Chapter 13
Long-Term Effects of Pain and Opioid Use in the ICU

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Introduction

Many critically ill patients admitted to an intensive care unit (ICU) will experience moderate-to-severe pain during their admission [1, 2]. This includes pain at rest [3] and pain experienced during common ICU procedures [4]. As a result, adequate treatment of pain is a recognized priority in critical care medicine.

Survivors of critical illness, a population that is growing due to advances in care, often experience chronic pain. In the context of the coronavirus disease 2019 (Covid-19) pandemic, the disease due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), these issues have never been more salient.

While there is growing recognition of chronic pain after ICU admission, fundamental questions remain unanswered. Specifically, is acute pain during critical illness related to the chronic pain that survivors experience? Does this chronic pain, combined with frequent exposure to opioids in the critical care setting, present a risk for post-ICU opioid dependence? As critical care delivery in the twenty-first century is designed to improve both short- and long-term outcomes, these are vital questions for the bedside provider.

In this chapter, we review international pain guidelines and the long-term implications of current pain management practices in the ICU. We then explore the epidemiology of pain following critical illness, with a focus on chronic pain that

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Table 13.1 Non-pharmacologic interventions and non-opioid pharmacologic adjuvants recommended in clinical practice guidelines to mitigate pain and opioid use in the ICU [5]

Non-pharmacologic interventions	Non-opioid pharmacologic adjuvants
Music therapy	Acetaminophen
Massage	Nefopam
Cold therapy	Low-dose ketamine
Relaxation techniques	Neuropathic pain medications (e.g., gabapentin)

develops or worsens after an ICU admission. We then consider the impact of chronic post-ICU pain on quality of life and evaluate the existing data regarding changes in opioid use after critical illness. Finally, we conclude by discussing strategies to prevent and mitigate chronic post-ICU pain.

International Pain Guidelines and Current Practices

In 2018, the Society of Critical Care Medicine published its updated Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption (PADIS) in Adult ICU Patients [5]. The pain management recommendations emphasize a multimodal approach to analgesia that includes non-pharmacologic interventions and non-opioid pharmacologic adjuvants as strategies to reduce opioid use and minimize the risks associated with opioid exposure (Table 13.1) [5]. These guidelines also recommend protocol-based pain assessment and management using standardized pain assessments (e.g., behavioral pain scale (BPS) or critical-care pain observation tool (CPOT)) to facilitate sedation minimization and, explicitly, to reduce opioid consumption [5].

Despite this emphasis on non-opioid alternatives and adjuncts for the treatment of pain in critically ill patients, opioids remain the mainstay of pain management in the ICU. Opioids are also frequently used in critically ill patients to enhance sedation, improve mechanical ventilation synchrony, and reduce agitation, with many patients receiving continuous opioid infusions for prolonged periods of time during their ICU stay [6]. In one retrospective study of 286 US acute care facilities, 56% of nonsurgical patients admitted to an ICU received opioids during their admission [7]. This high exposure to opioids in the ICU raises concern for the potential of ICU-acquired opioid dependence and subsequent long-term opioid-related morbidity.

Life After the ICU

In addition to concerns for ICU-acquired opioid dependence, critical illness has also been associated with the development of chronic pain [2, 8–10]. As advances in critical care medicine have led to increased survival, there has also been a growing

awareness among critical care providers of the long-term impairments that follow critical illness, sometimes termed "survivorship" ailments.

Post-Intensive Care Syndrome (PICS) refers to the series of impairments in cognition, mental health, and physical health that survivors of critical illness commonly endure [11]. Fifty-six percent of survivors of critical illness experience a new and lasting impairment in one or more of these domains, with 21% continuing to experience two or more impairments one year after their critical illness [12]. These impairments contribute to the reductions in health-related quality of life and inability to return to employment that afflict many survivors.

As the understanding of life after critical illness matures, chronic pain has emerged as an important, life-altering, functionally incapacitating condition. Chronic pain may contribute to PICS, and vice versa. It remains unclear whether chronic pain results from acute pain experienced in the ICU and/or residual inflammation exacerbated by disuse and functional impairment [6, 13]. Notably, the presence of chronic pain following critical illness may serve to further aggravate the risk of opioid use and dependence among ICU survivors. An understanding of these suspected long-term consequences of acute ICU pain and opioid use in the ICU is needed to inform the judicious use of opioids in the critical care setting.

Epidemiology of Chronic Pain After Critical Illness

Chronic pain is common among survivors of critical illness [2, 8–10]. In a 2019 review of nine studies evaluating chronic post-ICU pain, the prevalence of chronic pain among ICU survivors ranged from 33% to 73% [14], with an incidence of moderate to severe pain of 45% in one study [10]. A separate, narrative review similarly found prevalence rates that varied substantially [2].

Yet, it is not entirely clear what proportion of patients has pain that is directly attributable to their past critical illness. Most studies of chronic post-ICU pain did not assess patients' baseline chronic pain status, leaving open the possibility that patients reporting chronic post-ICU pain may have had some measure of chronic pain that predated their ICU stay.

Few studies have sought to address this question. In one study of 47 ICU survivors participating in a post-ICU recovery program, 66% reported new pain that had not been present prior to their ICU admission [8]. Another study of 207 ICU survivors found that, 6 months after a medical or surgical ICU stay, 16.3% of patients who had no preexisting chronic pain developed a chronic pain condition that they attributed to their ICU admission, while another 16.8% had chronic pain prior to admission but reported new sources of chronic pain following their ICU stay [10]. Combined, one-third of patients in the study reported chronic ICU-related pain specifically [10].

The results of these studies suggest that most patients experience new pain after their ICU admission, with as many as one-third reporting persistent (i.e., chronic) pain at 6 months [8–10]. The declining prevalence could reflect symptom

improvement over time, survivor bias, or both. While some post-ICU pain may be unrelated to the ICU admission, either as preexisting pain or new pain attributable to other causes, a substantial proportion is believed by patients to be new and specifically attributable to their ICU stay. However, a number of confounding factors may be at play in self-reported pain assessments, such as poor patient recall of pain prior to their ICU admission and the presence of new functional impairments following critical illness that may impact perceptions of pain.

The etiology of chronic pain following critical illness is not fully understood. Several possible mechanisms for this acute-to-chronic pain transition have been proposed [6]. One potential mechanism is that sustained activation of peripheral nociceptive fibers during acute pain may lead to eventual structural remodeling of the central nervous system with subsequent hyperactivity that manifests as chronic pain [13]. Additional theories regarding the mechanisms that underlie the transition from acute to chronic pain include interaction between the immune system and central nervous system during the sickness response, as well as alterations in emotional and cognitive processing that impact pain affect [15].

Apart from the acute-to-chronic pain transition, common sequelae of critical illness may also serve as additional mediators of chronic post-ICU pain. Functionally limiting joint contractures, for example, are relatively common. In one study, contractures were found in 39% of ICU patients at the time of transfer out of the ICU, and were associated with limited range of motion and pain [16, 17]. This provides another possible mechanism for the new chronic pain that many ICU survivors experience, and presents an important opportunity for further research and intervention.

For patients who experience chronic pain following an ICU admission, the shoulder joint is the most frequently affected joint [8, 9]. This may be the result of prolonged immobility of the shoulder joint during critical illness due to the location of central lines, ventilator tubing, and other equipment, as well as pressure placed on the shoulder during common nursing procedures such as rolling [9]. Other common sites of pain include the trunk, back, upper limb, and head [8]. Notably, 39% of patients presenting with new chronic post-ICU pain have pain at more than one site [8].

Relatively few studies have attempted to identify risk factors associated with the development of chronic pain following critical illness. Some noted risk factors include severe sepsis [9], admission for trauma or surgery [18], acute respiratory distress syndrome (ARDS) [19], and increasing patient age [9]. Other factors such as ICU length of stay and days of mechanical ventilation have not been found to be predictive of post-ICU pain [10, 20]. Data is lacking on whether acute pain intensity and/or duration during an ICU stay is associated with chronic post-ICU pain conditions [14].

Given the frequent overlap between postoperative patients and patients admitted to the ICU, findings from studies of risk factors for chronic pain and/or chronic postsurgical pain may help shed light on possible additional risk factors for chronic pain following critical illness [8]. A 2016 review of risk factors for the development of chronic postsurgical pain proposed an extensive framework that included

patient-related, psychosocial, preoperative, intraoperative, and postoperative variables associated with a higher likelihood of chronic pain [13]. This included risk factors such as severity or duration of pain, female gender, preoperative opioid use, and patient anxiety and depression [13]. These variables present opportunities for further investigation to determine whether they may in fact be risk factors for the development of chronic post-ICU pain as well.

Impact of Chronic Post-ICU Pain

Chronic post-ICU pain contributes to the decreased quality of life seen in survivors of critical illness, with 60% of patients with chronic post-ICU pain reporting moderate to severe impairments in daily life, family activities, and work [10]. Among survivors of severe accidental injuries, those with chronic post-ICU pain were more likely to have a physical disability and inability to work as a result of their critical illness than those without chronic pain [21]. Notably, while chronic pain in general is known to be associated with anxiety and depression, studies of chronic post-ICU pain in particular have yet to find this association [22].

While the consequences of post-ICU pain are severe and long-lasting, recent data suggests that the impact of these impairments on patients' daily functioning may decrease over time. In one study of patients with new chronic post-ICU pain, the mean Brief Pain Inventory (BPI) interference score at baseline assessment was 6.5, representing a high level of interference in daily activities [8]. The two domains with the highest level of interference secondary to chronic pain were "enjoyment of life" and sleep [8]. Notably, though pain severity did not improve at 1 year, pain interference did improve with a reduced mean BPI interference score of 4.5 [8]. This suggests that patients suffering from chronic post-ICU pain achieve some return of their ability to carry out their daily activities despite steady pain levels. This may be due to the development of coping strategies to better manage their pain, an improved sense of self-efficacy over time [8], and/or reflect adaptation, resilience [23], and post-traumatic growth [24].

Patterns of Opioid Use Among ICU Survivors

As noted previously, the frequent use of opioids in the ICU has raised concern for the potential of ICU-acquired opioid dependence and subsequent long-term opioid-related morbidity among survivors of critical illness. As a result, a small number of studies have attempted to evaluate whether or not there is in fact increased opioid use among ICU survivors.

In a retrospective review of 2595 adult patients admitted to the ICU of one tertiary care center, 76.9% were nonusers, 16.9% were intermittent opioid users, and 6.2% were chronic opioid users 3 months prior to admission [25]. At discharge, the

proportion of nonusers had increased to 87.8% while intermittent users and chronic users decreased to 8.6% and 3.6%, respectively [25]. Finally, at 4 years of follow-up the proportion of nonusers had further increased to 95.6%, with intermittent users dropping to 2.6% and chronic users dropping to 1.8% [25]. This represents a statistically significant change in the distribution of patients among the three categories of opioid usage before and after their ICU admission, with an increase in nonusers and decrease in both intermittent and chronic users after their ICU stay [25]. Therefore, this study did not find an increase in chronic opioid use following ICU admission. Notably, pre-admission opioid use and prolonged hospital length of stay were associated with chronic opioid use in the study, while age, gender, type of patient (medical vs surgical), and ICU length of stay were not [25].

A separate population-based cohort study of all adult ICUs in Ontario, Canada, sought to evaluate patterns of opioid use following critical illness for the subset of elderly patients who were chronic opioid users prior to their admission [26]. Among the 19,584 patients studied, the median daily dose of opioids filled prior to admission was 32.1 g of morphine equivalent [26]. At 6 months following hospital discharge, 22% of patients had filled a prescription for a higher daily morphine equivalent, 19.8% were unchanged, 21.5% had filled a prescription for a lower daily morphine equivalent, and 36.7% had no prescription filled [26]. These findings suggest that among chronic opioid users, at least among those who survive to 6 months, ICU admission is not associated with an increase in opioid use at 6 months following discharge [26]. Taken together, the two studies described in this section appear to refute the notion that exposure to opioids in the ICU increases the risk of ICU-acquired opioid dependence among adult nonusers or leads to escalating opioid doses among elderly chronic opioid users.

Prevention and Mitigation of Chronic Post-ICU Pain

Because chronic post-ICU pain is a common consequence of critical illness, one that interferes with daily function and quality of life [8–10], strategies to prevent and mitigate chronic post-ICU pain are urgently needed to improve outcomes for ICU survivors. Given the role of acute pain in the development of chronic post-ICU pain, adequate pain management is an essential component of chronic pain prevention [6, 13]. Despite this, only 35.5% of ICU patients have their pain assessed by a physician, and fewer still are assessed using a validated pain assessment tool [27]. Accurate and frequent pain assessment in the ICU is needed to promptly treat acute pain and decrease the likelihood that chronic pain will develop.

While opioids remain the mainstay of acute pain management in the ICU, their use must be balanced against the risk of adverse effects as well as the potential for subsequent ICU-acquired opioid dependence and morbidity. An individualized pain management plan that uses a multimodal analgesia approach as recommended in the PADIS guidelines [5] is therefore needed to achieve this goal. Such an approach should incorporate non-opioid analgesics as well as non-pharmacologic pain management interventions such as music, massage, and relaxation techniques to reduce the need for opioids and minimize the risk of adverse effects (Table 13.1) [5]. For

Table 13.2 The ABCDEF (A2F) bundle elements [28–31]

A	Assess, prevent, and manage pain
B	Both spontaneous awakening trials and spontaneous breathing trials
C	Choice of analgesia and sedation
D	Delirium: assess, prevent, and manage
E	Early mobility and exercise
F	Family engagement and empowerment

patients at risk of joint contractures, which may function as a mediator of chronic post-ICU pain, preventive steps should be taken to minimize the risk that contractures will develop. This may include interventions such as the use of steroids which have been shown to have a protective effect against joint contractures, though further research in this area is still needed [16].

At present, in the absence of an evidence-base to rely upon to mitigate post-ICU chronic pain, we encourage use of the recommended ABCDEF (A2F) bundle. The bundle (Table 13.2) encourages care practices that align with PADIS clinical practice guidelines and foster care delivery designed to limit the immobility, sedation, and brain dysfunction that contribute to the development of PICS and its related consequences [28–31]. Among the realized benefits of the A2F bundle is a greater degree of functional independence after critical illness, a finding that may translate into less post-ICU chronic pain. Specifically, emphasizing early mobility and physical therapy for patients in the ICU may contribute to the prevention of chronic post-ICU pain [8]. Future research is needed to test this important potential benefit of the A2F bundle, adopted by the Society of Critical Care Medicine as the centerpiece of the ICU Liberation collaborative.

For patients who do develop chronic post-ICU pain, outpatient follow-up paired with referral to a specialized pain clinic can ensure that patients receive adequate analgesia tailored to their needs [14]. Follow-up should also include appropriate screening, counseling, and management of any other PICS-associated impairments that may be present, such as cognitive impairment [32], anxiety [33], depression [33], and impairments in activities of daily living [34, 35]. The growing rise of post-ICU clinics presents a promising model for the delivery of comprehensive care for survivors of critical illness [36]. However, regardless of where patients receive their follow-up care, providers must ensure that they are conducting thorough medication and functional reconciliation to identify patients who have been continued on opioids or who may be receiving higher doses of opioids than they had been prior to their ICU stay and to identify patients with new, functional impairments [35].

Conclusion

In summary, critically ill patients often experience pain both at rest and during standard ICU procedures. This acute ICU pain has been associated with the development of chronic pain in survivors of critical illness, leading to significant interference

in daily functioning and decreased quality of life. Prevention of chronic post-ICU pain requires appropriate ICU pain assessment and management using a multimodal analgesia model as one element of the evidence-based ABCDEF bundle recommended to improve short- and long-term outcomes for critically ill patients. With opioids continuing to play a large role in ICU pain management, providers must take care to use opioids judiciously in order to avoid adverse events and reduce the theoretical risk of ICU-acquired opioid dependence. While existing studies suggest that opioid use in the ICU does not pose an obvious risk of increased chronic opioid use after the ICU stay, additional studies are needed to further characterize the long-term consequences of opioid use in the critical care setting.

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