

Chronic critical illness: the price of survival

Alessandro Marchioni, Riccardo Fantini, Federico Antenora, Enrico Clini and Leonardo Fabbri

Respiratory Disease Clinic Department of Oncology, Haematology and Respiratory Disease, University of Modena and Reggio Emilia, Modena, Italy

ABSTRACT

Background The evolution of the techniques used in the intensive care setting over the past decades has led on one side to better survival rates in patients with acute conditions and severely impaired vital functions. On the other side, it has resulted in a growing number of patients who survive an acute event, but who then become dependent on one or more life support techniques. Such patients are called chronically critically ill patients.

Materials & Methods No absolute definition of the disease is currently available, although most patients are characterized by the need for prolonged mechanical ventilation. Mortality rates are still high even after dismissal from intensive care unit (ICU) and transfer to specialized rehabilitation care settings.

Results In recent years, some studies have tried to clarify the pathophysiological characteristics underlying chronic critical illness (CCI), a disease that is also characterized by severe endocrine and inflammatory impairments, partly accounting for the almost constant set of symptoms.

Discussion Currently, no specific treatment is available. However, a strategic early therapeutic approach on ICU admission might try to prevent the progress of the acute disease towards chronic critical illness.

Keywords chronic critical illness, mechanical ventilation, systemic inflammation, wasting syndrome.

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Clinical case overview

A 60-year-old man was admitted to ICU for acute respiratory failure secondary to ARDS. The patient underwent mechanical ventilation via endotracheal tube with protective strategy, and started antibiotics and steroids intravenously. Chest CT scan showed diffuse bilateral ground glass with atelectasis in dorsal areas. After 10 days of treatment, due to the persistence of severe respiratory failure, a tracheostomy was performed. The patient's clinical conditions and gas exchange improved in the following days, but an evolution towards lung fibrosis was radiographically detected. Thirty days after admission, the patient presented with severe muscle wasting, while weaning from mechanical ventilation was difficult due to the onset of severe alveolar hypoventilation during spontaneous breathing trial. Blood tests showed hyperglycaemia requiring insulin administration at high doses. Furthermore, the patient experienced periods of delirium, treated with sedatives and antipsychotics, forcing the patient to prolonged immobility. After 40 days of hospitalization in ICU, the patient was transferred to a weaning centre.

What is the patient's prognosis? Will he recover functional autonomy?

Intensive care units (ICUs) were devised to artificially maintain vital functions that were previously impaired due to an acute condition, while the patient is recovering from the disease [1,2]. Their set of treatments is quite commonly applied to a population presenting with an increasingly advanced average age and with multimorbidities [3,4]. Although significantly achieving a reduction in mortality rates, ICUs also led to a growth in the number of patients who overcome the acute stage of the disease, but who become dependent for a long time on techniques supporting one or more vital functions, therefore becoming 'chronically critically ill'.

Definition and epidemiology

The definition of 'chronically critically ill patient' was coined by Girard and Raffin in 1985, in an article describing a set of patients who remained dependent on vital support treatments after an acute critical disease requiring admission to ICU [5].

Due to the clinical difficulty in identifying the progression from the acute phase of the disease to its becoming chronically critical, an absolute definition of chronic critical illness is currently unavailable. However, as prolonged mechanical ventilation is required by the vast majority of the affected patients, this feature is a primary indicator for the definition of chronic critical illness [6]. 'Prolonged mechanical ventilation' has been defined as the need for ventilatory support for more than 21 consecutive days for at least 6 h per day [7].

Another element for the identification of these patients is the need to perform tracheotomy at ICU, when the patient requires prolonged mechanical ventilation and on the basis of a clinical judgment regarding patient stability. However, these definitions are limited, take into account the need for prolonged mechanical ventilation and fail to cover the entire spectrum of conditions that fall into this syndrome.

Epidemiologically, chronic critical illness has become a relevant emerging issue: some studies report that up to 5–10% of patients admitted to ICU require prolonged mechanical ventilation, with 100 000 patients assessed in the US only [8]. Around 30–50% of chronically critically ill patients can be discharged from ICU or other acute care settings without ventilatory support, although comorbidities, weak functional compensation and common infectious complications are the main factors affecting prognosis [9,10]. One-year mortality is assessed to be around 48–68%, and some studies report that only 10% of chronically critically ill patients achieve functional autonomy and live at their home at 1 year after the onset of the acute condition requiring admission to ICU [11–13].

Clinical features

Although the main marker in patients with chronic critical illness is respiratory failure requiring prolonged mechanical ventilation, other clinical features are always present and outline a specific clinical syndrome (Fig. 1). Endocrine alterations and prolonged inflammation cause myopathy, neuropathy and changes in body composition including loss of lean body mass. Neurological changes often occur such as coma or delirium extending over a long period. These patients present with different levels of nutritional deficiency, while prolonged immobility and enhanced susceptibility to infections are extremely common.

Physiopathological mechanisms

Currently, no explanation is available on the reason why among patients with similar severity and requiring intensive treatment some experience a rapid recovery of vital functions while others become chronically critically ill. Moreover, there are no biomarkers that can assist in predicting the development of this condition. Risk factors for chronic critical illness include

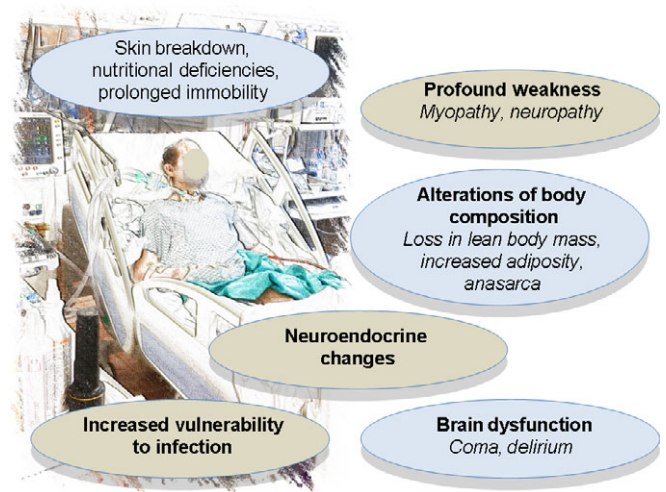


Figure 1 Clinical features of chronic critical illness

old age, comorbidities and type of disease, while the most frequent acute conditions involved are sepsis and ARDS (acute respiratory distress syndrome), both characterized by an immune response triggering a significant systemic inflammation [14]. The progress from acute disease to chronic critical illness leads to significant changes in endocrine response, partly accounting for the clinical syndrome present in such patients (Fig. 2). Systemic inflammation and endocrine derangement are related with malnutrition, brain dysfunction and muscle weakness.

Systemic inflammation

Chronic critical illness can also be defined as a persistent systemic inflammation triggered by an initial insult. The progress from an acute condition into chronic critical illness may be favoured by two factors: (i) inflammation insult severity during acute phase and (ii) missed resolution of inflammation. For example, ARDS patients present with a significant increase in TNF- α , IL-1 β , IL-6 and IL-8 plasma levels.

Patients presenting with higher inflammation levels at disease onset and persistent blood cytokine increase during its course show worse prognosis and higher incidence of multiple organ failure [15]. This group of patients, whose survival depends on life support techniques, requires prolonged mechanical ventilation and therefore faces an increased risk of developing chronic critical illness. Old age, as a risk factor, is associated with the chronic increase in the levels of some inflammatory markers, such as IL-6, TNF, IL-1 receptor antagonist and CPR, on which an acute condition may trigger and amplify an inflammatory response [16].

The process leading to the resolution of inflammation is not a passive mechanism, as it involves a complex biological

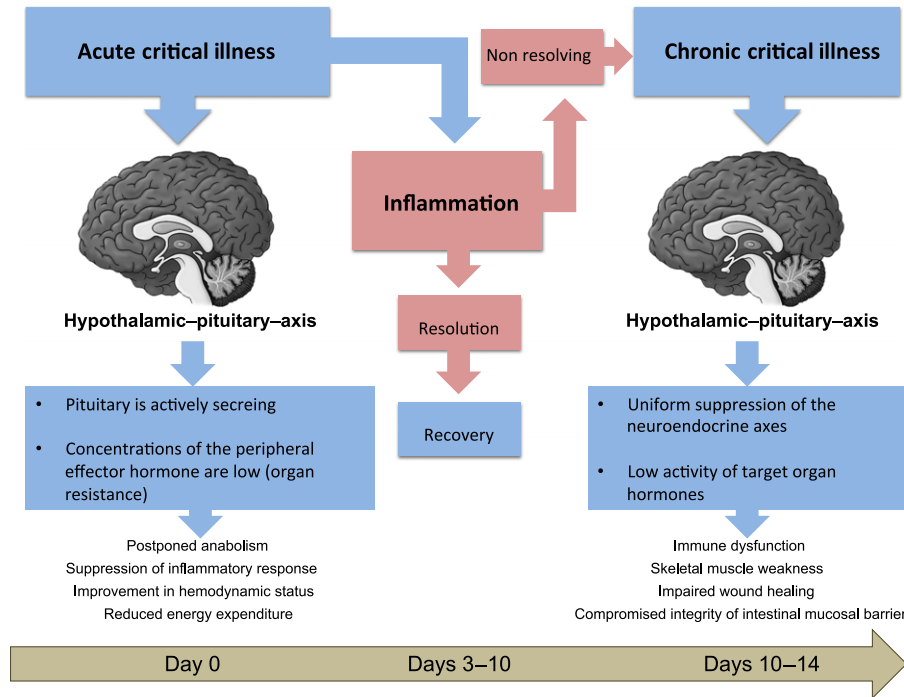


Figure 2 Pathophysiology of progression from acute disease to chronic critical illness. The acute disease is characterized by the presence of a significant inflammatory response and the activation of the hypothalamic-pituitary axis, with the purpose of delaying the anabolism and increase the catabolism to make available the energy substrates. The resolution of the inflammatory process results in healing and restoration of normal neuroendocrine activity. If inflammation fails to resolve, the persistent disease leads to the development of an exhaustion of the neuroendocrine response with the appearance of chronic critical illness.

programme requiring the function of specific mediators and cells. The main stages involved are as follows: (i) clearance of disease triggering event, (ii) apoptosis of polymorphonucleates and efferocytosis with tissue macrophages, (iii) anti-inflammatory cytokine release (TGF- β , IL10), and (iv) removal of macrophages from the body or apoptosis [17]. This complex mechanism is regulated by over 80 genes whose mutation, in animal models, can develop persistent spontaneous inflammation even without any pathogen trigger [18]. The impaired regulation of the processes aimed at limiting damage associated with inflammation might be involved in the progression of the acute critical disease into chronic critical illness.

Despite the fact that the persistence of inflammation is probably a major cause of development of a chronic critical illness, even the presence of a low-inflammatory state and a subsequent immunosuppressive phase following sepsis may play a role [19]. After an initial cytokine storm, some patients experience an immunosuppression phase characterized by apoptosis and cell loss of the innate and adaptive immune system involving CD4, CD8, B-type and dendritic cells [20]. This condition of immuno-paralysis can last longer and

increases host susceptibility to infections, thus promoting the persistence of critical illness.

Endocrine alterations

Endocrinological abnormalities have been recognised for patients with acute critical illness, but not for patients with chronic critical illness.

During the acute stage of a critical disease, a complex neuro-immune response is activated, most presumably aimed at providing immediate availability of energy substrates for the cellular processes required to maintain vital functions [21] (Table 1). The hypothalamic-pituitary axis activation promotes lipolysis, proteolysis and gluconeogenesis, while the anabolic process is temporarily suspended. During the first hours after an acute insult, circulating growth hormone (GH) levels increase secondary to the rise in secretion peaks and in pulse frequency of pituitary gland. This central activation is associated with a reduction in serum concentration of effector proteins IGF-I (*insulin-like growth factor-I*), IGFBP3 (*IGF binding protein 3*) and ALS (*acid-labile subunit*). An acquired peripheral GH resistance is then established, inhibiting anabolic and activating catabolic processes. Moreover, neuroendocrine response

Table 1 Endocrine abnormalities in acute and chronic critical illness

Hormone	Acute critical illness	Chronic critical illness
Somatotrophic axis		
Pulsatile GH secretion	↑	↓
GHBP	↓	↑
IGF-I	↓	↓↓
ALS	↓	↓↓
IGFBP-3	↓	↓↓
Thyroid axis		
Pulsatile TSH secretion	↑	↓
T4	↑	↓
T3	↓	↓↓
Adrenal axis		
ACTH	↑	↓
Cortisol	↑↑	↑↓*

*Adrenocortical insufficiency.

to acute stress results in hypercortisolism caused by the increased secretion of ACTH (*adrenocorticotrophic hormone*) from anterior pituitary, which in turn is stimulated by the hypothalamic factor called CRH (*corticotropin-releasing hormone*). The rise in cortisol levels, not only contributes to the availability of energy substrates, but it also causes a positive hemodynamic effect through intravascular fluid retention and increase in inotropic and vasopressure response to catecholamines and angiotensin II. Moreover, cortisol has an anti-inflammatory effect, which might be involved in the mechanisms aimed at limiting the damage produced by the acute triggering event.

During sepsis, a relative adrenal insufficiency may develop: in such condition, despite an increase in ACTH, cortisol production is insufficient to maintain hemodynamic stability [22]. The most common clinical feature is the appearance of hypotension refractory to fluid challenge and requiring the use of vasopressors [23].

Diagnostic criteria for this condition are controversial, but the most common method is the detection of an insufficient increase in plasma cortisol (<9 µg/dL) after stimulation with a bolus of 250 µg of ACTH [21].

The hypothalamic–pituitary–thyroid axis is also activated with a sharp but short rise in TSH and T4 levels paired with T3 reduction, which is presumably secondary to the drop in T4 to T3 conversion in peripheral organs. The latter changes might be

interpreted as an attempt to curb tissue energy expenditure to face reduced substrate availability.

While such process may be considered as the Darwinian response to an acute stress, the chronic process of a critical illness involves significant changes in neuroendocrine response. Evolution has not provided our nervous and endocrine system with the ability to withstand a prolonged inflammation requiring artificial life support.

The main consequence to this condition is a reduction in pulsatile secretion of anterior pituitary hormones associated with the so-called wasting syndrome [24].

Pulsatile secretion of GH is reduced and correlates with the lower circulating levels of IGF-I and of binding proteins (IGFBP-3, ALS, IGFBP-5). This hyposomatotrophism also accounts for the occurrence of the waste syndrome usually detected in these patients. Serum ACTH levels fall sharply while cortisol levels remain high. This typical dissociation in the chronic stage shows that cortisol production is not ACTH dependent, but that it is probably triggered by other factors such as cytokine cascade secondary to persistent inflammation. Another factor promoting persistently high cortisol levels is the reduction in cortisol metabolism regardless of the inflammatory condition in the patient [25]. The persistent increase in cortisol levels may play a decisive role in the onset of some typical clinical features of the chronically critically ill patient: (i) increased susceptibility to infections, (ii) reduced wound-healing capacity and (iii) onset of myopathy.

The prolonged absence of ACTH stimulation during chronic critical illness may in the long-term lead to adrenal gland atrophy and cause symptomatic adrenal insufficiency, an event with a 20-fold higher incidence in patients admitted to ICU for more than 14 consecutive days.

A reduction in pulsatile TSH secretion is also detected in the hypothalamic–pituitary–thyroid axis, resulting in low plasma levels of specific hormones (T3, T4). T3 plasma levels inversely correlate with muscle weakness and bone loss markers.

Another endocrine impairment is hyperglycaemia secondary to the response to acute stress, resulting from the activation of gluconeogenesis and from the reduction of insulin sensitivity in peripheral tissues [26]. The onset of stress-induced hyperglycaemia is influenced by a number of clinical factors, such as age, glucose tolerance, presence of comorbidities, need for parenteral nutrition, obesity and severity of the underlying disease. Once hyperglycaemia is present, it may persist even in the course of chronic critical illness, involving an increased risk of mortality [27].

Malnutrition

One of the characteristics found in chronic critical illness is a state of malnutrition associated with chronic inflammation and hormonal changes. The increase in proteolysis and the reduced

hepatic synthesis of albumin result in hypoalbuminaemia and in a hypo-oncotic state [28–30]. This condition resembles the typical wet malnutrition of children in African countries (kwashiorkor) that occurs when protein malnutrition predominates compared to the reduction in total calories. Therapies used in ICU, especially fluid resuscitation, can worsen this condition and promote anasarca.

In addition, protein wasting causes weakness of the skeletal muscles, increases the risk of hospital infections (i.e. deficiency in wound healing) and prolongs hospitalization [31].

Refeeding by enteral route supplies protein and energy required for cellular and organ functions, but also improves immune function through hormonal changes. In particular, the secretion of glucagon-like peptide-1 (GLP-1) by L cells of the distal ileum in presence of food [32] is able to stimulate insulin secretion, slow down gastric emptying and influence the cell-mediated immunity [33,34,35]. A recent clinical trial showed that early enteral nutrition can improve cell-mediated immunity via different routes by the secretion of GLP-1 and is associated with positive clinical effects [36].

Brain dysfunction

Brain dysfunction is another common condition complicating the course of a critical illness in ICU, presenting with coma and delirium. Studies analysing patients with acute critical illness showed that brain dysfunction is associated with increased mortality and long-term cognitive impairment in survivors [37–41].

Even during chronic critical illness, brain dysfunction appears to affect 29–69% of patients, whereas its prognostic impact is less clear [42–45]. Ten to 77% of patients who survive present with long-term brain dysfunction and different degrees of cognitive impairment [46,47]. Risk factors for developing long-term brain dysfunction include advanced age, high gravity score and the presence of cerebral dysfunction in the period of hospital care for chronic critical illness [48].

The pathophysiology of cerebral dysfunction appears to be multifactorial. Delirium seems to be related to the imbalance between dopamine production (which increases neuronal excitability) and acetylcholine depletion (which has an inhibitory effect) in controlling cognitive functions [49,50]. During a critical illness, cytokines and chemokines produced by the systemic inflammation may be able to cross the blood–brain barrier, as demonstrated by studies in animal model [51]. These mediators can promote brain dysfunction through endothelial damage, impaired cerebral vascular permeability, formation of microaggregates, reduction of cerebral blood flow and alteration of neurotransmitters' synthesis [52]. A recent study enrolled 147 patients in ICU and showed that in patients with worse systemic endothelial function acute brain dysfunction persisted for longer [53]. Among the other mechanisms which

may contribute to the development of delirium, the increase in brain uptake of some amino acids such as tryptophan and phenylalanine (precursors in the synthesis of dopamine) is most likely [54].

Finally, exposure to analgesics and sedatives and/or sleep deprivation may also play a role in precipitating delirium. Some studies have identified the use of meperidine, midazolam and lorazepam as potential risk for developing delirium [50–55].

Muscle weakness

Survivors to acute illness in ICU often develop neuropathy and myopathy. These conditions are common in chronic critical illness, limiting mobilization and weaning from mechanical ventilation [56]. Two main recognized clinical conditions cause muscle weakness in these patients: (i) critical illness polyneuropathy (CIP) and (ii) critical illness myopathy (CIM).

CIP is a distal axonal sensory-motor polyneuropathy, which can affect the limbs but also respiratory muscles [57]. Electrophysiological studies show a reduction in the compound muscle action potential (CMAP), while the sensory nerve action potential (SNAP) has almost normal conduction velocity [56]. Pathophysiology is not known, but it is assumed that axonal injury derives from a microvascular dysfunction and impairment in the blood–nerve barrier (BNB) [57] leading inflammatory mediators to produce the neuropathy damage [58].

CIM is an acute primary myopathy presenting with muscle atrophy, and a characteristic pattern of selective loss of myosin on muscle biopsy [56]. The cause is the imbalance between muscle protein breakdown and synthesis determined by multifactorial events during acute illness. The molecular basis of muscle atrophy involves activation of the ubiquitin–proteasome (UPS) and autophagy–lysosome systems [59]. Activation of these two systems is coordinated by the family of transcription factors forkhead box O (FoxO) that is translocated into the nucleus and induces transcription of target genes during conditions such as muscular inactivity, inflammation and malnutrition [57,60]. Interestingly, studies on animals showed that the activation of autophagy results in muscle atrophy, but also that the complete suppression of this pathway leads to muscle degeneration through accumulation of protein aggregates, mitochondrial abnormalities and enhanced oxidative stress [61]. Therefore, autophagy must be finely adjusted to maintain appropriate muscle mass.

Several studies show that there is significant overlap between CIP and CIM, and therefore, the term critical illness polyneuropathy (CIPNM) was coined to better underline the coexistence of both neuropathy and myopathy [62]. Drugs (corticosteroids, neuromuscular blocking agents), high blood glucose levels, immobility and deep sedation represent risk factors for developing CIPNM [56].

Prevention and treatment

To date, no specific treatment for chronic critical illness is available. The attempts made to activate the hypothalamic–pituitary axis with hormone treatment can reduce hypercatabolism and increase anabolism, but they have shown no clear impact on prognosis [63,64]. Conversely, the implementation on ICU admission of a combination of strategies aimed at preventing the progression of an acute disease into chronic critical illness has proved to be fundamental. Such procedures are aimed at reducing systemic inflammation, treating endocrine alterations and preventing mechanical ventilation-induced diaphragmatic dysfunction.

With reference to systemic inflammation, protective mechanical ventilation, that is with lower tidal volumes (6 mL/kg) and lower pressures (plateau pressure lower than 30 cmH₂O), compared to standard mechanical ventilation has proved to reduce the concentration of pulmonary and systemic inflammatory mediators during acute respiratory distress syndrome (ARDS) [65]. Early rehabilitation therapy in patients undergoing mechanical ventilation showed to reduce systemic cytokine levels, increase the number of ventilator-free days, shorten the duration of delirium and promote the recovery of functional independence [66,67].

Among endocrine alterations, the control of stress-induced hyperglycaemia is one of the main therapeutic goals in case of acute critical illness requiring ICU admission. Insulin therapy for hyperglycaemia with a tight glucose monitoring can reduce the incidence of mortality, renal failure, sepsis and polyneuropathy (CIPNM) and can also facilitate weaning from mechanical ventilation [68,69]. However, such positive effects are offset by an increase in mortality in case of onset of severe hypoglycemia [70].

One of the primary causes of progression towards chronic critical illness is mechanical ventilation-induced diaphragm dysfunction. Human studies show that controlled mechanical ventilation, even after a few days, may lead to significant fibre atrophy in both fast and slow muscle fibres of the diaphragm, associated with signs of oxidative stress and increase in muscle proteolysis [71]. After six consecutive days of controlled invasive mechanical ventilation, the pressure generated by the diaphragm during phrenic nerve stimulation drops by 30% [72]. Therefore, the implementation of strategies aiming at reducing as much as possible the days requiring mechanical ventilation is paramount to prevent the onset of diaphragm dysfunction. A randomized and controlled study performed in patients undergoing invasive mechanical ventilation evidenced that daily sedative interruption associated with spontaneous breathing cycles can reduce the total number of ventilator days and increase the chances of dismissal from ICU [73].

Association of early rehabilitation treatments, daily sedative interruption and application of spontaneous breathing trials aimed at early weaning from mechanical ventilation are useful strategies to try to prevent an evolution towards chronic critical illness.

Nutritional support can play a role both in the prevention and treatment of chronic critical illness, although currently no data are available on this specific group of patients.

The evidence regarding nutritional support in ICU suggests that in patients with preserved gastrointestinal tract, enteral nutrition is to be preferred, providing trophic stimulus to enterocytes, reducing bacterial translocation and determining the secretion of hormones [28]. Moreover, compared to parenteral nutrition in critical patients, early (48 h after admission to ICU) enteral nutrition has shown to reduce septic complications, improve the course of the disease and reduce the length of hospital stay [74,75], thus suggesting a preventive role in the development of chronic critical illness.

Another issue related to the nutritional support in chronic critical illness is the global amount of protein and calories to be administered to the patient [76]. Opinion of experts suggests to administer a sufficient amount of protein (from 1.0–1.2 to 1.2–1.5 g/kg/day, but up to 2 g/kg/day in subjects with renal failure, ulcers or conditions associated with loss of nitrogen) to compensate hypercatabolic state [28].

Regarding calories intake, both under- and over-feeding are associated with poor prognosis in patients admitted to ICU [77–79]. Experts recommend to set to 20–25 kcal/kg dry adjusted weight/day to provide sufficient energy. Due to the lack of specific data on this topic and the complex nutritional management, the presence of a nutrition specialist is recommended in the healthcare team.

Delirium is another frequent condition in ICU patients, representing a significant burden both to the patient and to the healthcare system. The management of this condition in chronic critical illness is one of the most problematic issues for clinicians. One of the goals is to reduce as much as possible the administration of sedatives such as midazolam and lorazepam, which are one of the main risk factors for delirium [80]. Haloperidol is the first line drug for the management of agitation and delirium, and it is related with lower hospital mortality in mechanically ventilated patients [81]. As an alternative, olanzapine was found to have comparable efficacy of haloperidol in controlling delirium, but with fewer extrapyramidal side effects [82].

Ethical issue

Chronic critical illness also poses important ethical issues: what is the dividing line between care and futility? When should

decisions on the suspension of life support be considered? When should we qualify and quantify quality of life as unacceptable and when should palliative care be considered as mandatory?

Patients at this stage are often unable to decide on their fate, while family members are often emotionally involved. Therefore, medical staff faces the difficult decision whether to continue treatments, replacing one or more vital functions, and so on.

Practically, chronic critical illness may be considered as the result of a previous decision, made by the clinicians, when caring for an acutely ill patient admitted to ICU. Thus, this is probably the right moment in which, depending on the patient's condition, age and prognosis, professionals have to debate the limitations of therapies and the best setting for caring. The difficult task that medical science will face in the coming years will be to understand under what circumstances the afflictions following intensive care may make sense ('The limit of every pain is an even greater pain', Emil Cioran).

Conclusion

Recent advances in the intensive care setting have led to better outcomes for patients with acute diseases, by applying a number of techniques aimed at restoring their vital functions. However, these medical advances have also led to an unexpected drawback: an increasingly larger population of patients remain dependent on organ replacement techniques such as mechanical ventilation. This condition, also known as chronic critical illness, has a significant economic impact on the healthcare system and requires a major effort in medical and nursing care. The pathophysiological features of the condition remain partially unclear, and at present, no specific treatment is available, although a number of measures applied on ICU admission may reduce its incidence. The challenge for the coming years is to identify the risk factors and mechanisms leading to the progression of an acute disease into chronic critical illness, aiming at reducing its occurrence.

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Address

Respiratory Diseases Clinic, Policlinico di Modena, via del Pozzo, 71, 41124 Modena, Italy (A. Marchioni, R. Fantini, F. Antenora, E. Clini, L. Fabbri).

Correspondence to: Dr Alessandro Marchioni, Policlinico di Modena, via del Pozzo, 71, 41124 Modena, Italy. Tel.: +39

0594225859; fax: +39 0594224231; email: marchioni.alessandro@unimore.it

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