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Review Article

Post-intensive care syndrome: its pathophysiology, prevention, and future directions

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Expanding elderly populations are a major social challenge in advanced countries worldwide and have led to a rapid increase in the number of elderly patients in intensive care units (ICUs). Innovative advances in medical technology have enabled lifesaving of patients in ICUs, but there remain various problems to improve their long-term prognoses. Post-intensive care syndrome (PICS) refers to physical, cognition, and mental impairments that occur during ICU stay, after ICU discharge or hospital discharge, as well as the long-term prognosis of ICU patients. Its concept also applies to pediatric patients (PICS-p) and the mental status of their family (PICS-F). Intensive care unit-acquired weakness, a syndrome characterized by acute symmetrical limb muscle weakness after ICU admission, belongs to physical impairments in three domains of PICS. Prevention of PICS requires performance of the ABCDEFGH bundle, which incorporates the prevention of delirium, early rehabilitation, family intervention, and follow-up from the time of ICU admission to the time of discharge. Diary, nutrition, nursing care, and environmental management for healing are also important in the prevention of PICS. This review outlines the pathophysiology, prevention, and future directions of PICS.

Key words: Cognitive impairment, end-of-life, ICU-acquired weakness, intensive care unit, mental impairment, physical impairment, PICS-p, post-intensive care syndrome

BACKGROUND

EMERGENCY AND INTENSIVE care medicine have evolved dramatically in the past quarter-century due to technical innovation and guidelines for improving and standardizing auxiliary circulation and respiratory equipment in the intensive care unit (ICU) and standardization and enhancement of educational programs. For these reasons, the short-term outcomes of ICU patients, including mortality and 28-day survival rates, have dramatically improved; however, the long-term prognosis and quality of life of sepsis patients have not yet improved.[1]

Furthermore, the increase in the elderly population is a major social challenge for developed countries. In addition to Japan, the average age of citizens is rising even in advanced countries of Europe as well as the USA, China, Korea, and many other Asian countries. Furthermore, by 2050, the percentage of elderly people over the age of 65 years will be over 20% in most of the world except for countries in Africa and the Middle East, making them super-

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aged societies.[2] The increase in the elderly population is a major social problem in Japan and worldwide and the number of elderly and elderly patients is increasing rapidly. Along with the aging of the population and progress in medical technology, the number of elderly people requiring intensive care increases annually and management of the elderly is essential in the emergency department and ICU.

Age is a poor prognostic factor for mortality in ICU patients, especially those with sepsis.[3] Elderly people aged 65 years and older comprise approximately 60% of sepsis patients and account for approximately 80% of deaths.[4] With aging worldwide, the number of patients with sepsis has increased, greatly influencing the long-term prognosis of ICU patients. Yende and colleagues analyzed two multinational randomized controlled trials (RCTs) including approximately 2,000 sepsis patients, reporting that one-third of patients who left the ICU died within 6 months and the 8 remaining one-third had 6 months. These findings indicate the presence of persisting functional impairment and obstructed activities of daily living.[1] Thus, not only short-term prognoses, such as 28-day and ICU survival rates, but also long-term outcomes in ICU patients should be assessed.

In view of the current and evolving ICU situation, the Society of Critical Care Medicine held a stakeholder conference to address subacute/chronic physical and psychological problems after ICU discharge, in which post-intensive care syndrome (PICS) was proposed.[5] Post-intensive care syndrome is a physical, cognitive, and mental disorder that occurs during ICU stay or after ICU or hospital discharge and includes the long-term prognosis of ICU patients and effects on the patient's family (Fig. 1). Furthermore, Nakamura *et al.*[6] recently proposed the concept of post-acute care syndrome, based on evidence that acute care for elderly people involves difficulties in dysphagia and is related to prolonged ICU stay.

Pathophysiology of PICS

Physical impairments in PICS

With reduced mortality among critically ill patients due to advances in critical care medicine,[7,8] long-term physical impairment in ICU survivors is a growing concern.[1,9] Intensive care unit-acquired weakness (ICU-AW) is one factor related to muscle weakness.[10,11] It is defined as the acute muscle weakness of the extremities in a symmetric pattern, which is caused by critical illness. Intensive care unit-acquired weakness is classified as critical illness polyneuropathy (CIP), critical illness myopathy (CIM), critical illness neuromyopathy (CINM), and muscle deconditioning (Fig. 2).[12]

The diagnosis of ICU-AW is made according to the Medical Research Council scale for grading the strength of various muscle groups in the upper and lower extremities, and a combined score of <48 in all testable muscle groups noted on more than two occasions separated by 24 h is diagnostic of ICU-AW.[13] The incidence of ICU-AW is 40% in critically ill adult patients.[14] Critical illness polyneuropathy is the most common category, followed by CINM, whereas

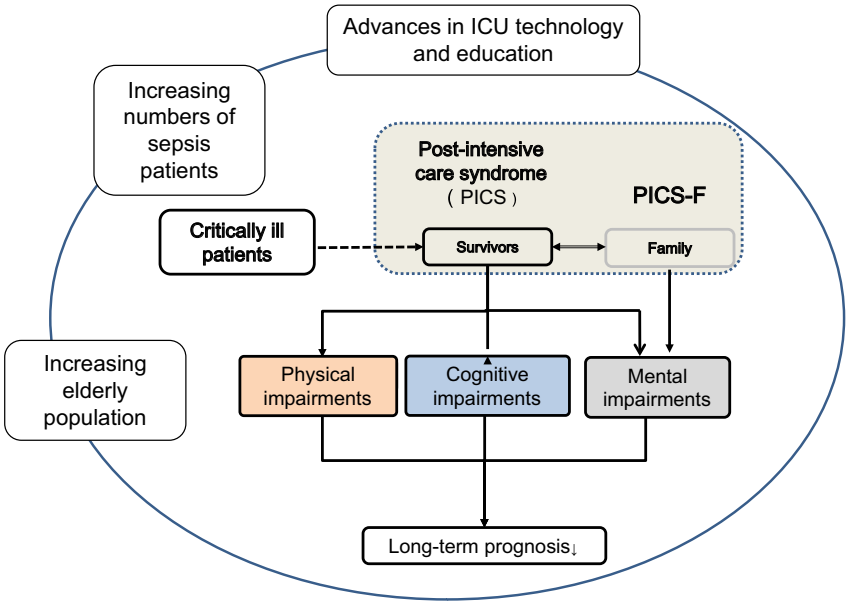

Fig. 1. Conceptual framework of post-intensive care syndrome (PICS). ICU, intensive care unit; PICS-F, PICS – family.

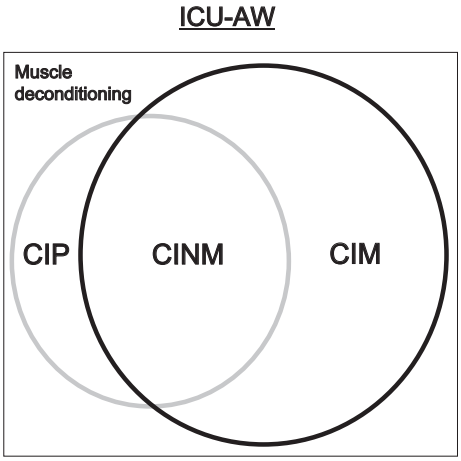

Fig. 2. Subclassification of the mechanisms of intensive care unit-acquired weakness (ICU-AW) into two main groups. The first group is ICU-AW with electrophysiologic and histopathologic findings (critical illness polyneuropathy [CIP] and critical illness myopathy [CIM]); the other is ICU-AW with normal diagnostic studies. CIM, abnormal reduction in the amplitude of compound muscle action potentials (CMAPs) and an increase in their duration, normal sensory nerve action potentials (SNAPs), reduced muscle excitability on direct stimulation, and myopathic motor unit potentials on needle electromyography; CINM, critical illness neuromyopathy, coexistence of CIP and CIM; CIP, reduction in the amplitude of CMAPs and SNAPs with normal or mildly reduced nerve conduction velocity; Muscle deconditioning, normal nerve conduction velocity and compound motor action potential, absence of spontaneous activity.

CIP is individually rare.[15–17] The pathophysiological mechanisms of ICU-AW are considered multifactorial.[10] Microvascular ischemia, catabolism, and immobility can lead to skeletal muscle wasting, while microvascular injury with resulting nerve ischemia, dysfunction of sodium channels, and injury to nerve mitochondria could contribute to critical illness-related neuropathy, myopathy, or both.[10]

Intensive care unit-acquired weakness contributes to prolonged mechanical ventilation, increased ICU and hospital lengths of stay, and mortality.[18–20] The quadriplegia aftereffect of disease usually resolves after several weeks to several months; rarely, impairment of motor function in survivors can persist from several months to several years.[21,22] The risk of ICU-AW is associated with female sex, sepsis, catabolic state, multiorgan failure, systemic inflammatory response syndrome, long duration of mechanical ventilation, immobility, hyperglycemia, glucocorticoids, and neuromuscular blocking agents;[10] however, a systematic review did not link glucocorticoids to this risk.[14] No consensus has been established regarding effective interventions to improve outcomes of patients who develop ICU-AW; however, preventive measures including early physical rehabilitation,[23] neuromuscular electrical stimulation,[24] and glucose control[25] have been applied.

Cognitive impairments in PICS

Critically ill patients experience high levels of physical and psychological stress in the ICU; these experiences result in cognitive impairments in patients with PICS. New or worsening impairments in cognitive function persist months to years after hospital discharge and are associated with poor daily functioning and reduced quality of life.[26,27] Cognitive impairments include impaired memory, executive function, language, attention, and visual–spatial abilities.

Hypoglycemia, hyperglycemia, fluctuations in serum glucose, delirium, and in-hospital acute stress symptoms have been identified as possible risk factors for persistent cognitive impairment after critical illness.[28–30] There is strong evidence that patients with delirium in the ICU are at a greater risk of long-term outcomes of cognitive dysfunction.[29,31,32]

Dementia is a relevant disease of cognitive dysfunction (Fig. 3) and a number of studies have reported the association between dementia and ICU treatment.[33–36] Among 10,348 intensive care patients who survived to hospital discharge, dementia was newly diagnosed in 1,648 (15.0%) over 3 years of follow-up compared to 12.2% in the general population.[33] Furthermore, pre-existing cognitive impairment in ICU populations is widespread. A cross-sectional comparative study reported that 37% of critically ill patients over 65 years of age in the ICU had pre-existing cognitive impairment.[34] Pre-existing cognitive impairment also affects cognitive function in PICS.

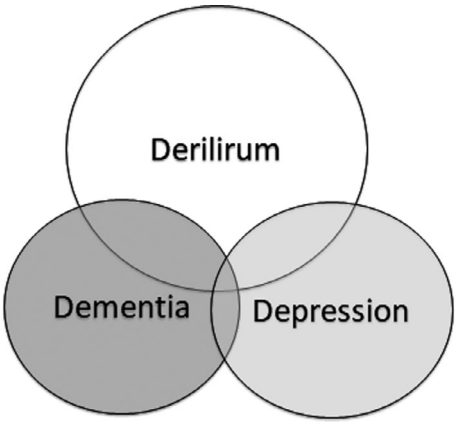

Fig. 3. Three common cognitive impairments among older adults: delirium, dementia, and depression.

The pathophysiology of cognitive impairment after ICU treatment remains unknown and might be a manifestation of brain dysfunction. However, further research is needed.

Mental impairment in PICS

Depression, anxiety, and post-traumatic stress disorder (PTSD) are the major mental illnesses that comprise PICS. The mental status impairments that can arise among critical illness survivors include depression in approximately 30% of survivors, anxiety in 70%, and PTSD, which is characterized by intrusive memories that arise from a combination of true events after ICU discharge, in 10–50%;[37] therefore, every patient with suspected PICS should undergo formal mental assessment if possible. A systematic review by Davydow *et al.*[38] showed that two of seven studies indicated female sex to be a significant predictor of PTSD after ICU care. Pre-existing depression, anxiety, PTSD, lower education level, and alcohol abuse also increase the risk of ICU-acquired mental illness.

Regarding prevention and treatment, a systematic review and meta-analysis on the effectiveness of early rehabilitation to prevent PICS in patients with critical illness undertaken by Fuke *et al.*[23] showed that early rehabilitation did not significantly improve patient mental status-related outcomes (hospital anxiety and depression). Among patients who had ICU diaries started on the fourth day of ICU admission, the PTSD symptom scores after 12 months were significantly reduced in surviving patients compared to those in the non-survivors (21 versus 34).[39] The diary was a daily record of the patients' ICU stay and was written in plain language by the healthcare staff and/or family, with accompanying photographs. A systematic review on the impact of ICU diaries reported that four of five randomized trials showed a significantly reduced rate of new-onset PTSD after 3 months with the use of ICU diaries (5% versus 13%, $P = 0.02$).[40]

With regard to long-term outcomes in mental illness in PICS, Patel *et al.*[41] prospectively observed 255 patients with shock and acute respiratory distress syndrome (ARDS), reporting an incidence of PTSD associated with ICU admission of 12% within 1 year of discharge; therefore, appropriate recognition of ICU-acquired mental illness followed by early treatment should be considered in ICU care.

Post-intensive care syndrome – family

Critical illness can not only have a significant physical and psychological impact on patients who survive but can also have a psychological impact on their families (Fig. 1). The factors associated with a high risk of adverse psychological conditions in the families of ICU survivors include anxiety, depression, acute stress disorder, PTSD, and complicated grief. The cluster of such adverse psychological reactions is called post-intensive care syndrome – family (PICS-F).[5,42]

Prevalence and risk factors

Prevalence of PICS-F conditions in the relatives of adult patients is shown in Table 1.[9,37,43–54] The wide range of rates is due to differences in each study's patient population, measurement tools, and time frames varying from 1 week to 1 year. The risk factors for PICS-F include female sex, younger relative and patient age, lower educational level, having a critically ill spouse, having more comorbidities, and being an unmarried parent of a critically ill child.[9,37,48,55,56] Other baseline risk factors include a history of anxiety, depression, or severe mental disease.[37]

Prevention

Several prevention interventions have focused on adverse psychological reactions, including improving communication, providing family support, family presence in the ICU, and using specific consultations.[39,57–62] Improving communication during end-of-life care, such as respect for the patient's values, preferences, and expressed needs and shared decision-making, alleviated grief symptoms in relatives of patients who had died in the ICU.[57,58,62] Emotional and social support involving psychologists,[59] caseworkers, and social workers[9,37] in family support can mitigate the impact of the crisis of critical illness and help prepare them for the patient's discharge. Intensive care unit diaries, when

Table 1. Prevalence of the elements of post-intensive care syndrome –family (PICS-F)[9,37,43–54]

Elements of PICS-F	Follow-up	Prevalence
Depression	1 week	14.6–66.7%
	1–3 months	8–48.5%
	1–6 months	17.9%
	1–12 months	6–43.4%
Anxiety	1 week	42–66%
	1–3 months	21–49.3%
	1–6 months	15–24%
PTSD	3–6 months	33.1–49.0%
Burden/overload	ICU–2 months	36%
Activity restriction	1–2 months	Activity restriction scale score 22.1–23
Complicated grief	3–12 months	5–46%

ICU, intensive care unit; PTSD, post-traumatic stress disorder.

read by the family members after patient discharge, can fill in memory gaps and help them to understand what happened.[39,60,61]

Post-intensive care syndrome in pediatrics

Several large critical-care databases have revealed mortality rates of critically ill children of approximately 2–4% in ICUs in developed countries, indicating that most of these children survive. However, some of these pediatric survivors experience long-term morbidity associated with their critical care.[63–67]

Ong *et al.*[68] recently undertook a scoping review for critical appraisal of existing published works on functional outcome and physical impairment among pediatric critical care survivors. They found that the rate of acquired functional impairment ranged from 10% to 36% at ICU discharge and from 10% to 13% after 2 years. They also extracted risk factors for acquired functional impairment, including illness severity, the presence of organ dysfunction, length of ICU stay, and younger age.[68] Pinto *et al.*[65] reported that some PICU survivors subsequently died after their hospital discharge and developed new morbidity even 3 years later. With a focus on specific diseases and conditions, the SPROUT study, a recent international point prevalence study of pediatric sepsis, showed that 17% of sepsis survivors suffered moderate to severe disability.[69] Among children who survived ARDS, Ward *et al.*[70] suggested that up to one-third showed pulmonary dysfunction and that their quality-of-life scores 12 months after discharge were lower than those in asthmatic children.

When the concept of PICS was established in 2012, the necessity for special considerations for children and their family was also mentioned. Since then, multiple surveys have been undertaken to describe long-term morbidity among children who survived critical illness as well as their families. In 2018, the framework of pediatric PICS (PICS-p) was conceptualized (Fig. 4).[71] The fundamental framework was similar to that of adult PICS, with several unique features.

First, the most important viewpoint is that children's critical illness occurs during the dynamic process of their growth and maturation and that both their outcomes and their family's response (i.e., their parents and siblings) can interdependently influence their subsequent development and quality of life. Second, PICS-p includes a "social health" domain for children and their families in addition to the three conventional domains of physical, cognitive, and emotional health. Critical illness affects the social functioning of both children and their families; that is, reintegration with their friends at school, their social capital, and their parents' unemployment while caring for a sick child. These social health impairments, intertwined with morbidity in other health domains, can negatively impact their development and survival quality. Finally, a variety of recovery trajectories of surviving children and their families are indicated in the PICS-p framework, including improvement, deterioration, vacillation, or plateau over days or decades. Available evidence, although still limited, suggests that their outcomes are more heterogeneous than those for adult ICU survivors and their spouses.[68,71,72]

Considerable obstacles involving PICS-p still exist, especially in the definition and evaluation of pediatric health status in each domain. Ong *et al.*[68] identified vast differences in measurement tools and follow-up timings of pediatric functional outcomes among 25 articles included in their

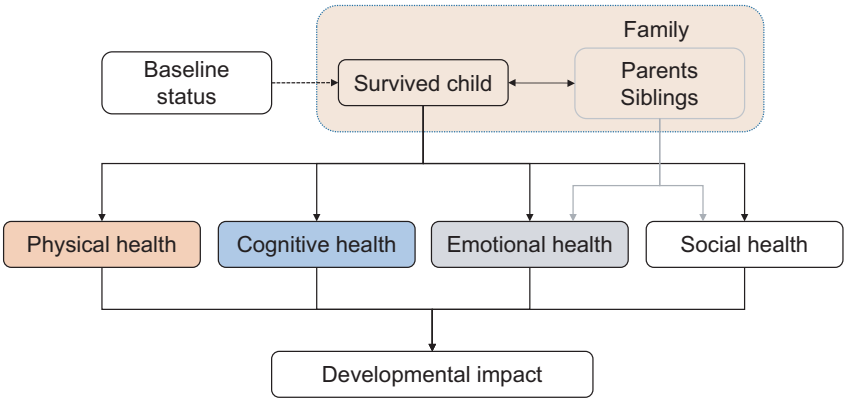

Fig. 4. Proposed framework for post-intensive care syndrome in pediatrics (PICS-p). Compared to the concept of PICS for adult intensive care unit survivors, the unique features of PICS-p include the importance of baseline status, system maturation and psychosocial development, stronger interdependence within the family, and recovery trajectories that can potentially impact a child's life for decades.

scoping review. Children have diverse functional status related to their age and developmental stage. The next step for PICS-p is to establish comprehensive sets of evaluation methods appropriate for each age group in each domain of the framework, which will enable elucidation of the natural history of PICS-p. Thereafter, interventional studies will be warranted to improve long-term outcomes among pediatric critical care survivors.

Prevention of PICS

ABCDEFGH bundle

The ABCDE bundle is widely known as the bundle that addresses the risks of sedation, delirium, and immobility. ABCDE is composed of: A, airway management, assess, prevent, and manage pain; B, breathing trials, including daily interruptions of mechanical ventilation, spontaneous awakening trials, and spontaneous breathing trials; C, choice of analgesia and sedation, coordination of care, and communication; D, delirium assessment, prevention, and management; and E, early mobility and exercise.[9,73,74] They are also risk factors for PICS. Furthermore, FGH can be added to the list for the prevention of PICS (Fig. 5). FGH includes: F, family involvement, follow-up referrals, and functional reconciliation; G, good handoff communication; and H, handout materials on PICS and PICS-F. The present review focused on early mobility (physical rehabilitation), follow-up referrals (ICU follow-up clinics) with new domains, including nutrition, nursing care, diary, and environment management.

Physical rehabilitation

The main purpose of rehabilitation in the ICU is to improve the quality of life by maintaining, improving, and reacquiring activities of daily living.[75] Both ICU-AW and delirium, as parts of PICS, are related to a decreased quality of life.[76,77] The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2016 (J-SSCG 2016) suggested implementing early-stage rehabilitation as a PICS preventative measure for sepsis or ICU patients.[78] Physical rehabilitation in the ICU could improve mobility status and muscle strength.[79] A recent systematic review clarified that physical rehabilitation decreases ICU-AW but not delirium-free days and did not improve mental health.[23] Additional large randomized controlled trials are needed to clarify the effect of physical rehabilitation on PICS.

The definition of "early" in early rehabilitation practice usually refers to intensive physical rehabilitation that is implemented in addition to regular care at any time during an ICU stay. The term "early" has yet to be defined as, among various studies, the onset of interventions could vary by as much as 1 week.[80] Many critically ill patients have PICS symptoms following ICU discharge. A previous systematic review reported no clear effect of intensive physical rehabilitation following ICU discharge on clinically relevant outcomes, such as quality of life.[81] Our updated review also clarified no improvement in quality of life or mortality.[82] Preventing PICS symptoms from ICU admission is more important than intensive treatment of PICS following ICU discharge.

Physical rehabilitation for mobility includes activities such as sitting, standing, and ambulation, as well as passive exercises including range-of-motion exercises and ergometers.[80] An ICU survey in Japan revealed that sitting on the edge of the bed was routinely provided in ICUs, whereas neuromuscular electrical stimulation and a cycle ergometer were rarely provided.[83,84] The J-SCCG 2016 recommended against neuromuscular electrical stimulation as an ICU-AW preventative measure.[78] The dose–response of physical rehabilitation for clinical outcomes is unknown.[85] High-dose rehabilitation might lead to a higher quality of life than that for low-dose rehabilitation;[79] however, further studies are needed to clarify this point.

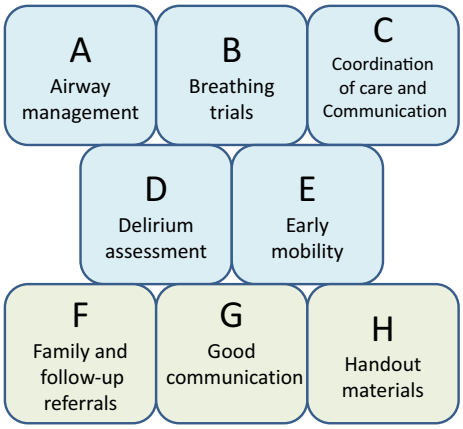

Fig. 5. ABCDEFGH bundle for prevention of post-intensive care syndrome.

Nutrition

Nutritional therapy is vital for the prevention of PICS, especially ICU-AW. Adequate energy delivery and protein intake are the most important factors for muscle synthesis;[86,87] moreover, energy debt is covered by catabolism mainly of the muscle, which is associated with lean body mass loss related to risk mortality.[88] Previous studies on nutrition therapy targeted mortality and infectious complications as outcomes. With the recent opinion that nutrition therapy should target muscle volume and strength,[89] there is a strong connection between nutritional therapy and PICS

(Fig. 6). Although studies have shown that the securement of minimum energy delivery with supplemental parenteral nutrition from the acute phase was associated with decreased PICS,[90] overfeeding could induce autophagy impairment and worsen ICU-AW.[91] Therefore, we should target appropriate energy delivery and avoid overfeeding.[92,93] Here is a paradigm that adequate proteins especially important for critically ill patients. Adequate protein delivery with total energy could reduce PICS;[94] however, a number of studies have reported that protein delivery alone does not reduce PICS.[95,96] As muscle protein synthesis is maximized with appropriate exercise in healthy individuals,[97] not only nutrition therapy alone but also appropriate exercise and rehabilitation together with adequate nutrition are also necessary in critically ill patients (Fig. 6).[98] As for the particular kind of nutrition, leucine is the amino acid reported to induce muscle protein synthesis.[99] Unfortunately, administration of specific amino acids including leucine has not shown efficacy in critical care.[100] Approaches to enhance anabolic power, such as β-hydroxy-β-methylbutyrate[101] or oxandrolone,[102] remain to be examined for the prevention of PICS and ICU-AW.[103]

Environmental management for healing

Patients admitted to the ICU experience environmental stimuli, particularly noise and light. Excessive noise in the ICU has been reported in numerous studies.[104]

A recent observational study in six ICUs suggested that background noise had a negative impact on sleep quality.[105] Five RCTs[106–110] examined the effects of noise reduction devices such as earplugs and noise-canceling headphones combined with or without eye masks on sleep quality among patients in the ICU.[106–110] All RCTs reported better perceived sleep quality in patients with the devices;[106–110] however, three of five studies were carried out mainly in post-surgical patients and one was for non-ventilated, mostly cardiac patients. Thus, these findings did not have external

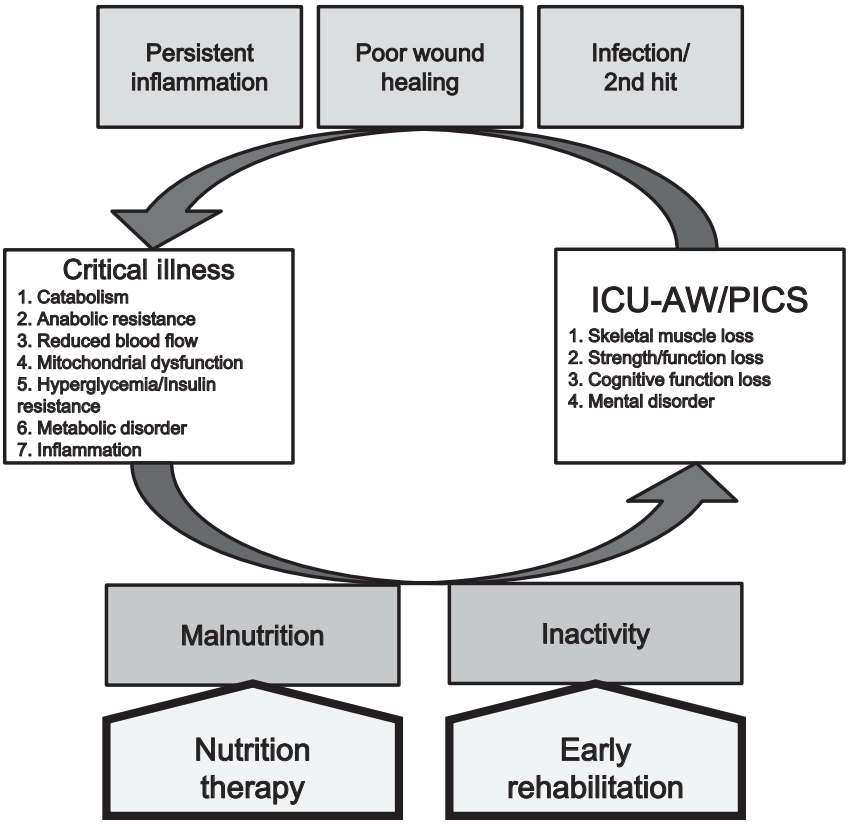

Fig. 6. Association between critical illness and intensive care unit-acquired weakness (ICU-AW)/post-intensive care syndrome (PICS) and the importance of nutrition therapy and rehabilitation. Malnutrition and inactivity accelerate ICU-AW/PICS, especially with skeletal muscle volume and strength/functional loss. Nutrition therapy and rehabilitation are essential factors and the basis for the prevention of PICS/ICU-AW.

validity to generalize to all ICU patient populations. Improved sleep quality by using noise reduction devices could reduce the development of delirium in the ICU. Litton *et al.*[111] undertook a meta-analysis of six RCTs and three non-randomized trials to assess the effects of earplugs on the development of delirium in ICU patients, reporting that earplugs significantly reduced the risk of delirium (relative risk, 0.59; 95% confidence interval, 0.44–0.78).

To date, there is no direct evidence of a relationship between environmental factors and long-term cognitive impairment; however, as mentioned above, some studies have reported a significant relationship between noise reduction strategies and delirium.[111] Delirium in the ICU was associated with long-term cognitive impairment; therefore, the possibility exists that environmental factors could affect long-term cognitive impairment through delirium during ICU stay due to impaired sleep quality.

Little is known about the contribution of environmental factors to the mental health of patients after intensive care. One RCT reported that music therapy or noise-canceling headphones reduced anxiety during ICU stay compared to usual care in patients with respiratory failure requiring mechanical ventilation.[112] These interventions could affect the symptoms of mental health after intensive care, despite the lack of verification.

Nursing care for PICS

One of the most important roles of nurses is the continuous implementation of measures to prevent PICS, including the ABCDEFGH bundle. Nurses spend most of their time on direct patient care.[113] In addition to optimal analgesia, nurses can support safe light sedation by staying near patients.[114] Through light sedation, patients can prepare to satisfy the higher levels of human needs.[115] To understand and address the patient's needs, nurses need to know the patient's living conditions prior to hospitalization.[73] Nurses should assess gaps between the patient's prehospitalization and current functional abilities and should support functional reconciliation. Non-pharmacological interventions can also be important to restore the patient's ordinary daily function in the hospital environment.[116,117] Family involvement also plays a key role.[118] The provision of information, including PICS, to family members and using an ICU diary can strengthen the connection between the patient and family members and medical staff.[119,120] Moreover, it can also promote family participation in patient care. Early rehabilitation and mobilization interventions can improve physical function in patients with critical illness.[23] Furthermore, short-term and high-frequency rehabilitation and mobilization interventions can improve the functional ability of patients.[121] Nurses facilitate patient mobility at all hours of the day and night[113,122] and, therefore, could contribute to improving patient functional ability. The recovery process from PICS is a continuum.[123] Functional reconciliation requires continuous and consistent care even after ICU discharge. Thus, good handoff communication including information about PICS is necessary to achieve this consistent care.[42,73]

Intensive care unit diaries

Intensive care unit diaries are completed by doctors and families of patients to record the patient's status while in the ICU and are kept to describe the patient's experiences. The icu-diary.org site has been introduced as one option for keeping an ICU diary.[124] The ICU diary is written for the patient by a family member or a medical person, such as a nurse, but could also be recorded by the patient. The ICU diaries can help to indicate the orientation of the patient, and could prevent PICS by alleviating anxiety, depression, and PTSD symptoms.[39,125] Keeping a diary has been shown to reduce PTSD symptoms not only in patients but also in their families.

In these facilities, the nursing team in charge, mainly the main bedside nurse, determine whether an ICU diary is appropriate. If the diary is judged to be useful, then the concept is explained to the patient and their family, and the diary is started after obtaining their consent. The diary is used to periodically record general notes on events and daily occurrences, the patient's life, rehabilitation situation, etc. at the discretion of the nurse in charge. If desired, it can also include photographs. The doctor in charge, physical therapist, and clinical engineering technicians involved in care might also add to the diary. The diary is presented to the patient at ICU discharge.

Intensive care unit follow-up clinics and PICS

Intensive care unit follow-up clinics are specialized clinics for patients who have survived and been discharged from the ICU. They have attracted attention as a place for the diagnosis and treatment of PICS. These follow-up clinics have been spreading mainly in Europe in the last 20 years but have also been gradually spreading in recent years in North America. The ICU follow-up clinics have no fixed form or patient evaluation method and treatment interventions vary between facilities. In addition to supporting rehabilitation, cognitive function, and mental symptoms, clinic pharmacists can also adjust medications.

The RaCTICaL study is a representative RCT that examined the usefulness of ICU follow-up clinics.[126] This open-label RCT undertaken at three UK institutions targeted all

patients who survived hospitalization after receiving intensive care. In the intervention group, rehabilitation was carried out from hospitalization until discharge to the third month and clinic follow-up observation was carried out at 3 and 9 months after discharge. Neither rehabilitation nor follow-up was carried out in the control group. The primary end-points were the health-related quality of life score and the SF-36 after 12 months, and the secondary end-points were the health-related quality of life score after 6 months and the quality-adjusted life years, PTSD presence and severity of the onset, hospital anxiety and depression scale after 12 months, and cost efficiency after 12 months. However, the nurse-led intensive care follow-up program showed no evidence of the effect or cost-effectiveness in improving patient quality of life in the year after discharge from intensive care. Further work should focus on the roles of early physical rehabilitation, delirium, cognitive dysfunction, and relatives in the recovery from critical illness. Intensive care units should review their follow-up programs based on these findings. In 2015, Jensen and colleagues undertook a lineage review and meta-analysis to examine the effects of ICU follow-up on patient-centric outcomes, that is, quality of life, anxiety, depression, PTSD, physical and cognitive function, and reinstatement.[127] The results indicated that follow-up consultations do not improve quality of life, anxiety, depression, physical or cognitive function, or return to work. However, consultations appeared to reduce the symptoms of PTSD after ICU admission, perhaps due to individualized interventions aimed at reframing the ICU experience. At present, it is uncertain if the intervention is effective. Post-ICU follow-up needs to be developed in collaboration with patients and their families and the effect should be investigated in larger studies and within comparable settings.

Intensive care unit follow-up clinics are expected to be a place for follow-up of PICS developed during hospitalization as well as for the discovery and treatment of newly developed PICS after discharge. The clinics have been developed mainly in Europe; however, their format and methods for patient evaluations have not been adequately studied and vary between facilities. There is also insufficient evidence regarding the usefulness of ICU follow-up clinics; therefore, further verification is necessary for future development.

End-of-life care in acute medicine

Due to the aging of the general population and declining birth rates, the demographic structure of Japan has become the most super-aged society in the world. Consequently, the disease structure and medical care demand have also changed. In these social backgrounds, ethical concerns regarding life-sustaining therapy often arise in acute care settings, where end-of-life care is frequently provided. The values and preferences for choice of treatment options vary widely, especially in end-of-life care. The cultural or social backgrounds of a country influence the practice of end-of-life care.[128–130] Physicians in Asian ICUs tend to avoid withdrawing life-sustaining therapy at the end of life compared to physicians in non-Asian countries.[131] Despite similarities in cultures, there are differences between Japan and other East Asian countries, such as China and Korea, in physician perceptions and practices regarding end-of-life care in intensive care.[129]

Thus, guidance on end-of-life care in acute care settings based on our own cultures and social circumstances is urgently required. In November 2014, Guidelines of the End-of-life Care for Acute Disease and Intensive Care were proposed by three related Japanese associations, namely, the Japanese Association of Acute Medicine, the Japanese Society of Intensive Care Medicine, and the Japanese Circulation Society. These guidelines describe that the withholding, withdrawing, or termination of resuscitation or life-sustaining therapy are chosen according to the directives of the patient and family and the conscience of the medical stuff.

Importantly, these guidelines were not based on legislation, which might be of concern for physicians in clinical settings. That is, we Japanese physicians at the front line of end-of-life care feel exposed to personal legal risks when limiting life-sustaining therapy. It is necessary for prefectures, municipalities, and local medical control authorities to take the initiative to establish an ordinance on clinical guidance for end-of-life care.

CONCLUSION

POST -intensive care syndrome includes physical, cognition, and mental impairments that occur during ICU stay or after ICU discharge, as well as the long-term prognosis of ICU patients. For prevention of PICS, it is important to carry out the ABCDEFGH bundle and new therapeutic strategies, including diary, nutrition, nursing care, and environmental management for healing. Additionally, PICS will be a new task for intensive care medicine in the 21st century that has reached the end of mature acute care, including several problems regarding end-of-life care.

DISCLOSURE

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