Role of anabolic testosterone agents and structured exercise to promote recovery in ICU survivors

CURRENT OPINION

Paul E. Wischmeyer[a], Oscar E. Suman[b], Rosemary Kozar[c], Steven E. Wolf[b,e], Jeroen Molinger[a,d], and Amy M. Pastva[f]

Purpose of review
ICU survivors frequently suffer significant, prolonged physical disability. 'ICU Survivorship', or addressing quality-of-life impairments post-ICU care, is a defining challenge, and existing standards of care fail to successfully address these disabilities. We suggest addressing persistent catabolism by treatment with testosterone analogues combined with structured exercise is a promising novel intervention to improve 'ICU Survivorship'.

Recent findings
One explanation for lack of success in addressing post-ICU physical disability is most ICU patients exhibit severe testosterone deficiencies early in ICU that drives persistent catabolism despite rehabilitation efforts. Oxandrolone is an FDA-approved testosterone analogue for treating muscle weakness in ICU patients. A growing number of trials with this agent combined with structured exercise show clinical benefit, including improved physical function and safety in burns and other catabolic states. However, no trials of oxandrolone/testosterone and exercise in nonburn ICU populations have been conducted.

Summary
Critical illness leads to a catabolic state, including severe testosterone deficiency that persists throughout hospital stay, and results in persistent muscle weakness and physical dysfunction. The combination of an anabolic agent with adequate nutrition and structured exercise is likely essential to optimize muscle mass/strength and physical function in ICU survivors. Further research in ICU populations is needed.

Keywords
critical illness, muscle, Oxandrolone, rehabilitation, testosterone

INTRODUCTION

Critical illness remains a major US public health crisis. Critical illness currently affects 5.7 million Americans per year and every American can expect to average 1.7 ICU admissions in their lifetime [1]. Cost savings of up to $1 billion/quality life-year gained can be achieved with improved management of ICU-related illness and disability [2]. Innovations in ICU care resulted in yearly reductions in hospital mortality from sepsis [3], and recent data indicates more than 90% of ICU patients survive ICU stays. However, survival comes at a cost. ICU survivors frequently experience significant disabilities, commonly physical including muscle weakness and functional impairments that can persist for years [4–6]. Muscle weakness in the ICU is associated with delayed liberation from ventilation, extended ICU and hospital stays, worse long-term survival, and physical functioning and quality of life [4–7]. These same data reveal many ICU 'survivors' do not return home to functional lives following ICU care, but

[a]Duke Human Pharmacology and Physiology Lab (HPPL), Center for Perioperative Organ Protection (CPOP), Department of Anesthesiology, Duke University School of Medicine, Durham, North Carolina, [b]Department of Surgery, University of Texas Medical Branch, 301 University, Galveston, Texas, [c]Shock Trauma Center, University of Maryland School of Medicine, Baltimore, Maryland, USA, [d]Department of Intensive Care Medicine, Erasmus MC, Erasmus University Rotterdam, Rotterdam, The Netherlands, [e]Shriners Hospital for Children – Texas, Galveston, Texas and [f]Division of Physical Therapy, Department of Orthopedic Surgery, Duke Claude D. Pepper Older Americans Independence Center, Duke University School of Medicine, Durham, North Carolina, USA

Correspondence to Paul E. Wischmeyer, MD, EDIC, FASPEN, FCCM, Professor of Anesthesiology and Surgery, Duke University School of Medicine DUMC, Box 3094 Mail # 41, 2301 Erwin Road, 5692 HAFS, Durham, NC 27710, USA. Tel: +1 919 681 6646; e-mail: Paul.Wischmeyer@Duke.edu

KEY POINTS

- ICU survivors experience a high burden of muscle weakness, functional impairment, and activity limitation, currently existing standards of ICU rehabilitative care when studied in trials are failing to successfully address these disabilities.

- One explanation for lack of success of ICU rehabilitation trials is most all ICU patients exhibit severe testosterone deficiencies early in ICU stay contributing to persistent catabolism and potentially underlying lack of response to current physical therapy interventions.

- Oxandrolone is an FDA-approved testosterone analogue for treating muscle weakness in ICU patients and a growing number of trials with this agent combined with structured exercise show clinical benefit, including improved physical function and safety in burns and other catabolic states.

- Currently, no trials of Oxandrolone or other anabolic testosterone analogues and structured exercise in nonburn ICU populations have been conducted – thus this research is urgently needed.

- The combination of an anabolic agent with adequate nutrition and structured exercise is likely essential to optimize muscle mass/strength and physical function in ICU survivors.

instead are discharged to rehabilitation settings where it is unclear if they ever return to a meaningful quality of life [6]. Collectively, these impaired physical functions are defined as ICU-acquired weakness (ICU-AW) or post-ICU Syndrome (PICS) [6,8■■]. Although we have improved therapies to increase the initial survival from critical illness, the challenge of optimizing recovery and survivorship after ICU care is yet to be meaningfully addressed.

WHY IS IT ESSENTIAL TO DEVELOP NOVEL, INNOVATIVE THERAPIES FOR ICU-ACQUIRED WEAKNESS?

Critical illness is characterized by muscle catabolism with early onset through upregulation of proteolytic pathways [9] associated with systemic inflammatory conditions, such as sepsis [10■] and pro-inflammatory cytokines associated with bedrest [11]. This acute catabolic response leads to rapid loss of lean body mass, weakness, and loss of physical function [6,12]. ICU-AW is a clinical diagnosis made via manual muscle strength testing and is reported in 25–65% of patients [13]. Catabolism, hypermetabolism, and muscle weakness, under current standard

of ICU care, often persists for a prolonged period after onset of critical illness, and is a major contributor to the prolonged physical disability and slow rehabilitation process [14■■].

Recent data shows that two of three ICU survivors (65%) suffer significant functional limitations and impaired quality of life [6]. Another recent study showed ICU patients (mean age: 55) are most likely to be discharged to postacute care facilities and incur substantial costs of ~$3.5 million per functioning survivor [15]. Studies of diverse populations consistently show ICU survivors experience a high burden of muscle weakness, functional impairment, and activity limitation [6,16]. In fact, recent data reveal persistent functional limitation results in only 50% of patients returning to employment at 1 year after receiving ICU care [17,18]. Patients also have difficulty performing activities of daily living, and only reach 60–65% of functional exercise capacity 12 months after onset of critical illness [8■■,19,20]. Finally, survivors report prolonged weakness and loss of function following ICU care as the most concerning disabilities they experience [8■■]. Thus, the question arises, are we creating survivors…or victims? In response, 'ICU Survivorship' and addressing impaired quality of life and function in ICU survivors has been named 'the defining challenge of critical care' for this century [21]. The NIH along with all major ICU societies have recommended giving priority to research addressing quality of life issues after ICU treatment [22]. Thus, a significant unmet need is thoroughly evident, and should engender development of new therapies to address the devastating impairments facing ICU survivors and improve their functional outcomes in this rapidly growing population.

PHYSICAL REHABILITATION/EXERCISE INTERVENTIONS ALONE FAIL TO CONSISTENTLY ADDRESS MUSCLE LOSS AND RECOVERY OF QUALITY OF LIFE IN ICU SURVIVORS

The landmark Schweikert trial [23] found very early mobilization in mechanically ventilated medical ICU patients improved measures of physical function at hospital discharge. However, this trial did not examine long-term quality-of-life outcomes. Further, this study is yet to be meaningfully repeated in a broader ICU population (i.e. including surgical ICU patients). Unfortunately, the most recent (2018) meta-analysis of early rehabilitation in the ICU was unable to conclude whether early exercise in ICU improves patient muscle strength or quality of life after ICU care [24■■]. Further, mixed results were seen for the effect of early exercise on physical

function [24■■]. In actual practice, initiation of ICU rehabilitation is often markedly delayed or sometimes not delivered for many days after ICU admission. The mean time to commence rehabilitation in the ICU in the only three RCTs that have examined this question is 9 days after ICU admission [19,23,25]. A large multisite point prevalence study showed that less than 20% of ICU patients were mobilized out-of-bed at all [26]. Unfortunately, the current usual standard of care of delayed ICU rehabilitation has shown limited benefit on any ICU-AW and quality-of-life outcomes [8■■]. As stated in a recent review of interventions for Post-ICU Syndrome (PICS) article 'Randomized controlled trials of physical rehabilitation interventions initiated several days after ICU admission have generally yielded no consistent evidence of benefit [8■■]'. Further, very few studies examined the effect of rehabilitation after ICU care. A recent summary of this limited evidence concluded insufficient evidence was present to determine any effect on functional exercise capacity or quality of life for an exercise-based intervention initiated after ICU discharge [27]. Unfortunately, no effect on quality of life was reported by any study examined. On balance, for optimal benefit, it is clear rehabilitation should begin early in ICU stay and continue after ICU discharge. These data indicate that ICU exercise and rehabilitation, even controlled interventions in RCTs, fail to consistently improve physical function or quality of life. Thus, despite promising signals on some early outcomes after discharge from the ICU, it does not appear that ICU rehabilitation alone is sufficient to meaningfully address ICU-AW and improve function and quality of life in patients receiving ICU care.

WHY DO ICU REHABILITATION EFFORTS FAIL TO ADDRESS MUSCLE AND PHYSICAL FUNCTION RECOVERY IN ICU SURVIVORS?

A primary explanation for the inability of current rehabilitation and exercise interventions to meaningfully address functional recovery and survivorship in ICU patients is the significant ongoing catabolism and anabolic resistance observed in critical illness that extends well into the time after ICU care. High levels of muscle protein degradation [28] and sustained muscle atrophy leading to impaired muscle recovery [29] are strongly related to ongoing catabolism and inability to utilize available substrate for muscle anabolism and recovery. This is known to occur, despite adequate nutrition delivery and physical rehabilitation [29]. Critically ill and injured patients can lose as much as a kilogram of

lean body mass (LBM) per day [30]. Patients often regain weight after ICU care but much of this is fat mass accumulation rather than functional LBM gain [4]. Adequate nutrition delivery is essential for ICU functional and LBM recovery and mitigates the extent of weight loss in ICU patients but this is mostly via acquisition of additional fat mass [31]. Interestingly, even with aggressive enteral feeding, where 2–3 g/kg/day of protein is provided, skeletal muscle wasting continues to persist in ICU patients with burns. This persistent hypermetabolism and catabolism, which is currently not meaningfully addressed by even aggressive nutrition and/or exercise/rehabilitation interventions appear to be markedly hindering recovery of muscle mass and function, and ultimately meaningful 'survivorship' in ICU survivors [30].

ROLE OF TESTOSTERONE DEFICIENCY IN ICU CATABOLISM AND POOR FUNCTIONAL RECOVERY

Critical illness is characterized by marked reductions in gonadal steroid production, significantly contributing to the catabolic state ubiquitously observed in the ICU [32]. Initially, this likely reflects the global hormonal dysregulation seen in acute illness, and is commonly observed with other well known hormones (insulin, cortisol). However, persistent hypotestosteronemia (low-T) in acute illness contributes to impaired recovery and rehabilitation [32], as low-T conditions are correlated with disease severity and survival [32]. Low-T discovered during hospitalization is associated with increased in-hospital [33] and long-term mortality [34], and predicts both all-cause mortality [35] and cardiovascular mortality [36■]. Specific to ICU patients who receive mechanical ventilation, low-T levels occur by day 3 in 94.4% (total T) and 100% (free T) of patients. In this study, total and free T levels correlated inversely with ventilator days and ICU length of stay [32]. Low-T levels are also known to persist throughout ICU stay and into the period after ICU discharge. A study in patients after ICU care showed 96% of patients were testosterone-deficient after ICU discharge [37]. Thus, any intervention targeted to attenuate catabolism and muscle loss, must continue into the post-ICU period.

Benefits of testosterone and its analogues combined with rehabilitative exercise on clinical outcome and physical function have been demonstrated in a range of illnesses, although no studies of a combined multimodal intervention examined physical function and muscle outcomes in nonburned critically ill patients at the greatest risk of ICU-AW. A recent meta-analysis showed that

testosterone improves exercise tolerance in heart failure patients [38]. A randomized trial of an anabolic-targeted testosterone analogue nandrolone versus testosterone or placebo for HIV muscle-wasting showed improved weight gain and quality of life [39]. COPD patients given the testosterone analogue nandrolone also showed improved muscle function and exercise capacity [40]. Oxandrolone, an easier to utilize oral anabolic-targeted testosterone analogue, is Food and Drug Administration (FDA)-approved for use in ICU and surgical patients. Although little research has been conducted to support this indication in nonburn ICU patients, two small trials examined Oxandrolone alone on basic clinical outcomes in surgical and trauma populations. A small trial in trauma patients gave Oxandrolone during acute ICU phase and did not find differences in mortality or length of ICU stay [41]. Another small study of patients with prolonged mechanical ventilation (>7 days) showed a signal of prolonged ventilation days in Oxandrolone group [42]. Limitations include the question of whether low tidal ARDS net volume strategies were employed, which is the current worldwide standard of care. Further, individuals in both groups only received ~50% of calorie/protein delivery during the study, limiting potential of anabolic agent to benefit patients. Finally, Oxandrolone was initiated later in ICU stay and was only given during ICU stay, and not in the critical period upon discharge from ICU when adequate nutrition delivery and recovery of muscle mass is more likely to occur. Neither described rehabilitation intervention nor collection of muscle/physical function, quality of life, nor direct muscle mass endpoints were conducted in either of these studies.

Oxandrolone has been used successfully in a range of other settings to improve clinical and functional outcomes [43]. In severe burns, many trials show benefits of Oxandrolone administration [30] and it is a common standard of care in burn centres worldwide (S. Wolf, personal communication). A recent burn injury trial shows Oxandrolone leads to gains in LBM, bone mineral content, and muscle strength in critically ill burned children [44]. Interestingly, lean mass was not found to be restored by the nutrition treatment and standard usual care rehabilitation/physical therapy alone group in this study, showing nutrition and usual care rehabilitation is not sufficient to recover LBM without an anabolic stimulus [44]. Importantly, the improvements from Oxandrolone were maintained 6 months after discontinuation of Oxandrolone. Other studies showed Oxandrolone reduces mortality in severely burned patients [45], reduced muscle protein catabolism via improved protein synthesis efficiency [46], and reduced wound healing times

and weight loss [47]. Significant reductions in length of hospital stay were observed in a prospective randomized, multicentre study of Oxandrolone in burn injury [48]. A key trial also showed Oxandrolone benefits were age-independent, as older adults (mean age 60 years) experienced similar benefits of reduced hospital LOS and improved muscle mass as younger patients [49]. A meta-analysis of 15 randomized controlled trials (RCTs) with 806 participants showed Oxandrolone has significant benefits in severe burns treated in the ICU including reduced weight loss, increased lean body mass loss, decreased nitrogen loss, improved donor-site healing time, and reduced LOS without any increase in infection, metabolic rate, hyperglycaemia, or liver dysfunction [50]. Overall, this systematic review suggests Oxandrolone is an effective and well tolerated treatment in critically ill burn patients.

One factor potentially limiting wider use of testosterone and its analogues in the ICU has been concern for association of testosterone and increased cardiacvascular and thromboembolic events [51]. Concerns for these potential risks were dispelled by two large studies, including a ~43 000 subject trial showing teststerone-deficient persons, including most ICU patients receiving testosterone had a 33% reduction in all-cause cardiovascular events and 28% reduced stroke risk compared with those not treated [52]. A second trial of 4736 testosterone-deficient subjects receiving testosterone had 26% reduced 3-year Major Adverse CV Event (MACE) rate, and 35% reduced death rate compared with untreated individuals [53]. In patients with known cardiovascular disease, untreated low testosterone levels were associated with higher 3-year MACE and death rates. Thus, testosterone supplementation, even in preexisting cardiovascular/stroke-related disease, does not appear to lead to risk of adverse events. In fact, testosterone supplementation appears to reduce cardiovascular/stroke risk in low-T patients. Thus, we suggest that treatment of common and pervasive testosterone deficiency in ICU patients may be a solution to facilitate the presumed benefit of structured rehabilitative exercise with adequate nutrition delivery, and improve function, quality of life, and recovery following ICU care. Studies to address this potential should be undertaken.

Suggestions for testosterone and Oxandrolone dosing

See Table 1 for summary of commonly used testosterone and testosterone analogues. Testosterone and testosterone analogues have two primary properties: androgenic and anabolic. The different mechanisms

Table 1. Commonly used forms of testosterone supplements in ICU/burn setting

Oxandrolone: commonly utilized dosing: 5–10 mg orally (PO) twice daily (typical adult dose: 10 mg) (doses used in [55–57]

    Primarily anabolic with minimal androgenic effects

    Minimal risk of liver enzyme elevation

    Anabolic : androgenic activity ratio 13 : 1 [54]

Nandrolone: commonly utilized dosing: 100–200 mg (male) and 50–100 mg (female) intramuscularly weekly (doses discussed in ref [58■])

    Primarily anabolic with minimal androgenic effects

    Anabolic : androgenic activity ratio 12 : 1 [54]

Testosterone Cypionate: commonly utilized dosing: 200–400 mg intramuscularly every 2 weeks (doses derived from package insert – see weblink[a])

    Relatively balanced ratio of anabolic to androgenic activity: 0.7–1.3 : 1 [54]

    Commonly utilized outpatient testosterone replacement intervention

Testosterone patches: example dose: 2–4 mg patch for patch specific number of days per application. Please note that different patch strengths and types exist? Check with local hospital pharmacy for specific patch type available and prescribing recommendations

    May be poorly absorbed in ICU patients because of oedema and poor skin perfusion

    May not adequately correct severe testosterone deficiencies present in ICU patients

Care Notes: check regular (weekly) testosterone levels when giving primary testosterone preparations to ensure adequate correction (testosterone level >240 ng/dl) and to avoid elevated testosterone levels (>950 ng/dl) (per Mayo Clinic Reference Lab normal values); check regular (weekly) liver function tests for AST/ALT to follow liver enzyme elevations that are rarely related to testosterone therapy.
[a]Testosterone Cypionate package insert: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=f60c5520-b336-44a2-95d5-f274939fa595&type=display.

include modulation of androgen receptor expression and interference of glucocorticoid receptor expression, which results in anticatabolic and anabolic effects. Targeted anabolic testosterone analogues have modified the testosterone structure to maximize anabolic properties, while attempting to eliminate/minimize unwanted androgenic effects. Targeted anabolic testosterone agents, such as Oxandrolone or nandrolone exhibit significantly higher selectivity for muscle recovery and anabolic properties, with minimal androgenic effects (anabolic : androgenic activity ratio of 12 : 1 and 13 : 1, respectively) [54]. Consequently, potential for adverse outcomes including aromatization and virilizing effects in women is significantly minimized.

Typical adult dosing used in studies of burned patients from our preliminary results and previous literature in burn injury and other illnesses show 10 mg two times a day has been effective in improving muscle strength, muscle function, and clinical outcomes [55–57]. In most studies, this is given starting a few days after hospital admission (typically within 96 h of ICU admission) until hospital discharge. Nandrolone, an anabolic-specific testosterone agent has also been published in case reports of ICU patients to address ICU-acquired weakness [58■]. Other testosterone delivery methods may also be effective, such as traditional intramuscular testosterone cypionate (which is a common outpatient testosterone replacement formulation) given at a dose of 200–400 mg every 2 weeks. Testosterone patches can also be utilized (typical dose supplied

4 mg patch), although this often is not as effective absorbed in critically ill patients with oedema and altered skin perfusion and may not adequately correct thee severe deficiencies seen in ICU patients. Following testosterone levels throughout care is essential to ensure adequate testosterone replacement is occurring with elevated levels being observed. Further, weekly liver function tests should be monitored, although elevations of LFTs from shorter term ICU Oxandrolone and testosterone use are relatively rare [55–57].

STRUCTURED, MULTIDOMAIN REHABILITATION

An intervention that addresses multiple domains necessary for independent physical function, that is individually tailored with targeted milestones for progression, and that extends through the hospital stay has yet to be fully explored in patients with critical illness. A potential model of interest is that used in the NIH-funded REHAB-Heart Failure trial (clinicaltrails.gov NCT02196038), which implemented multidomain rehabilitation (MDR) for heart failure patients with profound physical deficits paralleling those found in critical illness [59■■,60,61].

The REHAB-HF MDR intervention is an application of proven rehabilitation therapies selected and integrated specifically to target deficits in physical function precipitated by acute illness [59■■]. The goal of the intervention is to increase functional performance across the four physical function

domains of strength, balance, mobility, and endurance using reproducible, targeted exercises with, importantly, specific milestones for progression. The relative time spent on each physical function domain during a rehabilitation session is tailored to the patient's deficits. For example, a patient with poor balance and functional mobility spends a greater proportion of time performing balance and mobility exercises in the early stages of the intervention. Alternatively, a patient with adequate balance and mobility spends most of the session performing endurance and strengthening. Strengthening rehabilitation include functional strengthening exercises on the lower extremities (i.e. closed chain sit-to-stand, step-ups, calf/toe raises). Balance rehabilitation incorporates static exercises, including progressively narrowing base of support with eyes open or closed, and dynamic exercises, including reaching forward and backward starting within base of support and progressing to outside base of support. Mobility rehabilitation includes dynamic start and stop while walking, changing direction while walking, and episodes of decelerated and accelerated gait. Endurance rehabilitation includes walking as the preferred mode. The MDR intervention would begin once the ICU patient can voluntarily participate (i.e. postsedation, stable vitals) and continue through hospital discharge.

ROLE OF NUTRITION IN ICU RECOVERY UTILIZING ANABOLIC AGENTS AND STRUCTURED EXERCISE

Adequate nutrition delivery must be assured to optimize potential benefit of Oxandrolone and exercise intervention. A structured nutrition delivery strategy is optimal for achieving this successfully as described in recent review on ICU and post-ICU nutrition [62▪▪]. Another excellent algorithm is described in the recently published EFFORT trial. This multicentre randomized trial studied acutely ill hospitalized patients at high nutrition risk [63▪▪] and found a structured nutrition algorithm led to significant reductions in mortality and complications at 30 days. Importantly, the nutrition algorithm should be adapted for the ICU and after ICU discharge to lead to significant improvement in recovery and functional independence ($P < 0.006$)
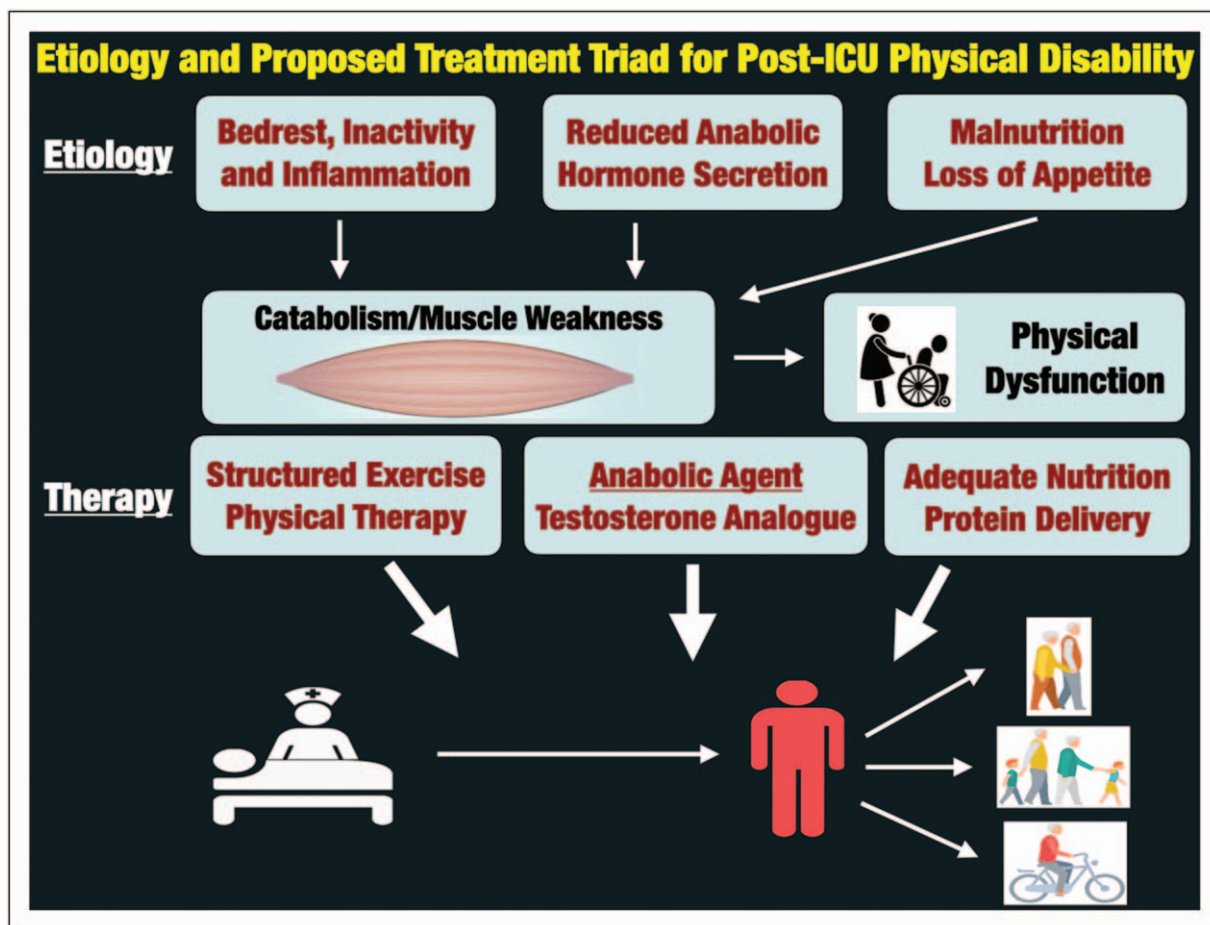
FIGURE 1. Aetiology and proposed treatment triad for post-ICU physical disability.

and EQ-5D QoL at 30 days ($P = 0.018$). Thus, we believe using a structured feeding algorithm and the long-studied nutrition strategies described should optimize necessary nutrition delivery in the ICU.

CONCLUSION

In conclusion, critical illness leads to a catabolic state, including severe testosterone deficiency that persists throughout hospital stay. This results in persistent muscle weakness, physical dysfunction, and impaired functional QoL. We believe the combination of an anabolic agent with early exercise and adequate nutrition is the essential triad required to optimize muscle mass/strength and physical function in ICU survivors (see Fig. 1). We believe all three key pathways (anabolism, exercise, and nutrition) must be addressed in an ICU recovery intervention if we hope to ultimately improve 'ICU Survivorship', address impaired post-ICU quality of life in ICU survivors and triumph over 'the defining challenge of critical care' for this century [22].

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