivors we must improve our post-ICU care “recovery” care and take responsibility for the deficits in strength, function, and cognition we create in the ICU. We owe it to our ICU patients to optimise and further study key recovery interventions such as nutrition delivery post-ICU if we are to end the epidemic of PICS victims.

### Metabolism and caloric needs for recovery after ICU

As patients improve and enter the “recovery phase”, seminal ICU metabolic cart data and landmark studies of starvation indicate caloric and protein intake needs to increase significantly (Uehara et al. 1999; Keys et al. 1950; Hoffer and Bistrian 2012). This should occur concurrently with implementation of aggressive rehabilitation and exercise interventions. Data from the landmark “Minnesota Starvation Study”, performed at the end of World War II (Kalm and Semba 2005; Keys et al. 1950) (a study all medical students and ICU caregivers should be taught or read themselves) provides fundamental data on the nutritional targets required to recover from the fundamental severe LBM loss observed after ICU. This seminal study demonstrates a healthy 70 kg human, following a significant weight loss, requires an average of 5000 kcal/day for 6 months–2 years to fully regain lost muscle mass and weight (Keys et al. 1950). Most all ICU and major surgery patients suffer similar marked weight and LBM loss. However, in addition to this significant LBM loss, ICU survivors also suffer prolonged hypermetabolism and catabolism (which Minnesota subjects did not have as they were healthy volunteers).

Thus, we must consider this additional challenge to recovery of functional LBM, and again emphasise significant calorie/protein delivery will be required to restore lost muscle mass and QoL. ICU metabolic cart studies demonstrate during the recovery phase post-ICU, the body has a marked increase in metabolic needs, with total energy expenditure (TEE) increasing as much as ~1.7-fold above resting energy expenditure (REE) (Uehara et al. 1999). In the 2<sup>nd</sup> week following sepsis this reveals caloric need (TEE) of ~3250 kcal/d or 47 kcal/kg/d. Interestingly this is virtually identical to WHO requirements for normal, healthy humans to maintain weight. In younger trauma patients (mean age: 34), this data indicated an even greater increase in caloric need (TEE) in the 2<sup>nd</sup> week post-injury to ~4120 kcal/d or 59 kcal/kg/d, nearly identical to the 4000 kcal/d Dr. Ansel Keys showed was required to recover from starvation in young subjects in the Minnesota study. Further, need for additional protein intake has been well-described by our research group and Hoffer et al. in a number of recent publications questioning whether it is actually protein deficit and not calorie deficit that is important to improving outcome in critical illness (Hoffer and Bistrian 2012; 2014; 2015). This data demands we ask: *Is it possible our septic patients have been unable to recover their QoL post-ICU for months to years (Needham et al. 2011; Wischmeyer and San-Millan 2015; Kamdar et al. 2017; Dinglas et al. 2017) due to our lack of understanding of their fundamental metabolic needs in different phases of illness, especially following ICU and hospital discharge?*

### How to optimise nutrition delivery after ICU for recovery

We must ask ourselves: “Will patients leaving

our ICU be able to consume adequate calories and protein to optimally recover?" Unfortunately, in most cases the answer is a resounding no!... At least not without help. Recovering patients, especially elderly individuals, are challenged by decreased appetites, persistent nausea and constipation from opiates, and lack of education about how to optimise their diet. Further, dysphagia following ICU stay occurs in nearly 60% of patients who are intubated in ICUs after extubation, and approximately 50% of these suffer from aspiration (Brodsky et al. 2017). Recent data has shown these dysphagia symptoms persist beyond hospital discharge in one-third of intubated ARDS survivors (Brodsky et al. 2017). Dysphagia must be actively assessed for and treated in ICU survivors. Thus, many challenges exist to recovery of oral intake post-ICU discharge. Actual post-ICU oral caloric intake has been explored in ICU patients in the week following extubation. An observational study demonstrated an average spontaneous calorie intake of 700kcal/d and the entire population studied consumed < 50% of calorie/protein needs for 7 days (Peterson et al. 2010). These data emphasise the importance of closely observing food intake in post-ICU patients.

Given these data and the many challenges to oral intake, patients following ICU discharge are highly unlikely to take in the required calorie and protein delivery for recovery via routine oral intake. *To address this, a large body of data demonstrates that oral nutrition supplements (ONS) must become fundamental in our post-ICU and hospital discharge care.* A recent meta-analysis in a wide range of hospitalised patients demonstrated ONS reduce mortality, reduce hospital complications, reduce hospital readmissions, shorten length of stay and reduce hospital costs (Cawood et al. 2012; Elia et al. 2016; Stratton et al. 2013; 2003). A large hospital database analysis of ONS use in 724,000 patients matched with controls not receiving ONS showed a 21% reduction in hospital LOS and for every US\$1 spent on ONS \$52.63 was saved in hospital costs (Philipson et al. 2013). Finally, a recent large post-hospital discharge randomised controlled trial of 652 patients in 78 centres studied the effect of high protein ONS (HP-ONS) with  $\beta$ -Hydroxy  $\beta$ -Methylbutyrate (HP-HMB) versus placebo ONS in elderly

malnourished (Subjective Global Assessment [SGA] class B or C) hospitalised adults for 90 days following hospital discharge. Results demonstrated that HP-HMB reduced 90-day mortality ~50% relative to placebo (4.8% vs. 9.7%; relative risk 0.49, 95% confidence interval [CI], 0.27 to 0.90;  $p = 0.018$ ). The number needed to treat to prevent 1 death was 20.3 (95% CI: 10.9, 121.4) (Deutz et al. 2016). As it is well known that patients recovering from sepsis and the ICU will not consume sufficient calories and protein to recover optimally, the use of HP-ONS will be essential and is strongly recommended for all patients once oral intake is resumed for at least 3 months (up to 1 year) following ICU.

### Role of specific anabolic/anti-catabolic agents, vitamin D and microbiome/probiotics in recovery

#### Anabolic/Anticatabolic Agents

Data from the large HP-ONS trial using HMB above (Deutz et al. 2016) and other recent review articles (Stanojic et al. 2016) emphasise that anabolic and anti-catabolic interventions, such as propranolol, oxandrolone and other agents targeted at restoring lean muscle mass (such as HMB) may be vital in optimal recovery and survival post-ICU. As shown in **Table 1**, it is likely targeted nutrition with

adequate protein delivery and muscle recovery-targeted agents when combined with exercise will play a vital role in improving survival and recovery of QoL post-ICU (Wischmeyer and San-Millan 2015). The data for these novel anabolic/anti-catabolic agents are covered in detail by a recent review by Stanojic and colleagues (Stanojic et al. 2016). These interventions are summarised in **Table 1**.

#### Vitamin D

A rapidly growing body of data demonstrate a significant portion of the U.S. (and industrialised world) population is Vitamin D deficient (Holick 2007) and data in ICU and surgical patients show that Vitamin D deficiency has a significant relationship to postoperative complications and adverse ICU outcomes (Iglar and Hogan 2015; Higgins et al. 2012; Moromizato et al. 2014). A key recent RCT published in *JAMA* showed ICU patients with Vitamin D levels < 12 ng/ml experienced a significant improvement in hospital survival when vitamin D was aggressively supplemented (Vitamin D<sub>3</sub> or placebo given orally or via nasogastric tube once at a dose of 540,000 IU followed by monthly maintenance doses of 90,000 IU for 5 months) (Amrein et al. 2014). This will be a difficult dose for many centres to administer if concentrated Vitamin D solutions

## Nutrition and metabolic support Post-ICU Discharge

**Nutrition** - Assess and treat for dysphagia pre-discharge

### High Protein Oral Nutrition Supplements Essential!

- Caloric Delivery 3000-4000 kcal/day for 6 months – 2 years
- Protein Goals: 1.2-2.0 g/kg/day

### Supplements

- Vitamin D – If Deficient – 50,000 I.U. D3 2 x week for 2-4 weeks- then 2000 I.U./day
- HMB- 3g/day
- Consider Probiotics
- Consider Anabolic Agents
  - ▶ Propranolol- Adult Starting Dose- 0.2-0.6 mg/kg/d- Titrate to HR < of 20% or < 95 BPM
  - ▶ Oxandrolone- Adults: 10 mg BID PO

are not available. Alternatively, a recent double-blinded pilot RCT of 50,000 IU vitamin D<sub>3</sub> or 100,000 IU vitamin D<sub>3</sub> daily for 5 consecutive days enterally was conducted (Han et al. 2016). There was a significant decrease in hospital length of stay over time in the 50,000 IU D<sub>3</sub> /day and 100,000 IU D<sub>3</sub> /day groups compared to the placebo group (25 ± 14 and 18 ± 11 days compared to 36 ± 19 days, respectively; p = 0.03). Thus, vitamin D levels are recommended to be checked at ICU admission and once weekly after in all septic shock patients. A repletion dose of 100,000 units of Vitamin D3 for 5 days in the first week and once-twice weekly thereafter (monitoring levels) for the ICU stay in patients found to be deficient (< 30 ng/ml) is reasonable. Further, the emerging role for Vitamin D to reduce mortality in vitamin D deficient ICU patients has been recently reviewed by Christopher (2016). Correction of Vitamin D deficiency is essential for recovery of muscle mass and for optimising patient outcomes. In the post-ICU discharge setting, Vitamin D supplementation should consist of Vitamin D3 at 50,000 IU 2 x weekly for 2 weeks followed by 2000 IU/day. Larger trials on the role of vitamin D supplementation in sepsis and critical illness are currently underway.

#### Microbiome/Probiotics

Finally, new data expanding our understanding of the microbiome in the ICU and “dysbiosis” therapies including probiotics and faecal microbiota transplantation have been described by our research group (Wischmeyer et al. 2016; McDonald et al. 2016). Dysbiosis results from many factors, including ubiquitous antibiotic use and overuse. Despite advances in antibiotic therapy, infections and mortality from often multidrug-resistant organisms (i.e. *C. Difficile*) are increasing. This raises the question of whether restoration of a healthy microbiome via probiotics or other “dysbiosis therapies” would be an optimal alternative, and should be a parallel treatment option with antibiot-

ics. This may be particularly true as patients recover following ICU. Our research group’s recently published updated meta-analysis of 14 randomised controlled trials (RCT) found that probiotic therapy significantly reduced the incidence of infectious complications in the ICU (RR 0.80, 95% CI 0.68 to 0.95, p = 0.009) (Manzanares et al. 2016). Further, probiotics (Goldenberg et al. 2013) or faecal microbial transplantation (Kassam et al. 2013, Gupta et al. 2016) have been successful as an intervention in *C. Difficile*. Specifically, a meta-analysis looking at probiotic use for the prevention of *C. Difficile*-associated disease (CDAD) combined 23 studies and over 4,200 patients and found probiotics reduced CDAD incidence 64% and mitigated the side effects associated with the use of CDAD-specific therapy (Goldenberg et al. 2013). This contributes to recent recommendations that probiotics should be considered to prevent infection in ICU ([criticalcarenutrition.com](http://criticalcarenutrition.com)). It is possible that not only does a patient’s LBM and nutrition status need to be recovered, but also recovery of their microbiome may be required to optimise recovery. This may indicate that repletion or “re-sodding” of beneficial bacteria known to be lost following critical illness could begin to provide a targeted therapeutic avenue to pursue following ICU discharge.

#### Conclusions

In conclusion, we need to consider basic metabolism and historic understanding of starvation and recovery to employ targeted nutritional care to our critically ill patients as they recover following ICU discharge. If we are to optimise patient outcomes and start creating “survivors” we must optimise nutrition delivery post-ICU. It is clear that most patients will be unable to take in adequate nutrition using traditional oral “food”-based diets. It is essential we utilise high protein oral nutrition supplements (HP-ONS) to provide a realistic opportunity for our patients to achieve adequate calorie and protein

delivery during the years required to recover functional lean body mass post-ICU discharge. We also must address issues such as dysphagia and need for targeted rehabilitation exercise efforts post-discharge. Finally, we must learn to target and incorporate nutritional therapies such as vitamin D, probiotics, and anabolic/anti-catabolic agents to optimise our patients’ chance to survive and thrive against all evolutionary odds. We have long known Mother Nature does not want our ICU patients to win this war and become “survivors...and not victims”. But, to begin winning this war on long-term ICU outcomes and give our patients back the lives they came to us to restore, we must ensure, especially post-ICU discharge, our patients get enough nutrition for enough time post-ICU discharge! ■

#### Conflict of interest

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#### Abbreviations

CDAD *C. Difficile*-associated disease  
 FMT faecal microbiota transplantation  
 HP-HMB B-Hydroxy B-Methylbutyrate  
 HP-ONS high protein oral nutrition supplements  
 ICU intensive care unit  
 ONS oral nutrition supplements  
 PICS post-intensive care syndrome  
 RCT randomised controlled trial  
 REE resting energy expenditure  
 QoL Quality of life  
 SGA subjective global assessment  
 TEE total energy expenditure

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