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Chronic Critical Illness: Application of What We Know

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Abstract

Over the last decade chronic critical illness (CCI) has emerged as an epidemic in ICU survivors worldwide. Advances in ICU technology and implementation of evidence based care bundles has significantly decreased early deaths, and have allowed patients to survive previously lethal multiple organ failure (MOF). Many MOF survivors, however, experience a persistent dysregulated immune response that is causing increasingly predominant clinical phenotype called the Persistent Inflammation, Immunosuppression and Catabolism Syndrome (PICS). The elderly are especially vulnerable, and thus, as the population ages the prevalence of this CCI/PICS clinical trajectory will undoubtedly grow. Unfortunately, there are no proven therapies to prevent PICS and multimodality interventions will be required. The purpose of this review is to discuss a) CCI as it relates to PICS, b) identify the burden on health care and poor outcomes of these patients, and c) describe possible nutritional interventions for the CCI/PICS phenotype.

Keywords

Chronic Critical Illness; ICU acquired weakness; Persistent; Inflammation; Immunosuppression; Catabolism; Syndrome; PICS

Introduction

Critical illness phenotypes continue to evolve as mortality from acute critical illness has dramatically decreased, especially when discussing severe sepsis and septic shock.[1, 2] Nevertheless, patients who survive the acute phase of critical illness continue to linger much longer in the ICU developing a much more chronic phase. The term Chronic Critical Illness (CCI) was first coined by Girard and Raffin in 1985 when discussing acutely ill patients requiring ongoing support in the ICU setting.[3] In the late 1990's, reports continuing to

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describe chronic critical illness (CCI) emerged under a variety of descriptive terms including: “neuropathy of critical illness”, “myopathy of critical illness”, “ICU acquired weakness” and most recently “post intensive care unit syndrome”.[4] These reports largely originated from medical ICU’s, and included a rather heterogeneous mixture of admission diagnoses. A common thread among most reports describing CCI seemed to have an acute exacerbations of chronic diseases, and need for prolonged mechanical ventilation. Thus, persistent low grade organ dysfunctions appears to be a common thread linking most etiologies of CCI.

A clinical definition of CCI as a prolonged mechanical ventilation support for more than 21 days for at least 6 hours per day or patients who require tracheostomy within the course of their ICU admission was described in 2005.[5] Khan and colleagues used a combined quantitative and qualitative measure to define CCI: >8 days in an ICU with one of five eligible clinical conditions (mechanical ventilation for at least 96 hr in a single episode; tracheostomy; sepsis and other severe infections with multiple organ failure (MOF), ischemic stroke, intracerebral hemorrhage, or traumatic brain injury).[6] In the search to define Persistent Inflammation, Immunosuppression, Catabolism Syndrome (PICS), Vanzant et al, defined CCI is: > 14 days in ICU with organ dysfunction.[7] CCI and PICS both represent patients with aberrant immunology where homeostasis is not achieved and dysfunction persists. These CCI patients experience ongoing immunosuppression (e.g. lymphopenia), inflammation (e.g. neutrophilia with elevated acute phase response proteins), and significant lean muscle mass wasting associated with catabolism.[8–10]

Unfortunately, PICS is the consequence of optimal evidence based ICU care and currently the therapies to prevent or treat CCI and PICS are limited. Given the complex and persistent nature of the underlying dysregulated immunity, multimodality treatment will be required that will need to be extending beyond hospitalization to enhance rehabilitation. The purpose of this review is to discuss a) CCI as it relates to PICS, b) identify the burden on health care and poor outcomes of these patients, and c) describe possible nutritional interventions for the CCI/PICS phenotype.

The CCI/PICS Clinical Trajectory

CCI, as discussed above, is organ dysfunction that persists longer than 14 days in an ICU patient. This is surprisingly common in surgical ICUs. Originally, it was thought that the leading risk for CCI was age >65, chronic comorbidities, and admission to the ICU.[7–9] Recently, in accordance with previous thoughts, new evidence suggests that after major torso trauma, CCI occurs in roughly 20%, while after sepsis the incidence approaches 50%.[11, 12] These CCI patients compared to patients who rapidly recover are typically older (>55), have poorer premorbid health status, and have sustained more severe trauma or septic insults.[7, 13–17] Mira and Brakenridge et al. concluded that CCI is a common trajectory of critically ill poly-trauma survivors and is associated with poor long-term outcomes. In this recent review of major torso trauma patients, the multivariate analysis revealed age ≥55-years, systolic hypotension ≤70-mmHg, transfusion ≥5-units packed red blood cells within 24-hours, and Denver MOF score at 72-hours as independent predictors of CCI (AUC 0.87, 95% CI [0.75, 0.95]).[11] In contrast a recent review of surgical septic patients revealed of

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145 septic patients enrolled, nineteen (13%) died during their hospitalization and 71 (49%) developed CCI based on the definition of CCI >14 days ICU length of stay and persistent organ dysfunction.[18]

There are several other ICU pathophysiologic states that are either similar in nature or are part of the CCI spectrum. Among these entities are ICU acquired weakness, diaphragm dysfunction associated with prolonged mechanical ventilation, and PICS.[10] Most of these patients, if not all, were observed to lose tremendous amounts of lean body mass despite optimal nutrition causing profound weakness (catabolism), suffer from recurrent nosocomial infections (immunosuppression), typically develop decubitus ulcers, have poor wound healing, sepsis recidivism, and ultimately poor long-term outcomes.[8–10, 19] A recent report by Puthucheary et al described demonstrated the basis of ICUAW associated with CCI. In this prospective observation trial of 63 critically ill patient with an average APACHE II score of 23.5 he found that the rectus femoris cross sectional area (CSA) decreased on average 17.7% by day 10, as well as, the ratio of protein to DNA decreased by 29.5%.[20] He also observed that with increasing organ failure the muscle breakdown and decrease in CSA was more significant despite adequate nutrition. In fact, “leg protein breakdown remained elevated throughout the study with the pattern of intracellular signaling supporting increased breakdown and decreased synthesis”.[20] The novel observation of the study was 40% of these patient had evidence of muscle necrosis associated with inflammatory cell infiltrate on serial muscle biopsies. This provocative observation indicated that the muscle is likely a target of the dysregulated immunity related to CCI/PICS and may explain why early aggressive nutrition may be ineffective in preventing the progressive muscle loss seen in these patients.[20] Additionally, CCI patients tend to be or become frail and suffer from significant levels of pain, dyspnea, psychological distress, thirst, fatigue, delirium, and distress related to impaired communication.[21–26] These symptoms not only stem from the protracted course of their hospital stay, but are associated with their exposure to ICU interventions that cause distressing symptoms, as well.[21, 22, 25, 27] Ultimately, CCI and PICS victims have poor long term quality of life; suffering from depression, cognitive impairment, complex physiologic abnormalities, organ dysfunction, neuroendocrine deficits, and immunologic dysfunction. [13, 14, 25, 28–33]

While the underlying mechanism for these devastating ICU syndromes is undoubtedly multifactorial, the laboratory work of Moldawer and Efron et al using chronic murine models of sepsis and trauma have identified the expansion of myeloid derived suppressor cells (MDSCs) to explain the persistent immune dysregulation observed in CCI/PICS. A recent focused translational study of 67 surgical patients with severe sepsis confirmed the clinical relevance of these laboratory observations. It showed that the numbers of MDSCs rapidly increase after sepsis and are persistently elevated out to 28 days.[34] Importantly, these MDCSs were shown to suppress T lymphocyte proliferation and decrease the release of T_{H1} and T_{H2} cytokines. Moreover, MDSC expansion correlated with adverse outcomes including: a) early increased expansion was associated with early mortality, b) persistent expansion was associated with prolonged ICU stays and c) persistent expansion was a strong independent predictor of nosocomial infections and poor post discharge disposition.[34] These data provide the theoretical basis for the use of immune-stimulants that modulate

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MDCSs similar to what has been successfully utilized in advanced malignancies to achieve durable response rates.

Burden on Healthcare and Poor Outcomes

Now that CCI/PICS patients are surviving and being discharged from ICUs health care costs reflect this struggling patient population and places significant burden on their care-takers. In fact, Kahn and Iwashyna et al. estimated that 5–7.6% of patients admitted to the ICU develop CCI, accounting for more than 380,000 cases, 107,000 in-hospital deaths, and over $26 billion in health care expenses.[6, 35] Iwashyna also demonstrated that despite CCI accounting for only 5% of ICU admissions, patients that develop CCI have over 30% of ICU utilization [36]. Both authors report that these patients are less likely to be discharged home and have higher inpatient mortality. [6, 36] In fact, of the patient that ultimately develop CCI, Cox et al, found that only 10% will achieve enough functional capacity to independently live at home within one year of discharge.[37]

In new data discussed above, Mira and Brakenridge et al demonstrate that CCI patients are more likely to be discharged to a long-term care (LTAC) setting (56% vs 34%, p=0.008) than to a rehabilitation facility or home. Additionally CCI patients at four-months had higher mortality (16.0% vs 1.9%; $p<0.05$), compared to survivors scoring lower in general health measures ($p<0.005$).[11] In another recent report, CCI patients were more likely to be discharged to long-term acute care facilities (32% vs 3%, $p<0.0001$), whereas those with rapid recovery were more often discharged to home. 6-month mortality was significantly higher in CCI as compared to a rapid recovery cohort (37% vs 2%; $p<0.01$).[18] These two studies only affirm that CCI patients have reduced rehab potential and poor discharge disposition.

Ultimately, these CCI patient live through the acute illness only to have exuberant financial toll on Healthcare systems [13, 35, 38] and caregivers (strained relationships, depressed mood, adverse psychological responses, and underlying stress).[39, 40] To revisit Kahn et al, he published that the in-hospital mortality for a CCI patient was 30.9%, and that the overall population-based prevalence was 34.4 per 100,000. Extrapolating his data to the entire United States, for the year 2009, Kahn estimated a total of 380,001 cases of CCI; 107,880 in-hospital deaths and $26 billion in hospital-related costs.[6]

The Census Bureau estimates that between 2000 and 2025 the elderly population will grow by ~80%; making the incidence of CCI and PICS to likely increase, as well.[41] Thus, a P50 grant award to the University of ***, *** will continue to research CCI, frailty in surgery, and PICS through the grant by NIGMS entitled, “***”.

Possible Nutritional Interventions

The persistent smoldering inflammatory and catabolic state, hormonal elaboration, and perpetual downward spiral of CCI, produces a “cachexia” phenotype for which current ICU nutritional interventions are relatively ineffective. Current literature surrounding supportive care for CCI patients is unified by two crucial strategies: early mobilization and anabolic

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nutrition. In this section the role of protein and anabolic supplements, immunonutrition, and specialized pro-resolving mediators will be reviewed.

Protein and Anabolic Supplements

In reviewing the literature on sarcopenia, a slower, yet similar pathologic state to CCI, Fiatarone et al recommends resistance exercise and anabolic nutrition. She stresses the need for high resistance exercise (early mobilization of ICU patients) coupled with supplemental nutrition to maintain lean muscle mass.[42–44] Reinforcing Fiatarone's claim, Paddon-Jones et al, established that daily protein consumption of 0.8–1.5 g/kg/d of daily protein and dietary derived amino acids potentially slows or prevent muscle protein catabolism.[45–47] Additionally, Morely et al, and The Society of Sarcopenia, Cachexia, and Wasting Disease recommended >1.5 grams/kg/day of protein, as well as, in combination with exercise and supplemental leucine and creatine.[48] Leucine is an amino acid that can stimulate the Mammalian Target of Rapamycin (mTOR) pathway increases protein synthesis and inhibits protein breakdown.

More recently, however, The Protein Summit met to re-establish new recommendations for nutritional guidelines. Historically, critically ill patients were recommended to receive >1.2grams/kg/day of protein supplementation.[8, 49, 50] As the literature evolves an understanding has emerged that the old recommendation may be underfeeding protein. During periods of physiologic stress the bodies tends to catabolize large amounts of protein. [51] In sepsis and blunt trauma, Plank and Monk et al. showed that resting energy expenditure peaks at about 4–5 days, can continue for up to 12 days, and can lose up to 16% of total body protein.[52–54] Similarly, in burn patients, "the hypermetabolic response to major burn injury is associated with increased energy expenditure, insulin resistance, immunodeficiency, and whole body catabolism that persists for months after injury".[55] This has lead Herdon et al. to recommend 2 grams/kg/day protein supplementation for appropriate compensation of the catabolic insult.[56] Nevertheless, the current guidelines have raised the recommendation to at least >1.5 grams/kg/day protein supplementation to provide adequate nutrients for the critically ill, catabolic patient. The questions remains: Is 1.5 grams/kg/day enough for CCI patients?

In the past half-decade, studies have emerged showing clear benefit to delivery of protein calories over non-protein supplements. Weijs et al, showed that early high protein delivery had survival benefit, yet energy overfeeding was linked to increased mortality.[50, 57] Allingstrup, echoed Weijs findings, adding that a higher provision of protein (>1.46 grams/kg/day vs 1.06 or 0.79 grams/kg/day) and amino acids was associated with a lower mortality.[58]

Importantly, Compher et al, showed that increased protein deliver had a significant survival benefit in nutritionally high risk patients based off the Nutrition Risk in the Critically Ill (NUTRIC) >5. Compher concluded that, greater nutritional and protein intake is associated with lower mortality and faster time to discharge alive in the high-risk, longer stay patients but not significantly so in nutritionally low-risk patients.[59] These are the CCI patients. The ones who "are high risk and longer stay patients". Moreover, in 2013 Wolfe and Deutz et al, described an "anabolic response" where higher protein supplementation suppresses

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endogenous protein breakdown. The anabolic response is a measure of fractional synthetic rate (FSR) minus the protein breakdown, and was even more positive with higher amounts of protein provided.[60] This has inordinate implications for CCI/PICS patients to combat catabolism and potential feed them with increasing doses of protein. Unfortunately, there is a paucity of literature prescribing large doses of protein in the CCI/PICS patient population, and that at this time only inferences can be made based off the body of literature we currently have.

In addition to protein delivery, there are increasing supplements intensivist could provide to help trigger anabolism or use as an anti-catabolism agent. Among these agents Herndon et al described in the pediatric burn population the use of a) growth hormone [55], b) intensive insulin therapy [61, 62], c) oxandralone [63, 64], d) propranolol [65] and e) exercise programs[66]. These hormones and medications have a net ability to be “potent anabolic agent and salutary modulator of posttraumatic metabolic responses”.[55] The conclusion was that they can increase lean muscle mass, bone mineralization, strength, and attenuate the hypermetabolic response to burn. In doing so, patients would have shortened recovery. [61, 62, 67]

Immunonutrition

Protein and amino acids (AA) are not only beneficial for this patient population, but also are intriguing as they can serve dual purpose with the capability for immunomodulation. Arginine is a conditional amino acid whereby endogenous production is insufficient during periods of metabolic stress (such as sepsis), and requires supplementation to restore maximal function of the immune system.[68] With regards to the immune system arginine has two important roles: production of nitric oxide (NO) and lymphocyte function. Three isoforms of NO synthase (eNOS, iNOS, nNOS) transform arginine into systemic NO.[8, 69–77] NO has been shown to be an intracellular signaling molecule, influencing a multitude of mammalian organ systems. NO is also responsible for improved bactericidal action in macrophages. Arginine also has a potent modulatory role on the immune system via its effects on lymphocyte proliferation and maturation, as well as, lymphocyte and macrophage differentiation [78–87].

Thus, Arginine deficiency or unavailability leads to T-lymphocyte suppression and lack of proliferation [78, 81, 84]. Consequently, T-cell dysfunction leads to reduced circulating CD-4 cells, increased interleukin-2, increased interferon gamma production, and loss of T-cell receptor complex called the zeta-chain peptide rending the receptor incapable of recognizing antigen[68, 70, 84, 88]. Limited arginine coupled with a loss of T-cell receptor function results in multi-level impaired immune function and response. This immune-incompetence is believed to contribute to an increased infectious morbidity in critically ill patients. [84] Controversy exists as to the supplementation of arginine during sepsis, but the CCI/PICS patients are typically outside their initial septic insult. Thus, theoretical benefit would be derived by repleting this conditional AA in this patient population to restore some of the immunosuppression.

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Specialized Pro-Resolving Mediators

A relatively new agent that shows promise in treating and preventing CCI are lipid mediators collectively called Specialized Pro-Resolving Mediators (SPMs), of which resolvins have the most potential. SPMs are purified fish oil that promote resolution of the aberrant inflammatory cascade. Serhan et al, identified that SPMs decrease inflammation by cessation of leukocyte infiltration and activation, and "pro-resolve" inflammation through enhanced macrophage clearance of debris, bacteria, and apoptotic cells.[89, 90] Further research is needed, but these molecules could potentially attenuate the SIRS/Septic response allowing for early recovery back to functional status in our critically ill patient population.

Conclusion

Chronic critical illness is a pathophysiologic state, much like PICS, that is very difficult to treat. Identifying who is going to get chronic critical illness is of utmost importance to start various therapeutic strategies early to hopefully stop the potentiation to PICS. Breaking this downward spiral is going to take a multimodal approach combating the malnutrition, ICU acquired weakness/neuropathy, and restoring anabolism. Further research is needed at the cellular level to control MDSC proliferation, and in the outcomes arena to clinically see which nutritional strategies have impact. High protein supplementation has been shown to work, but now we need to see how much is best for patient with CCI. Finally, SPMs could hold the future for attenuating the overly robust and persistent immunosuppressive, inflammatory, catabolic nature CCI patients have with the ultimate goal to regain muscle mass, increase the possibility of rehab, and regain baseline function/independence once discharged from the ICU.

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