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Special article

[Translated article] Post-intensive care syndrome: Epidemiology, pathophysiology, and the role of the pharmacist in its management

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ABSTRACT

With the progressive decline in mortality rates in intensive care units in recent decades, increasing attention has been drawn to the fact that many patients who survive their stay in the intensive care unit develop long-lasting physical, cognitive and psychological impairments, which can last for months or even years after their critical illness. This health problem, known as post-intensive care syndrome, can be alleviated by implementing certain practices during hospitalisation, and its treatment generally requires attention upon discharge from hospital. The stress and trauma associated with the intensive care unit experience can also affect family members in the long term, manifesting as mental health problems known as family post-intensive care syndrome.

In this context, pharmacists play a key role in the prevention and treatment of post-intensive care syndrome, integrating into multidisciplinary teams in both the intensive care unit and post-intensive care unit recovery clinics. Their intervention includes comprehensive optimisation of pharmacotherapy, reconciliation, identification and prevention of adverse drug events, and health education for patients and their families.

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Síndrome poscuidados intensivos: epidemiología, fisiopatología y rol del farmacéutico en su manejo

Palabras clave:
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RESUMEN

Con la disminución progresiva de las tasas de mortalidad en las unidades de cuidados intensivos en las últimas décadas, ha cobrado creciente atención el hecho de que muchos pacientes que sobreviven a la estancia en estas unidades desarrollan alteraciones físicas, cognitivas y psicológicas de larga duración, que pueden extenderse durante meses o incluso años tras la enfermedad crítica. Este problema de salud, conocido como síndrome poscuidados intensivos, puede aliviarse mediante la implementación de ciertas prácticas durante la hospitalización, y su tratamiento generalmente requiere atención al alta hospitalaria. El estrés y el trauma asociados con la experiencia en la unidad de cuidados intensivos pueden también afectar a los familiares a

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largo plazo, manifestándose como problemas de salud mental, conocidos como síndrome poscuidados intensivos familiar.

En este contexto, el farmacéutico desempeña un papel fundamental en la prevención y el tratamiento del síndrome poscuidados intensivos, integrándose en equipos multidisciplinarios tanto en la unidad de cuidados intensivos como en clínicas de recuperación posteriores. Su intervención incluye optimización integral de la farmacoterapia, conciliación, identificación y prevención de eventos adversos relacionados con medicamentos, y educación sanitaria del paciente y su familia.

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Introduction

Short-term clinical outcomes have improved dramatically among intensive care survivors in the last 50 years; however, a high proportion of critical care survivors (ICU survivors) develop persistent physical and cognitive impairment after hospital discharge. The evidence available demonstrates that ICU survivors and their caregivers often develop psychological symptoms including anxiety, depression and post-traumatic stress disorder (PTSD). In 2010, the American Society of Critical Care Medicine defined Post-Intensive Care Syndrome (PICS) to describe new or worsening impairments in physical, cognitive, or mental health status arising after a critical illness that are unrelated to a traumatic brain injury or a stroke.[1]

Post-Intensive Care Syndrome-Family (PICS-F) occurs in caregivers of ICU patients who develop post-discharge mental health symptoms, with sleep deprivation, anxiety, depression and complicated grief disorder being the most common.[2]

PICS requires a tailored approach in pediatric intensive care units (PICUs), given that it occurs in a dynamic environment where patients are experiencing critical illness during crucial stages of physical and cognitive development.[3] Moreover, a child's recovery after admission to the pediatric intensive care unit inevitably affects the entire family, as well as the child's reintegration into school and other social environments or contexts. Siblings also experience severe social and emotional stress. Parents of PICU patients frequently experience work-related disruptions, including reduced working hours or interruption of employment, which may result in a substantial and long-lasting economic burden after the child's critical illness.

Critical care should be viewed as a continuum of care that begins upon ICU admission and extends beyond hospital discharge, requiring a multidisciplinary approach to the prevention and management of PICS. In this setting, hospital pharmacists play an increasingly critical role in inpatient medication management and in the prevention of PICS-related adverse outcomes. The involvement of hospital pharmacists in optimizing sedation and analgesia, performing medication reconciliation, identifying drug–drug interactions, and reducing polypharmacy has been associated with reduced mortality rates and drug-related adverse events, and shorter ICU stays.[4] Additionally, their involvement in patient and family education and in post-discharge care supports a continuum of care and positions pharmacists as key stakeholders within multidisciplinary teams for the prevention and management of PICS.

Causes and mechanisms of post-intensive care syndrome

Persistent PICS-related physical impairment is caused by Intensive Care Unit-Acquired Weakness (ICUAW). ICUAW is defined as symmetrical and diffuse muscle weakness that has no identifiable cause other than the critical illness that led to ICU admission. Clinical manifestations embrace failed or delayed mechanical ventilator weaning, impaired speech or deglutition, and generalized weakness in the extremities. ICUAW is categorized into muscle wasting, polyneuropathy and critical illness myopathy (CIM). Co-occurrence of the two latter is defined as critical illness neuromyopathy (CINM).[5]

Beyond disuse-induced skeletal muscle atrophy, the interaction of other factors contributes to the development of ICUAW, including systemic inflammation, endocrine dysfunction, electrolyte abnormalities, and inadequate nutritional status. These factors impair protein synthesis and promote the activation of proteolytic pathways.[5] Vitamin D deficiency-exacerbated by ICU patients' lack of exposure to sunlight-is an undervalued reversible factor contributing to ICUAW.[6] These factors, alongside microvascular ischemia, have been suggested to constitute the neuropathic components of ICUAW.[7]

Manifestations of cognitive impairment in PICS cases include impaired memory and attention and decreased mental processing speed long after ICU discharge.[7] Persistent or recurrent episodes of hypo- or hyperglycemia, along with pre-existing cognitive impairment, have been recognized as potential risk factors for the development of PICS among ICU survivors.[7] A study conducted in 1999 among patients with acute respiratory distress syndrome (ARDS) found that prolonged or severe hypoxia was associated with an increased risk of cognitive impairment one year after hospital discharge.[8] The most recent evidence identifies hypoxia as a major risk factor for the development of persistent cognitive impairment among survivors of ARDS and acute respiratory failure.[9] The literature also provides evidence of a significant association between delirium in ICU patients and subsequent PICS-related cognitive impairment. The 2013 BRAIN-ICU trial involving over 800 ICU patients reported a direct association between the duration of delirium and the risk of developing persistent cognitive impairment.[10]

Furthermore, PICS has an impact on mental health, contributing to the development of depression, anxiety and PTSD due to the isolating, distressing and dehumanizing experience of being admitted to an ICU. ICU patients are repeatedly exposed to pain and physical discomfort and often feel disoriented and confused due to sedation and prolonged delirium. Risk factors include a history of mental illness, female sex, a young age, and physical dependency.[11] The use of sedatives, particularly benzodiazepines, during ICU admission and the limited memories of the ICU experience also increase the risk of developing mental health disorders. Intrusive traumatic recollections and nightmares during admission may be a predictive factor of persistent mental health problems following discharge.[12] Evidence has been provided that hypoglycemia and hypoxia both increase the risk of experiencing cognitive impairment and depression symptoms among ICU survivors.[13,14]

Finally, factors contributing to PICS-F include female sex, a young age, a low education level and a history of mental illness. Partners of ICU patients and single-parent families of pediatric ICU patients are at an increased risk of adverse psychological outcomes. Despite the aforementioned, families of pediatric ICU patients are less likely to develop PICS, as compared to families of adult ICU survivors.[15]

Epidemiology

The incidence of physical impairment in adult ICU survivors ranges from 25 to 80%, being more prevalent among sepsis survivors,[16] potentially due to the role of inflammatory cytokines in the pathogenesis of ICUA.[17] As many as 80% of adult ICU survivors experience cognitive impairment.[18] Although cognitive dysfunction generally improves over time, it may persist for years, particularly among patients

recovering from ARDS or sepsis. The prevalence of PTSD may reach 50% among adult ICU survivors and persist for years following hospital discharge.[19]

In a cohort of 406 adult ICU survivors, 64% and 56% had experienced one or more PICS-related impairments at 3 and 12 months after discharge, respectively. Co-occurrence of impairments in two or more domains–especially cognitive and psychological problems–persisted in the long term.[20] The BRAIN-ICU study conducted in Nashville reported a prevalence of 29% of depression at 12 months after discharge, with a relatively low incidence of PTSD at 7 months. Around 25% of patients needed assistance for performing daily living activities one year after discharge.[21]

As many as 75% of family members of ICU patients developed symptoms consistent with PICS-F; and a third needed drug therapy for the management of symptoms. Anxiety is the most common mental health problem among family members, leading to the exacerbation of pre-existing physical illnesses, financial difficulties, and consumption of abuse substances.[22]

Among pediatric ICU survivors, a meta-review reported incidence rates of 36% at discharge, 26% at 6 months and 19% at 2 years.[23]

Screening and follow-up

Telemedicine and novel clinical tools for outpatient assessment of PICS symptoms have been proven to be effective remote PICS symptom screening methods.[24]

Challenges in the identification and management of PICS-related symptoms include fragmented continuity of care across the different stages of recovery, encompassing the intensive care unit, rehabilitation services, and post-discharge home care. In the United Kingdom, dedicated post-intensive care clinics have been established to facilitate the assessment and follow-up of ICU survivors, whereas in the United States, screening for PICS is more commonly conducted within primary care settings. In Spain, post-ICU clinics–coordinated by intensivists–are available at some hospitals. These clinics are composed of multidisciplinary care teams involving endocrinologists, rehabilitation and pain specialists, and psychiatrists.

In 2012, the University of Vanderbilt established an ICU Recovery Center aimed at providing comprehensive care to ICU survivors.[25] The first visit is conducted two weeks after hospital discharge and includes an assessment of the patient's physical, mental and cognitive status. At this Center, a critical care pharmacist is engaged in the therapeutic follow-up of survivors. Their tasks include performing medication reconciliation, conducting a clinical interview with the patient, providing pharmaceutical counseling, and assessing treatment adherence.

An observational study assessing the role of pharmacists[26] demonstrated their key role in identifying and resolving multiple drug-related problems. This, along with the implementation of preventive pharmaceutical interventions, underscores their significant contribution to successful post-ICU care. In the study, a total of 62 outpatient care visits were analyzed, of which 56 included a comprehensive medication review. The median number of pharmaceutical interventions per patient was 4, with each patient having received at least one intervention. These included medication discontinuance in 39% of cases; the incorporation of new medications in 32%, and the detection of an adverse drug reaction in 16% of patients.

Treatment and management

Prevention is the best strategy. The ABCDEF bundle for the prevention of PICS has been implemented across a wide range of hospitals.[27,28] Through this patient-centered approach, unnecessary immobility and sedative exposure are minimized, thereby reducing the risk of physical, cognitive, and psychological impairments associated with critical illness and ICU admission.[10]

The *ABCDEF bundle*

In 2013, the American Society of Critical Care Medicine published The Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit (the PADIS guidelines), which summarizes the available evidence with the purpose of improving patient comfort and safety (pain, agitation and delirium). These guidelines were reviewed and updated in 2018.[29]

Other scientific societies[27,28] have subsequently reviewed and adapted current evidence to their respective environments to complement the PADIS guidelines and facilitate their regional implementation.

The ABCDEF bundle involves a 6-step approach aimed at optimizing ICU patient care by standardizing and coordinating processes to "liberate" them from the ICU as soon as possible.

The different components of the ABCDEF bundle, added to the PICS prevention and PICS-F expansion, are summarized in Tables 1 and 2.

This ICU care bundle has been adapted to the pediatric population through the integration of new components and adjusting to the ABCDEFGH approach (Table 3)[30]:

Contribution of the pharmacist to preventing post-intensive care syndrome

The involvement of the clinical pharmacist in the ICU in keeping with the skills described for ICU care[31] represents a structural intervention for the prevention of PICS. Their intervention is not limited to occasional medication reviews, but embraces comprehensive optimization of drug therapy across the different stages of critical illness, including care transition.

Table 1
Components of the ABCDEF bundle for ICU patients.

A	Assess, Prevent, and Manage Pain	Assess pain through validated scales at least four times a shift. Pain should be treated within 30 min when pain is identified, with subsequent reassessment of treatment response. Combine pharmacological and non-pharmacological. Prevent pain: Administer analgesia and implement non-pharmacological interventions prior to the procedures. Analgesia should be optimized before initiating sedative therapy.
B	Both Spontaneous Awakening Trials and Spontaneous Breathing Trials	Interrupt sedative medications, orient the patient to time and day, and conduct a spontaneous breathing trial to liberate the patient from mechanical ventilation.
C	Choice of Analgesia and Sedation	This element comprises a multidisciplinary assessment, at least once a day, of the continued appropriateness and need for pharmacological interventions initiated for the management of pain and agitation.
D	Delirium: assess, prevent, and manage.	STOP: consider sedatives, review pharmacological treatment and design a drug downtitration schedule. THINK: toxic situations, hypoxemia, hospital-acquired infections/sepsis, non-pharmacological interventions, potassium (K^+) or other water and electrolyte imbalance TREAT: current recommendations support the use of non-benzodiazepine sedatives
E	Early mobility and exercise	This element focuses on multidisciplinary implementation of early mobilization schedules.
F	Family engagement and empowerment	Assessing the relevance of family engagement in the ICU

ICU: Intensive Care Unit.

Table 2
Extended ABCDEF(G and H) bundle for the prevention and management of post-intensive care unit syndrome and PICS-family.

G	Good handoff communication	Ensuring seamless patient transitions between ICU and general wards, but especially between the multidisciplinary care team and the patient's family. Achieving this goal involves ensuring effective communication with the family and engaging them in patient care, using empathetic listening, avoiding medical terminology, and involving other professionals such as social workers and psychotherapists.
H	Handout materials.	Designing and handing out PICS and PICS-F educational material to the patient and the family

ICU: Intensive Care Unit.

Medication reconciliation during patient transition from the ICU to outpatient care

Medication reconciliation during ICU-ward transitions and upon hospital discharge enables pharmacists to identify and correct discrepancies, duplicities, drug–drug interactions, dosing errors and polypharmacy. Likewise, this intervention facilitates the detection of untreated indications and discontinuance of unnecessary medication started during acute illness. This intervention plays a key role in preventing adverse events that may result in persistent functional, cognitive and psychological impairment after discharge. An example is maintaining antipsychotic or benzodiazepine therapy initiated during delirium without a review or withdrawal plan.

Optimizing analgesia and sedation therapy

ICU patients frequently experience pain even at rest. PADIS guidelines[29] recommend prioritizing the use of non-opioid analgesics with the aim of reducing exposure to opioids and their potential adverse effects. The pharmacist can support the implementation of multi-modal analgesia strategies by prioritizing non-opioid analgesia and selecting opioids with a lower associated risk of delirium. Similarly, the pharmacist favors the use of sedatives associated with a lower duration of mechanical ventilation and a lower incidence of delirium through the use of validated tools such as RAAS. The tailored administration of this treatment contributes to reducing unnecessary exposure to deep sedation, which is associated with poorer long-term neurocognitive outcomes.[29]

They play a key role in the individualized optimization of analgesic and sedative regimens by adjusting dosing, administration intervals, and treatment duration according to the pharmacokinetic-pharmacodynamic (PK–PD) characteristics of critically ill patients, as well as individual patient-specific factors such as obesity and the presence of organ dysfunction. These interventions contribute to reducing oversedation, thereby potentially reducing the incidence of PICS.

Metabolic monitoring

Both hypoglycemia and hyperglycemia in ICU patients are associated with a higher risk of persistent cognitive impairment.[32] Pharmacist-led monitoring of metabolic balance includes the assessment and management of glycemic control, the identification of hypo- and hyperglycemic episodes, and the optimization of insulin therapy, which remains the primary pharmacological strategy for glycemic management.

Additionally, pharmacist involvement in nutritional support planning contributes to optimizing nutritional therapy and preventing metabolic events, ultimately favoring patient functional recovery.[33]

Promotion of unnecessary medication deprescription

Diagnosis of delirium is established through assessment using validated screening scales (CAM-ICU). Atypical antipsychotics (particularly quetiapine) are frequently administered for the management of delirium; however, their use is supported by a weak level of evidence regarding efficacy in the prevention and treatment of delirium and may trigger the development of delirium symptoms or occurrence of other adverse effects, potentially increasing the risk of PICS. Current evidence suggests that antipsychotics should be reserved for patients experiencing severe agitation, hallucinations or symptoms that pose a risk to themselves or others. When indicated, their use should be limited to the shortest possible duration (PADIS).

Notably, antipsychotics and other drug therapies prescribed for the management of delirium are maintained after discharged and their use continues beyond care transition. In this context, pharmacists can also play a key role in optimizing pharmacotherapy through dose adjustments and the reduction of exposure to medications associated with an increased risk of delirium, including anticholinergic agents, benzodiazepines, opioids, antihistamines, tricyclic antidepressants, corticosteroids, and antimuscarinic drugs.[34]

Patient and family education regarding appropriate medication use to optimize treatment adherence

Coordination of post-ICU follow-up favoring functional and psychological recovery. Tasks of pharmacists integrated in post-ICU clinics include reviewing regular therapies modified during ICU admission, monitoring late adverse effects to facilitate the patient's functional and psychological recovery.[35]

Other preventive measures

A key intervention to prevent mental health problems involves keeping an ICU diary that is shared with patients and their family to help them overcome limited recollections due to sedation and delirium. Having an ICU diary may reduce the risk of depression and anxiety among survivors and improve their quality of life.[36]

Patient prognosis

Unfortunately, post-ICU clinics and other services for the management of PICS after onset have limited efficacy. A Cochrane's review addressing ICU follow-up services found their limited effectiveness in improving health-related quality of life.[2] The integration of a pharmacist in these clinics may contribute to optimizing pharmacotherapy and correcting medication-related issues, such as potential drug–drug interactions or the use of unnecessary medications overlooked on hospital discharge or that were subsequently added. Additionally, the pharmacist can provide therapeutic patient and family education.[26]

Long-term prognosis of PICS patients varies according to the severity of the critical illness that led to ICU admission, the patient's health status at hospital discharge and their pre-admission functionality. Physical impairments may improve, particularly with physical therapy, whereas cognitive and mental health disorders may persist over time. A cohort of 406 ICU survivors in the USA demonstrated modest improvements in cognitive and mental health outcomes, with a third of patients and their families having experienced deficiencies in the two domains 3 to 12 months after discharge.[29]

Table 3
Extended ABCDEF(G and H) bundle for the prevention and management of post-intensive care unit syndrome in the pediatric population.

G	Nutrition and sleep	Reviewing nutritional needs, type of nutrition, caloric needs, and rehabilitation needs. Protecting the circadian rhythm, creating a quiet environment to avoid sleep disturbances during the night.
H	Humanistic Medicine	This element is focused on home care and involves follow-up to screen PICS symptoms in patients and family after discharge and long-term coordination with rehabilitation and other healthcare specialists after discharge.

ICU: Intensive Care Unit.

PICS-related complications are associated with a substantial socioeconomic burden, as affected patients and their families may experience persistent functional limitations that hinder their ability to resume full-time employment. A study conducted in the UK found that 22% of ICU survivals still needed assistance for performing daily living activities one year after discharge, which was generally provided by unpaid family members. Additionally, 28% reported a negative impact of ICU admission and recovery on family income.[37]

Conclusions

PICS is a common adverse outcome among ICU survivors, having a significant impact on the quality of life of both patients and their family. Preventive multidisciplinary approaches such as the ABCDEFG bundle and the integration of hospital pharmacists in critical care teams are essential for reducing the incidence of PICS and improving long-term clinical outcomes.

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The authors used the Artificial Intelligence tool ChatGPT and Deep Translate to support manuscript translation into English and for the appropriate writing of the manuscript.

CRediT authorship statement

Laura Doménech-Moral: Writing – review & editing, Writing – original draft. **Meri Martin-Cerezuela:** Writing – review & editing, Writing – original draft. **Esther Domingo Chiva:** Writing – review & editing, Writing – original draft. **Aurora Fernández Polo:** Writing – review & editing, Writing – original draft. **Tatiana Betancor García:** Writing – review & editing, Writing – original draft. **Miguel Angel Amor García:** Writing – review & editing, Writing – original draft. **Irene Aquerreta González:** Writing – review & editing, Writing – original draft. **Marta Albanell Fernández:** Writing – review & editing, Writing – original draft. **Carla Bastida Ferndández:** Writing – review & editing, Writing – original draft. **Sara Ortiz Pérez:** Writing – review & editing, Writing – original draft. **Sara Cobo Sacristán:** Writing – review & editing, Writing – original draft. **Fernando Becerril Moreno:** Writing – review & editing, Writing – original draft. **Amaia Egüés Lugea:** Writing – review & editing, Writing – original draft.

Authorship

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Conflict of interest

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