Supportive Care of Patients on Mechanical Ventilation

Martin Urner MD, Bruno L Ferreyro MD, Ghislaine Douflé MD, and Sangeeta Mehta MD

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The paradigm of supportive care of patients who are critically ill has changed significantly over the past 20 years. Patients on mechanical ventilation are no longer heavily sedated; the goal is a comfortable patient who can interact with health-care professionals and with their family members. Systematic, regular assessment of the patient for pain, anxiety, and sleep deprivation allows early recognition of these distressing symptoms. Appropriate treatment of patients' symptoms should be based on a multimodal pharmacologic and non-pharmacologic approach. Early mobilization and avoidance of physical restraint are additional patient-centered goals. The presence of family members during daily rounds and at the bedside can reduce the distress of the patient and enhance communication with the health-care team. All of these changes have created new challenges and opportunities for the multidisciplinary health-care team. This review aimed to describe the main components of evidence-based supportive care of patients on mechanical ventilation, beyond the specific settings of the ventilator. *Key words: intensive care unit; critical illness; sedation; pain; analgesia; delirium; agitation; caregivers; family members; early mobilization.* [Respir Care 2018;63(12):1567–1574. © 2018 Daedalus Enterprises]

Introduction

Mechanical ventilation is a life-saving intervention that has evolved and been refined since the second half of the 20th century. Classically, patients on mechanical ventilation were routinely exposed to deep sedation and even paralysis, with little mobilization.[1,2] As a consequence of research over the past 2 decades that focused on supportive care, there has been a shift in the paradigm of the management of sedation, mobilization, and family engagement in the ICU.[2] This review aimed to describe the main components of evidence-based sup-

Drs Urner, Ferreyro, Douflé, and Mehta are affiliated with the Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada. Drs Urner and Ferreyro are affiliated with the Institute for Health Policy, Management, and Evaluation, University of Toronto, Toronto, Ontario, Canada. Dr Douflé is affiliated with the Department of Anesthesia, University of Toronto, Toronto, Ontario, Canada. Dr Mehta is affiliated with the Department of Medicine, Sinai Health System and University of Toronto, Toronto, Ontario, Canada.

Drs Urner and Ferreyro contributed equally to this work.

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Correspondence: Sangeeta Mehta MD, Sinai Health System, 600 University Ave, Suite 18–216, Toronto, ON, Canada M5G 1X5. E-mail: geeta.mehta@utoronto.ca.

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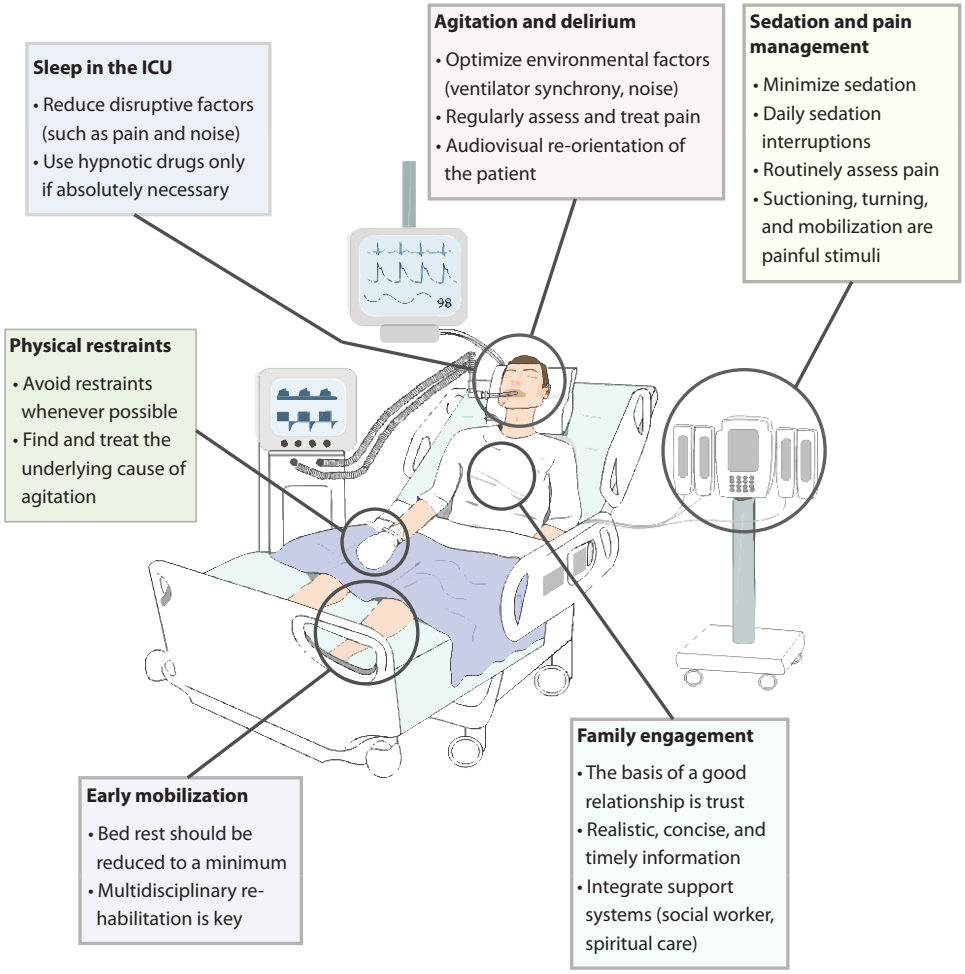

Fig. 1. The main components of evidence-based supportive care of patients on mechanical ventilation.

portive care of patients on mechanical ventilation, beyond the specific settings of the ventilator. For didactic purposes, the text was divided into different sections and addressed each of these components (Fig. 1). However, there is a significant natural overlap between all these management strategies.

Sedation and Pain Management

Patients who are critically ill and require mechanical ventilation often experience a combination of pain, restlessness, anxiety, and delirium, which is promoted and influenced by a complex interplay of physiologic, pathological, and external factors.[3] Traditionally, patients in the ICU who undergo mechanical ventilation were heavily sedated and frequently received muscle paralysis.[1] Sedation management of patients who are critically ill, however, has experienced a dramatic shift during the past 15 years.[4] There is growing evidence that indicates that prolonged and deep sedation is associated with poor outcomes;[3-5] whereas minimization of sedation is associated with reduced duration of mechanical ventilation and with shorter ICU and hospital length of stays.[6-9] Only a small subset of patients in the ICU require deep sedation, mainly those with severe respiratory failure, shock, or intracranial hypertension, and those who require paralysis (usually for the same aforementioned conditions).

Benzodiazepines, propofol, and dexmedetomidine remain the most frequently used agents for sedation of patients in the ICU.[10] Benzodiazepines' sedative properties are mediated by the gamma-aminobutyric acid (GABA) receptor; maintenance of sedation with benzodiazepines is generally characterized by good cardiovascular safety, with only mild reduction in arterial blood pressure as a response to altered systemic vascular resistance.[11,12] Benzodiazepines represent a valid option if prolonged deep sedation is needed. They have particularly favorable effects in case of seizures, acute anxiety, and withdrawal syndromes. However, the long half-life (intermittent bolus dosing is preferred over continuous infusion) and active metabolites,

and a potential association with delirium and longer duration of mechanical ventilation are drawbacks of benzodiazepines; therefore, their use is not recommended as a first-line sedative strategy.[4]

As with benzodiazepines, propofol acts through GABA receptors. Propofol is characterized by a fast onset, undergoes rapid metabolism, and has a short half-life, with no bioaccumulation or prolonged sedative effect. Importantly, propofol does not have an analgesic or amnestic effect. Due to the risk of propofol infusion syndrome, prolonged infusions and dosing of >80 μg/kg/min should be avoided.[13] In contrast to benzodiazepines and propofol, dexmedetomidine is a selective α_2-receptor agonist that has gained use in recent years. One of the benefits of this agent is that it can induce sedation without significant respiratory depression.[3] The main adverse effect is bradycardia. The use of dexmedetomidine may be associated with less delirium[14] and reduced duration of mechanical ventilation,[15] but strong evidence is still lacking.

Sedation should always be delivered in a patient goal-directed manner by using a validated sedation assessment tool, such as the Richmond Agitation-Sedation Scale or the Riker Sedation-Agitation Scale.[11,12,16] For most patients who receive mechanical ventilation in the ICU, a reasonable target is a Richmond Agitation-Sedation Scale score of -2 to 0 or a Riker Sedation-Agitation Scale score of 3–4; both targets are representative of a calm, interactive or lightly sedated patient. The use of sedation protocols and a daily wake-up trial have each been associated with reduced duration of mechanical ventilation, and the ICU and hospital lengths of stay.[6,16-19] This evidence is reflected by a statement in *Choosing Wisely Top 5 List in Critical Care Medicine*[20] from multiple critical care societies: "Do not deeply sedate mechanically ventilated patients without a specific indication and without daily attempts to lighten sedation." Independent of the pharmacologic strategy chosen for patients who are receiving invasive mechanical ventilation, it is currently recommended to maintain a light level of sedation that aims for an interactive and calm patient.[2,4,5]

In 2010, Strøm et al,[9] in a randomized controlled pilot trial, showed that a no-sedation strategy was feasible in the majority of mechanically ventilated subjects and had beneficial effects compared with usual care, including reduced duration of mechanical ventilation and reduced ICU and total hospital length of stays. An important current general principle for patient comfort management is "analgesia first."[4] If a sedative agent is required in addition to analgesia, then the lightest level of sedation should be targeted. Neither lighter sedation, daily wake-up trials, nor no-sedation strategies have been shown to increase the risk of long-term psychological complications in patients on mechanical ventilation.[4,5,9,21] These insights have led to a change in practice, with patients being awake and able to interact during mechanical ventilation, and have also created new challenges for the multidisciplinary health-care team. Patients on mechanical ventilation frequently experience significant pain and anxiety but may have limited ability to communicate their comfort needs.

Pain is one of the most common unpleasant memories that patients retain from their ICU experience,[3,5] and the vast majority of patients experience pain during their ICU stay.[3,22] The approach to pain in patients who are critically ill involves 3 different components: prevention, assessment, and treatment. Of these, the identification and objective assessment of pain represent significant challenges for the ICU team. Self-reported pain is considered the reference standard for pain assessment,[4] but patients on mechanical ventilation often exhibit limitations in expressing their pain. Clinical practice guidelines suggest that pain should be routinely assessed in the ICU, and, if impossible to assess from a patient's self-report, then behavioral pain assessment tools should be incorporated.[4] Our knowledge about the underlying biologic mechanisms of pain is still limited, and patients in the ICU often experience a combination of different types of specific pain components.[23]

In mechanically ventilated patients, it is particularly difficult to assess if the type of pain is acute or chronic and whether a nociceptive or neuropathic component is predominant. Ultimately, pain management of patients in the ICU should always comprise a multimodal approach that involves pharmacologic and nonpharmacologic interventions. Painful stimuli in patients on mechanical ventilation include suctioning, turning, mobilization, catheter insertion, and wound care.[22] Pain due to these stimuli should be anticipated and prevented with pharmacologic analgesia. In patients who are critically ill, opioids are the most common pharmacologic agents for pain and are first-line agents for non-neuropathic pain; generally intermittent rather than continuous dosing is preferred.[4] Non-opioid analgesics, such as acetaminophen and nonsteroidal anti-inflammatory drugs, can be used as opioid-sparing agents.[4] Non-pharmacologic interventions include relaxation techniques and music therapy, and there is evidence that indicates an opioid-sparing effect.[22]

Agitation and Delirium

Delirium is defined as an acute disturbance in attention and awareness, with additional disturbances in cognition, not explained by a preexisting neurocognitive disorder or caused by another medical condition.[24,25] In patients who are critically ill, the term delirium has been used ambiguously to describe different neurological states, such as encephalopathy and acute brain failure.[3] Delirium is associated with increased mortality and with long-term sequelae, for example, post-ICU cognitive impairment.[26,27]

Identification of delirium is crucial to identify reversible precipitants and to implement environmental measures. Nevertheless, delirium is often not diagnosed in patients on mechanical ventilation.[3,28] Currently, the two most commonly used validated tools for the assessment of delirium in the ICU are the Confusion Assessment Method for the ICU[29] and the Intensive Care Delirium Screening Checklist.[30] They both have shown similar sensitivity for detection of delirium compared with Diagnostic and Statistical Manual of Mental Disorders criteria,[31] although the Confusion Assessment Method for the ICU[29] has higher specificity.[3] Delirium cannot be attributed to a single precipitating factor but is likely always of multifactorial etiology. Important precipitating factors for delirium include acute illness, exposure to medications, withdrawal syndromes, and environmental factors (sleep deprivation, noise from monitors). In particular, some studies indicate that continuous infusions of benzodiazepines, opioids, and corticosteroids have been associated with the development of delirium in subjects on mechanical ventilation.[4,25]

The treatment of the underlying critical illness that necessitated ICU admission is crucial for delirium resolution. Patient-ventilator asynchrony should be avoided during mechanical ventilation, pain management optimized, and early mobilization attempted to minimize environmental factors that trigger delirium.[31] Simple non-pharmacologic interventions that may be helpful include frequently reorientating the patient; maintaining a normal day-night routine; and ensuring that the patient has his or her hearing aids, eyeglasses, and dentures. A single randomized controlled trial showed faster delirium resolution, less agitation, and a greater rate of transfer home or to rehabilitation when the subjects were treated with quetiapine, in addition to as-needed haloperidol.[33] However, there is no definitive evidence that specific pharmacologic interventions, such as the administration of haloperidol or atypical antipsychotics, prevent or reduce the duration of delirium in patients on mechanical ventilation.[26,34,35]

Sleep in the ICU

Patients who require mechanical ventilation experience sleep deprivation, which is explained by a combination of multiple factors that can be classified broadly as environmental and non-environmental.[36-38] Environmental factors may include noise disruption, patient-care monitoring (blood pressure, blood sampling, diagnostic testing), and 24-h light exposure. Non-environmental factors include acute illness, pain, medical equipment (eg, endotracheal tube, nasogastric tubes, urinary catheters), and medications, particularly psychotropics.[37,38]

The typical sleep architecture involves a period of rapid eye movement and a period of non–rapid eye movement, which is subdivided into 3 phases: N1, N2, and N3. The rapid eye movement stage usually accounts for 15 to 20% of sleep time and is associated with active dreaming.[39] This physiological sleep architecture is severely altered in mechanically ventilated patients.[37,40] In this setting, sleep is usually fragmented with frequent arousals, decreased rapid eye movement and N3 sleep, and an increase in the N1 stage.[36] There is evidence that patients in the ICU who experience poor sleep quality have an increased risk of poor outcomes, possibly related to the association of sleep deprivation, with decreased ability to resist infections, reduced pain tolerance, short-term memory loss, and cognitive impairment.[40] It has also been shown that sleep deprivation in the ICU setting is an independent risk factor for delirium.[41]

There is a paucity of data on successful interventions to improve sleep duration and quality in patients on mechanical ventilation, which is likely due to the challenges of measuring sleep in patients who are critically ill. Although, with the lack of strong evidence from randomized controlled trials, there are specific interventions that will logically improve the patient's experience in the ICU.[39] The adequate treatment of acute illness, review of concomitant medications and prescription regimen for polypharmacy, and reduction of nighttime interruptions are some examples.[4] With regard to pharmacologic interventions, although these are widely used in the ICU setting, there is no evidence of any beneficial drug to improve sleep in this setting.[4] Hypnotic drugs, when absolutely necessary, should be individualized and selected based on the patient's condition, age, comorbidities, potential interactions, and pre-ICU use of sleep aids. In our ICU, melatonin is often the first-line agent because it is well tolerated and associated with minimal adverse effects. However, 2 recent systematic reviews found insufficient evidence for the use of melatonin and propofol, to promote sleep in the ICU.[42,43]

The Use of Physical Restraints

Restraints are defined as any method, physical or mechanical device, material, or equipment that immobilizes or reduces the ability of a patient to move his or her arms, legs, body, or head freely.[44] Despite the existence of guidelines that recommend physical restraint minimization, restraining patients is still a common practice in many ICUs around the world, with vast regional and between-hospital differences in the prevalence of physical restraints.[45,46] The restraint of a person—and patients who are critically ill are among the most vulnerable persons—represents a very aggressive measure and should be the very last (and temporary) option for the prevention of self-harm or harm to others.[47] Clinicians often justify the use of restraints for prevention of patient-initiated device removal, unplanned extubation, or disruption of life-sustaining therapies.[46,47] However, results of some studies indicate that restraints do

not prevent accidental device removal.[48,49] Mechanical ventilation, sedation (especially benzodiazepine use), delirium, and large ICUs with a lower nurse-to-patient ratio are common factors associated with the use of restraints.[50,51] Interestingly, no patient-specific characteristics were found to be related to the use of restraints, which indicates that their use seems to be mainly associated with treatment characteristics and modalities.[30]

The use of restraints in the ICU not only causes patient stress, anxiety, increased oxygen consumption, elevated heart rate, and hypertension[52] but may also have detrimental long-term consequences, as illustrated by Jones et al[53] in a multi-center follow-up study of subjects after ICU discharge. Physical restraints and prolonged sedation were associated with the development of posttraumatic stress disorder independent of case mix and illness severity. Therefore, the goal must be to avoid or reduce the use of restraints whenever possible. To achieve this goal, a multimodal non-pharmacologic and pharmacologic approach should be used for patients who are agitated, with sedative infusions in the short term and on a longer term with the treatment of the underlying condition that causes agitation. Pain is the most frequent cause of agitation and, consequently, should be assessed and treated.[54] Anxiety should be addressed with non-pharmacologic approaches and, if necessary, in the acute setting, with intermittent administration of low doses of benzodiazepines. Furthermore, iatrogenic and non-iatrogenic substance withdrawal should always be considered as a potential precipitant for agitation and delirium, and should be assessed and treated.[53]

Early Mobilization

When patients who are critically ill are admitted to the ICU, clinicians primarily focus on hemodynamic stabilization and recovery from acute organ failure.[18] Patients often require mechanical ventilation and receive sedatives to minimize distress and oxygen consumption. Furthermore, given the invasive life-support systems connected to the patients, sedation is reduced only hesitantly due to concern for accidental self-extubation or unplanned disconnection from life-support systems.[56] Also, bed rest was traditionally espoused as a treatment that supports the patient toward recovery from critical illness.

However, there is little evidence for bed rest as a form of treatment to recover from critical illness. In fact, complete bed rest is a highly non-physiological and harmful form of therapy, and patients should be mobilized as early as possible.[57] A variety of detrimental effects have been observed after prolonged periods of bed rest, such as muscular atrophy and remodeling (which includes changes in myosin fibers) as well as various alterations in energy metabolism.[58] Regardless of nutritional support, patients who are critically ill experience a dramatic loss of skeletal muscle mass, especially in the first weeks of immobilization.[59] Bed rest for as little as 7 d is associated with substantial resistance to effects of insulin on glucose metabolism.[58] Immobilization has also been shown to induce orthostatic intolerance, which might be related to an attenuation of the vestibulosympathetic reflex observed after prolonged bed rest.[61]

Observational studies in subjects who survived ICU stay reveal that long-term sequelae of immobilization included persistent physical impairments and incomplete recovery of neuromuscular function.[18,62] In a cohort of subjects with ARDS who survived ICU stay, Herridge et al[63] observed that lung function returned to levels comparable with the healthy population, but physical limitations and varying degrees of exercise weakness were among the most-significant long-term burdens. Mobilization and physical activity may have a beneficial influence in states of severe systemic inflammation by protecting muscles and may ultimately result in improved functional outcome after critical illness.[64] Therefore, the prevention of neuromuscular dysfunction by reducing bed rest and implementing early mobilization is of crucial importance for patients who are critically ill.

Safety concerns are often cited to justify the decision not to mobilize patients who are critically ill and on mechanical ventilation. However, Bailey et al[65] demonstrated, in cohort of subjects with respiratory failure, that early activity was feasible and safe. Of those subjects who survived ICU admission, the majority (69%) were able to ambulate $>$ 100 feet at the time of ICU discharge. Thomsen et al[66] showed that unnecessary immobilization throughout the course of acute respiratory failure could be avoided by using an early activity protocol and by minimizing administration of sedatives. Burtin et al[67] implemented daily exercise sessions for subjects who were critically ill by using a bedside cycle ergometer and observed beneficial effects on functional exercise capacity and recovery of muscle force at hospital discharge. Schweickert et al[68] demonstrated that mobilization in the earliest days of critical illness was safe and well tolerated, and, most importantly, reduced the incidence of delirium and duration of mechanical ventilation, and led to a better functional outcome at hospital discharge.

Altogether, there is moderate evidence that early mobilization is safe, may improve functional outcomes, and may reduce the occurrence of delirium in patients with critical illness. There is certainly a need for more research in this area, given the mixed results from published trials, likely related to heterogeneous patient populations and differences in intensity and timing of the start of mobilization. Bed rest should be reduced to a minimum and early involvement of a multidisciplinary rehabilitation team during the ICU stay might be one of

the multiple strategies to reduce the long-term sequelae of critical illness.

Family Engagement

Family engagement has been defined as an active partnership between caregivers and relatives.[69] In the critical care setting and, especially during the early phases of critical illness, patients are often unable to express themselves; hence, patient-centered care is inseparably tied to the concept of family-centered care. When the severity of illness or delirium prevents the patient from verbalizing his or her wishes, the ICU team turns to family members to speak on behalf of the patient. A broad spectrum exists regarding the degree of family involvement in the care of their relatives, which mainly reflects different types of relationships among the patients, families, and ICU team.[70,71] The current standard of care is an approach that emphasizes interactivity and empowerment of the patient and family members.

A family engagement concept in the critical care setting consists of a multidisciplinary framework, which involves physicians, nurses, social workers, and spiritual care. Multiple opportunities are available at different levels to support families during the patient's critical illness and admission to ICU. These include providing realistic, consistent, and timely information about diagnosis, treatment, and prognosis; encouraging the presence of the family during nursing and medical rounds; enabling family members to assist with direct patient care; providing a variety of resources and support systems (eg, social services, spiritual care); and being sensitive to family members' personal comfort needs (eg, waiting-room environment).[72]

There is little evidence that directly links family engagement to improved patient outcomes.[73] However, critical illness may lead to significant anxiety and depression among family members, inherent to the severity of patients' condition and the likelihood of unfavorable outcomes.[74] Therefore, there are potential important benefits to both patient and family members of increased family engagement in the ICU.[75-79] Better engagement and involvement of the families of patients who are critically ill is associated with higher levels of family satisfaction.[71] Furthermore, establishing a trusting partnership between families and the treatment team ultimately serves a common goal, which is the patient's recovery from critical illness. A trusting partnership is also of utmost importance to approach sensitive topics for patients and their families, such as participation in research studies and goals of care discussions.

Conclusions and Future Challenges

During the past 20 years, there has been a significant change in the paradigm of supportive care of patients who are critically ill, with improvements in the assessment, prevention, and treatment of pain, agitation, and delirium. This was facilitated by a global increased interest in patient and family centered care, which led to landmark clinical trials and clinical practice guidelines.[6-8] Incorporating evidence-based strategies in daily practice remains challenging for ICU teams. Local understanding of the best effective interventions for culture change and knowledge translation, and interprofessional collaboration are crucial for the implementation of evidence-based medicine. Overall, patients who are critically ill are best treated with minimum to no sedation and should receive multimodal pain therapy, while considering potential painful stimuli, such as suctioning or early mobilization. Targeted pain management and the optimization of environmental factors have a positive effect on sleep and the development of ICU delirium. Family members play a key role in the recovery process and should be actively involved in patient care. A good relationship with the family should be sought and is based on mutual trust because the treatment team as well as the family share a common goal, which is in providing the best support for the patient who is critically ill.

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