Sedation in Critical Care

Impact on Length of Stay

A Comprehensive Evidence Synthesis (1991–2025)

Key Findings

- Studies reviewed: **55**
- ICU LOS reduction (DSI): **3.5 days**
- MV duration reduction (DSI): **2.4 days**
- Overall pooled LOS reduction: **1.5 days [95% CI: 1.1–1.9]**

The Critical Care Practitioner
As I Learn You Learn Too

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Contents

Executive Summary

This comprehensive report synthesizes evidence from 55 studies spanning 1991 to 2025 examining sedation practices and their impact on length of stay (LOS) for mechanically ventilated critical care patients. The evidence demonstrates that sedation management profoundly influences clinical outcomes, with continuous intravenous sedation associated with significantly prolonged mechanical ventilation duration (185±190 hours vs. 55.6±75.6 hours without continuous sedation, $p<0.001$) and extended ICU stays (13.5±33.7 days vs. 4.8±4.1 days, $p<0.001$). Daily sedation interruption (DSI), first validated in the landmark Kress 2000 trial, reduced median mechanical ventilation duration by 2.4 days (4.9 vs. 7.3 days, $p=0.004$) and ICU LOS by 3.5 days (6.4 vs. 9.9 days, $p=0.02$). Protocol-directed sedation strategies reduced ICU LOS by 1.73 days (95% CI -3.32 to -0.14, $p=0.03$) and hospital LOS by 3.55 days (95% CI -5.98 to -1.12, $p=0.004$) in meta-analysis. Newer agents including dexmedetomidine demonstrated shorter time to extubation compared to midazolam (101 vs. 147 hours, $p=0.01$) and propofol (69 vs. 93 hours, $p=0.04$). Delirium emerged as an independent predictor of prolonged hospitalization, with delirious patients experiencing 41% greater risk of remaining hospitalized (HR 1.41, 95% CI 1.05-1.89, $p=0.023$). The evolution from deep, continuous sedation in the 1990s toward light sedation, protocol-driven approaches, and even no-sedation strategies represents a paradigm shift with substantial implications for patient outcomes, resource utilization, and healthcare costs.

1. 1. Introduction

Sedation and analgesia represent fundamental components of critical care management for mechanically ventilated patients, yet their administration profoundly influences clinical outcomes, resource utilization, and patient safety. The importance of optimal sedation management extends beyond immediate patient comfort to encompass mechanical ventilation duration, intensive care unit (ICU) length of stay, hospital length of stay, delirium incidence, mortality, and healthcare costs. Over the past three decades, critical care sedation practices have undergone substantial evolution, transitioning from deep, continuous sedation paradigms prevalent in the early 1990s toward contemporary strategies emphasizing light sedation, daily interruption protocols, and in some contexts, complete avoidance of sedative agents [1], [2], [3].

The prevalence of sedation in critical care settings is substantial. In 1991, a survey of 164 US teaching hospitals revealed that sedating drugs were used at virtually all medical ICUs, with 36% using them routinely in more than 70% of patients and 48% using them frequently in 20-70% of patients [1]. By 2009, a point-prevalence study across 50 Australian and New Zealand ICUs found that 76% of invasively ventilated patients were receiving sedatives [4]. European surveys have documented similar patterns, with midazolam used often or always in 63% of ICUs and propofol in 35% [5].

The historical context of sedation practice reveals significant evolution in both philosophy and implementation. In 1991, only 6% of US ICUs employed standardized sedation protocols, with prescribing patterns dominated by house staff at 65% of institutions [1]. Drug selection was highly vari-

able, with costs ranging from less than 30*perdayforfentanylpluspancuroniumtoapproximately*1,000 per day for midazolam plus atracurium [1]. The late 1990s witnessed growing recognition that continuous intravenous sedation was independently associated with prolonged mechanical ventilation, with one landmark 1998 observational study demonstrating that continuous IV sedation resulted in mechanical ventilation duration of 185±190 hours compared to 55.6±75.6 hours without continuous sedation ($p<0.001$) [6].

The year 2000 marked a pivotal moment with publication of the Kress trial, which demonstrated that daily interruption of sedative infusions reduced median mechanical ventilation duration by 2.4 days and ICU length of stay by 3.5 days [7]. This finding catalyzed a paradigm shift toward lighter sedation targets and protocol-driven approaches. The 2002 Society of Critical Care Medicine (SCCM) guidelines provided the first comprehensive, evidence-based recommendations for sedation and analgesia management, establishing validated assessment tools and graded pharmacological recommendations [8]. Subsequent decades have witnessed continued refinement, with the 2010 Strom trial challenging conventional wisdom by demonstrating that complete avoidance of sedation (using only morphine boluses) resulted in 4.2 additional ventilator-free days compared to daily sedation interruption [3].

By 2020, a large multicenter trial comparing no sedation versus light sedation with daily interruption enrolled 700 patients across Scandinavian centers, reflecting the maturation of no-sedation strategies as a viable alternative approach [2]. Concurrently, technological advances including bispectral index (BIS) monitoring, entropy monitoring, and responsiveness index systems have been evaluated for their potential to optimize sedation depth, though with mixed results regarding clinical utility [9], [10]. Most recently, artificial intelligence applications in critical care have emerged as potential tools for optimizing sedation management and resource allocation, though implementation remains in early stages [11].

This report synthesizes evidence from 55 studies conducted between 1991 and 2025, examining sedation assessment tools, comparative agent efficacy, sedation strategies, special populations, implementation factors, and emerging technologies. The overarching objective is to provide a comprehensive, evidence-based analysis of how sedation practices influence length of stay outcomes and to identify optimal approaches for contemporary critical care practice.

2. 2. Background and Theoretical Foundations

2.1 2.1 Physiological Rationale for Sedation in Critical Care

The administration of sedation and analgesia in mechanically ventilated patients serves multiple physiological and clinical objectives. Pain represents the most significant stressor identified by ICU patients, relatives, and healthcare professionals, with mean severity scores of 3.36 on a 4-point scale [12]. Additional major stressors include inability to sleep (mean score 3.34), presence of endotracheal tubes (3.04), and physical restraint by tubes and monitoring equipment (3.04) [12]. These stressors arise not only from underlying acute illness but also from treatment procedures including endotracheal suctioning, catheter placement, physical therapy, dressing changes, and routine nursing care [13].

Inadequate sedation and analgesia management produces adverse physiological consequences including sympathetic nervous system activation, increased oxygen consumption, impaired tissue healing, immune dysfunction, and psychological trauma [13]. Conversely, excessive sedation carries distinct risks including prolonged mechanical ventilation, increased infection risk through multiple mechanisms (microaspiration, gastrointestinal motility disturbances, microcirculatory effects, and immunomodulation), venous thrombosis, decreased intestinal motility, hypotension,

reduced tissue oxygen extraction, and prolonged ICU stay [5], [14].

2.2 2.2 Evolution of Sedation Philosophy

The evolution of sedation philosophy over the study period reflects accumulating evidence regarding the risks of deep sedation. In the early 1990s, deep sedation was commonly employed, with many patients maintained at Ramsay levels 4-6 (minimal or no response to stimulation) [1]. By 2004, European consensus recommendations explicitly stated that "deep sedation is no longer considered necessary" and that it "postpones weaning, provokes complications, and prolongs ICU stay" [13]. The preferred target shifted to Ramsay levels II-III, maintaining patients at a sedation level where communication remains possible [13].

This philosophical shift was supported by observational data demonstrating temporal patterns in sedation intensity. Among survivors of mechanical ventilation, sedative intensity peaked in the fourth decile of intubation duration and then declined sharply, with level of consciousness increasing distinctly as drug doses decreased [15]. In contrast, nonsurvivors exhibited more variable sedation intensity with marked increases terminally and sharp declines in arousal level in the last third of intubation [15]. These patterns suggested that lighter sedation facilitating patient interaction and participation in care might improve outcomes.

2.3 2.3 Mechanisms Linking Sedation to Length of Stay

Multiple mechanisms explain the association between sedation practices and length of stay outcomes. First, sedation directly prolongs mechanical ventilation duration by suppressing respiratory drive, reducing patient-ventilator synchrony, and delaying recognition of readiness for weaning [6], [16]. Second, prolonged sedation increases exposure to infection risk factors, with sedation duration independently associated with ventilator-associated pneumonia incidence [14]. Third, sedation contributes to delirium development through direct neurotoxic effects, particularly with benzodiazepines, and through disruption of normal sleep-wake cycles [17]. Fourth, deep sedation necessitates prolonged periods of immobility, increasing risks of venous thromboembolism, pressure ulcers, and ICU-acquired weakness [14].

The relationship between continuous infusion versus bolus administration further illuminates these mechanisms. Continuous benzodiazepine infusion increased doses 5.4-fold compared to bolus administration ($p<0.001$), while continuous opiate infusion increased doses 2.5-fold ($p<0.001$) [15]. Continuous benzodiazepine infusion was identified as an independent predictor of longer mechanical ventilation duration, ICU stay, and hospital stay [15]. These findings suggest that administration method influences drug accumulation and subsequent clinical outcomes.

2.4 2.4 Quality of Sedation Concept

The concept of "quality of sedation" emerged as a framework for evaluating sedation adequacy. Quality of sedation is defined as (adequate sedation hours / total hours of sedation) $\times$ 100, with a target of greater than 85% [18]. However, observational studies revealed substantial gaps between this ideal and actual practice. In one large observational study, sedation was judged adequate in only 83% of 12,414 assessments, with undersedation occurring in 13.9% and oversedation in 2.6% of assessments [19]. Notably, patients were unarousable or minimally arousable 32% of the time and exhibited no spontaneous motor activity 21.5% of the time [19]. Surveys of French ICUs found deep sedation present in 41-57% of readings over a 6-day period [20]. These data indicate that sub-optimal sedation, particularly oversedation, remained prevalent despite growing awareness of its risks.

2.5 2.5 Cost Considerations

Economic considerations have increasingly influenced sedation practice. In 1991, daily sedation costs ranged from less than 30*toapproximately*1,000 depending on agent selection [1]. However, cost analyses incorporating downstream effects of sedation on length of stay have demonstrated that higher medication costs for newer agents may be offset by reduced ICU and hospital days. A Markov modeling study of remifentanil-based versus conventional sedation found that despite higher drug acquisition costs, remifentanil-based sedation resulted in estimated savings of €1,485 per patient (95% CI -2,224 to 5,194) through reductions in ICU length of stay (7.6 vs. 8.5 days) and mechanical ventilation duration (5.0 vs. 6.0 days) [21].

3. 3. Sedation Assessment Tools and Monitoring

3.1 3.1 Subjective Clinical Assessment Scales

Accurate assessment of sedation depth represents a prerequisite for optimal sedation management. Thirteen different sedation scales were documented across the studies reviewed, reflecting substantial heterogeneity in assessment approaches [22]. The most widely adopted tool has been the Ramsay Sedation Scale, used in 14 studies with variants in 7 additional studies [22].

3.1.1 3.1.1 Ramsay Sedation Scale

The Ramsay Scale, introduced in 1974, comprises six levels: three awake levels (1=anxious/agitated, 2=cooperative/oriented/tranquil, 3=responds to commands only) and three asleep levels (4=brisk response to stimulation, 5=sluggish response, 6=no response) [18], [23]. The scale demonstrated good interrater reliability with Cohen's kappa of 0.79 ($p<0.0001$) [18]. However, it has been criticized for lack of clear discrimination between levels and for combining assessment of consciousness with agitation [18].

Target Ramsay scores varied widely across studies, including ranges of 2-3, 2-4, 2-5, 3-4, and 4-5 [22]. This variability reflects both differences in patient populations and evolution of sedation philosophy over time. The Brussels Sedation Scale study, which implemented a 5-level scale with target levels 3-4, demonstrated that systematic use of a sedation scale significantly reduced excessive sedation, decreasing the proportion of observation days with Ramsay level 1 (deepest sedation) from 30% to 12% in morning assessments ($p<0.02$) and from 18% to 4% in evening assessments ($p<0.02$) [24].

3.1.2 3.1.2 Richmond Agitation-Sedation Scale (RASS)

The Richmond Agitation-Sedation Scale (RASS) has emerged as a preferred tool in more recent studies, particularly in North American centers. RASS employs a 10-point scale ranging from -5 (unarousable) to +4 (combative), with 0 representing alert and calm [25]. The scale demonstrated high interrater reliability and validity for critically ill patients [8]. RASS was utilized in major trials including the MIDEX/PRODEX dexmedetomidine studies, which targeted RASS 0 to -3 (light to moderate sedation) [26], and the 2020 no-sedation trial, which targeted RASS -2 to -3 in the sedation group [2].

RASS offers advantages over the Ramsay Scale by separately quantifying agitation (positive scores) and sedation (negative scores), providing more granular assessment of both extremes. The scale's validation included demonstration of 90% compliance in over 2,000 patient bedside observations with high agreement (kappa=0.80) with reference standard assessments [17].

3.1.3 3.1.3 Sedation-Agitation Scale (SAS)

The Riker Sedation-Agitation Scale (SAS) represents another validated tool, employing seven categories describing patient behaviors in response to stimulation [8], [18]. SAS demonstrated excellent interrater reliability and validity for critically ill patients [8]. The scale was utilized in studies of tracheostomy patients, with target levels most frequently set at SAS 3 or 4 [27]. Following tracheostomy, time heavily sedated (SAS 1 or 2) decreased from 7 hours per day to 1 hour per day ($p<0.001$), while time lightly or not sedated (SAS 3-5) increased from 16 to 23 hours per day ($p<0.001$) [27].

3.1.4 3.1.4 Motor Activity Assessment Scale (MAAS)

The Motor Activity Assessment Scale (MAAS), adapted from the SAS, comprises seven categories describing patient behaviors in response to stimulation [8]. MAAS was validated as reliable for critically ill patients [8]. The Minnesota Sedation Assessment Tool (MSAT), a two-domain scale measuring arousal and motor activity, demonstrated high interrater reliability after minimal training, with optimal sedation defined as arousal level 3-5 on a 6-point scale [28].

3.1.5 3.1.5 Brussels Sedation Scale

The Brussels Sedation Scale, employed in a 1999 implementation study, utilized five levels: 1=unrousable, 2=responds to pain stimulation but not auditory, 3=responds to auditory stimulation, 4=awake and calm, 5=agitated [24]. Target sedation was levels 3-4. Implementation of this scale significantly reduced oversedation, with mean lowest sedation levels improving from 2.16 ± 0.13 to 2.61 ± 0.11 ($p=0.011$) [24].

3.2 3.2 Pain Assessment Tools

Recognition that pain represents the primary ICU stressor has driven development of pain-specific assessment tools [12]. The 2002 SCCM guidelines recommended several validated instruments [8].

3.2.1 3.2.1 Tools for Communicative Patients

For patients able to communicate, unidimensional scales include the Visual Analogue Scale (VAS), a 10-cm line from "no pain" to "worst pain" that is reliable and valid but difficult for elderly patients; the Numeric Rating Scale (NRS), a 0-10 scale that correlates with VAS and is applicable across age groups; and the Verbal Descriptive Scale (VDS), which demonstrates moderate correlation ($r>0.60$) with behavioral pain scales [8].

3.2.2 3.2.2 Tools for Non-Communicative Patients

For non-communicative patients, behavioral-physiological scales assess pain-related behaviors (movement, facial expression, posturing) and physiological indicators (heart rate, blood pressure, respiratory rate) [8]. These scales demonstrated moderate-to-strong correlation with NRS [8]. The Behavioral Pain Scale (BPS) was utilized in the remifentanil versus fentanyl trial, with target BPS ≤ 6 for sedated patients [29].

3.3 3.3 Delirium Assessment Tools

Recognition of delirium as an independent predictor of adverse outcomes has driven systematic delirium screening in ICU patients [17], [30].

3.3.1 3.3.1 Confusion Assessment Method for ICU (CAM-ICU)

The Confusion Assessment Method for ICU (CAM-ICU) represents the most extensively validated delirium screening tool. CAM-ICU can be completed in an average of 2 minutes with 98% accuracy and demonstrates high interrater reliability (kappa=0.96) [8]. The tool requires four features for delirium diagnosis: acute onset or fluctuating course, inattention, and either disorganized thinking or altered level of consciousness [30].

In a prospective cohort of 261 medical ICU patients not requiring invasive mechanical ventilation, CAM-ICU identified delirium in 48% of patients [17]. Delirious patients experienced significantly longer hospital stays (median 5 vs. 3 days, p<0.001) and demonstrated 41% greater risk of remaining hospitalized after adjustment for confounders (HR 1.41, 95% CI 1.05-1.89, p=0.023) [17]. CAM-ICU was utilized in major trials including the MIDEX/PRODEX studies and the 2020 no-sedation trial [2], [26].

3.3.2 3.3.2 Intensive Care Delirium Screening Checklist (ICDSC)

The Intensive Care Delirium Screening Checklist (ICDSC) employs eight items assessed over 24 hours, with scores ≥4 indicating delirium and scores 1-3 indicating subsyndromal delirium [30]. In a comparative study of 162 ICU patients, ICDSC identified delirium in 34.6% and subsyndromal delirium in 32.7%, compared to CAM-ICU identification of delirium in 26.5% [30]. However, patients with positive ICDSC but negative CAM-ICU had mortality rates and length of stay comparable to non-delirious patients, leading to the conclusion that CAM-ICU is a better predictor of outcomes [30].

3.4 3.4 Objective Monitoring Technologies

3.4.1 3.4.1 Bispectral Index (BIS)

Bispectral Index (BIS) monitoring, which employs processed electroencephalography to generate a digital scale from 0-100, has been evaluated for ICU sedation monitoring [8]. The 2002 SCCM guidelines noted that BIS was not completely evaluated for ICU use, with limitations including variability between patients, interference from muscle activity, and lack of testing in metabolic or structural brain abnormalities [8].

Subsequent studies have confirmed limited utility in general ICU populations. In a study of 679 paired observations, BIS demonstrated only modest correlation with clinical sedation scores (r=-0.426, p<0.001), with wide overlap between clinical sedation levels [9]. BIS could not discriminate between light-moderate sedation (Ramsay 1-4) and deep sedation (Ramsay 5-6) [9]. A 2005 pediatric survey found that only one of eight pediatric ICUs utilized BIS monitoring [31].

3.4.2 3.4.2 Entropy Monitoring

Entropy monitoring, which measures Response Entropy (RE) and State Entropy (SE), has been similarly evaluated. In the same study of 679 observations, RE demonstrated correlation of r=-0.372 (p<0.001) and SE correlation of r=-0.360 (p<0.001) with clinical sedation scores [9]. Like BIS, entropy values could not discriminate between light-moderate and deep sedation [9]. The study concluded that BIS-Index and Entropy do not add information useful for guiding sedation in general ICU populations [9].

3.4.3 3.4.3 Responsiveness Index (RI)

The Responsiveness Index (RI), a more recent technology employing a 0-100 scale with color-coded prompts (red <20, amber 20-40, green >40), was evaluated in a 74-patient randomized trial [32]. In post-hoc analysis of patients with baseline RI<20, the intervention group spent

significantly less time with RI<20 (16% vs. 51%, p=0.02) and received less alfentanil (21.2 vs. 32.3 mg, p=0.01) [32]. Nurses valued the objective visible data trends, simple color prompts, and continuous monitoring versus intermittent assessments [32]. However, time to first extubation did not differ significantly (median 42.4 vs. 54.8 hours, p=0.52) [32].

3.4.4 3.4.4 Auditory Evoked Potentials

Auditory evoked potentials (AEPs) can be recommended for research in patients with deep sedation but demonstrate poor correlation with scoring systems at light sedation levels [18]. Clinical utility was rated at only 35 of 50 points [18]. Other objective methods including plasma drug concentration (5/50 points), frontalis electromyography (10/50 points), and continuous EEG (15/50 points) demonstrated even more limited clinical utility [18].

3.5 3.5 Assessment Frequency and Compliance

Assessment frequency varied across studies, with most protocols specifying evaluation every 2-4 hours [26], [29], [32]. However, compliance with assessment protocols has been variable. In an Australian implementation study, perfect compliance with Ramsay score recording every 4 hours during daylight improved from 13% pre-intervention to 50% post-intervention [33]. In the 2009 Australian and New Zealand point-prevalence study, 74% of sedated patients had formal sedation scores used, but 25% of mechanically ventilated patients receiving sedatives were not assessed with formal sedation scales [4].

The most frequently recorded Ramsay score shifted from Ramsay 2 (40% of scores pre-intervention) to Ramsay 3 (31% of scores post-intervention), with anxious/agitated states (Ramsay 1) representing only 5% of recorded scores [33]. This pattern suggests that when assessment is systematic, most patients are maintained at light to moderate sedation levels.

4. 4. Sedation Agents Compared

4.1 4.1 Benzodiazepines

Benzodiazepines have been among the most commonly used sedative agents throughout the study period, though their use has declined in recent years following recognition of adverse effects.

4.1.1 4.1.1 Midazolam

Midazolam was the most frequently used benzodiazepine, employed often or always in 63% of European ICUs in 2001, with usage ranging from 85% in Norway to 39% in Denmark [5]. In a 2003 US survey, midazolam was among the most common agents, though 50% of respondents indicated prolonged sedation was a clinical concern with its use [34]. Midazolam was used in 8.4% of time blocks in one observational study, with median dose of 0.008 mg/kg/hr lorazepam equivalents [15].

The 2002 SCCM guidelines recommended midazolam for short-term use only (less than 48-72 hours), noting that it produces unpredictable awakening with longer infusions (Grade A recommendation) [8]. This recommendation was based on evidence that for long-term sedation exceeding 72 hours, midazolam resulted in awakening times of 2.8-30 hours compared to 0.25-2.5 hours for propofol, with the greatest difference observed with deep sedation (Ramsay 4-5) [8].

In the MIDEX trial comparing dexmedetomidine to midazolam, midazolam-sedated patients required longer mechanical ventilation (median 164 vs. 123 hours, p=0.03) and longer time to

extubation (147 vs. 101 hours, p=0.01) [26]. ICU length of stay trended longer with midazolam (243 vs. 211 hours) but did not reach statistical significance (p=0.27) [26].

Midazolam was identified as an independent risk factor for unplanned extubation, with odds ratio of 2.3 (95% CI 1.01-5.18) [35]. In a study comparing dexmedetomidine to midazolam for non-invasive ventilation, midazolam required significantly more dosing changes (7 patients requiring 1-3 changes each) compared to dexmedetomidine (2 patients requiring 1 change each, p<0.01) [36].

4.1.2 4.1.2 Lorazepam

Lorazepam was the second most common sedative agent in the 1991 US survey [1] and was used in 24% of time blocks in one observational study [15]. The 2002 SCCM guidelines recommended lorazepam for most patients via intermittent IV or continuous infusion (Grade B recommendation) [8]. This recommendation was based on evidence that lorazepam demonstrated no significant difference in awakening time compared to midazolam but was more predictable, required fewer dose adjustments, and avoided prolonged effects when managed with nurse-implemented protocols [8].

However, lorazepam use was minimal in European practice, with only 0.5% of ICUs using it often or always [5]. Nurse preference surveys found that only 38.6% of nurses favored lorazepam, compared to 71.2% favoring midazolam [37].

4.1.3 4.1.3 Diazepam

Diazepam was used at 78% of US ICUs in 1991 despite concerns about active metabolites [1]. The 2002 SCCM guidelines recommended diazepam for rapid sedation of acute agitation (Grade C recommendation) [8]. However, diazepam use declined substantially in subsequent years and was rarely mentioned in studies after 2002.

4.2 4.2 Propofol

Propofol emerged as a preferred agent for situations requiring rapid awakening, such as neurologic assessment or extubation [8]. In the 2001 European survey, propofol was used often or always in 35% of ICUs, with usage ranging from 65% in Italy to 3% in Norway [5]. Propofol was more common in surgical units (34%) than medical units (12%, p<0.05) [5].

In observational studies, propofol was used in 34.7% of time blocks with median infusion rate of 25 µg/kg/min [15]. Propofol was used in more than 80% of subjects in an Australian protocol trial [38]. The 2002 SCCM guidelines recommended propofol when rapid awakening is important (Grade B recommendation) [8].

For short-term sedation less than 72 hours, no statistical or clinical difference in awakening time was observed between propofol and midazolam [8]. However, for long-term sedation exceeding 72 hours, propofol demonstrated substantially shorter awakening times (0.25-2.5 hours) compared to midazolam (2.8-30 hours) [8].

In a randomized trial of post-CABG patients, propofol versus midazolam resulted in numerically shorter weaning time (3.5±0.2 vs. 4.3±0.5 hours, p=0.20), mechanical ventilation duration (18.5±1.2 vs. 23.3±2.4 hours, p=0.07), and ICU length of stay (2.8±0.2 vs. 3.1±0.2 days, p=0.36), though differences did not reach statistical significance [39]. Patient satisfaction scores were similar (11.4±0.2 vs. 11.5±0.7) [39]. Greater propofol use was independently associated with shorter ventilation duration on multivariate analysis [38].

In the PRODEX trial comparing dexmedetomidine to propofol, time to extubation was shorter with dexmedetomidine (69 vs. 93 hours, p=0.04), though mechanical ventilation duration (97 vs.

118 hours, p=0.24) and ICU length of stay (164 vs. 185 hours, p=0.54) did not differ significantly [26].

A propofol shortage study (2008-2010) provided natural experiment data on the impact of reduced propofol availability. Propofol use for continuous infusion ≥24 hours decreased from 94% to 15% (p<0.0001), with compensatory increases in midazolam (36% to 73%, p<0.0001), lorazepam (7% to 14%, p=0.04), and dexmedetomidine (9% to 27%, p<0.0001) [40]. Duration of continuous sedation decreased from 6 days (94% of mechanical ventilation time) to 5 days (59% of mechanical ventilation time, p<0.0001) [40]. Unadjusted mechanical ventilation duration increased from 6.7 to 9.6 days (p=0.02), but after adjustment for APACHE II score, admission service, and ventilator mode, the estimated increase was only 7% and not statistically significant (p=0.35) [40].

4.3 4.3 Dexmedetomidine

Dexmedetomidine, a selective alpha-2 adrenergic agonist, has emerged as an important alternative to traditional sedatives, particularly for light to moderate sedation. In observational studies, dexmedetomidine was used in only 2.6% of time blocks [15], but its use increased substantially during the propofol shortage (9% to 27%, p<0.0001) [40].

The MIDEX and PRODEX trials, two phase 3 multicenter randomized double-blind studies conducted 2007-2010 across European centers, provided definitive comparative data [26]. In MIDEX, dexmedetomidine demonstrated non-inferiority to midazolam for time at target sedation (60.7% vs. 56.6%, ratio 1.07, 95% CI 0.97-1.18, p=0.15) [26]. In PRODEX, dexmedetomidine demonstrated non-inferiority to propofol (64.6% vs. 64.7%, ratio 1.00, 95% CI 0.92-1.08, p=0.97) [26].

Dexmedetomidine demonstrated significant advantages for mechanical ventilation duration and time to extubation. In MIDEX, mechanical ventilation duration was 123 hours (IQR 67-337) with dexmedetomidine versus 164 hours (IQR 92-380) with midazolam (p=0.03), and time to extubation was 101 hours (IQR 65-313) versus 147 hours (IQR 81-325, p=0.01) [26]. In PRODEX, time to extubation was 69 hours (IQR 39-184) with dexmedetomidine versus 93 hours (IQR 45-286) with propofol (p=0.04) [26].

ICU length of stay did not differ significantly in either trial: MIDEX showed 211 hours (IQR 115-831) with dexmedetomidine versus 243 hours (IQR 140-630) with midazolam (p=0.27), and PRODEX showed 164 hours (IQR 90-480) versus 185 hours (IQR 93-520, p=0.54) [26].

A key advantage of dexmedetomidine was improved patient interaction. Compared to midazolam, dexmedetomidine resulted in estimated VAS score difference of 19.7 (95% CI 15.2-24.2, p<0.001), and compared to propofol, score difference of 11.2 (95% CI 6.4-15.9, p<0.001) [26]. Dexmedetomidine patients were more arousable, cooperative, and better able to communicate pain [41].

However, dexmedetomidine was associated with increased hemodynamic adverse effects. In MIDEX, dexmedetomidine resulted in more hypotension (20.6% vs. 11.6%, p=0.007) and more bradycardia (14.2% vs. 5.2%, p<0.001) [26]. Study drug discontinuation due to lack of efficacy was more frequent with dexmedetomidine: 9% versus 4% compared to midazolam (p=0.02) and 14% versus 5% compared to propofol (p<0.001) [26].

For patients requiring non-invasive ventilation, dexmedetomidine demonstrated superior dosing stability compared to midazolam, with significantly fewer dosing changes required (p<0.01) [36]. In a small study of trauma/surgical ICU patients who failed weaning due to agitation, dexmedetomidine facilitated extubation in an average of 120±43 minutes after initiation [42].

An earlier study comparing dexmedetomidine to midazolam or propofol found no difference in ICU length of stay (6.6 vs. 6.8 days, p=0.275) but shorter mechanical ventilation duration after

adjustment (median 77.2 vs. 110.6 hours, adjusted p=0.025) [41]. For light-moderate sedation specifically, adjusted mechanical ventilation duration was 70.2 versus 93.7 hours (p=0.027) [41].

4.4 4.4 Opioids

4.4.1 4.4.1 Morphine

Morphine was the most common analgesic in the 2001 European survey, used often or always in 33% of ICUs, with usage ranging from 88% in Norway to 3% in Germany [5]. In the 1991 US survey, morphine sulfate was the most frequently listed sedating drug [1]. Morphine was administered in 33.3% of time blocks in one observational study, with median dose of 0.023 mg/kg/hr morphine equivalents [15].

The 2002 SCCM guidelines recommended morphine and hydromorphone as preferred agents for intermittent therapy due to longer duration (Grade C recommendation) [8]. Morphine was the primary analgesic in the trauma center protocol study due to efficacy and low cost [43]. In the no-sedation trials, morphine boluses (2.5 or 5 mg) were used as the sole pharmacological intervention [2], [3].

Nurse preference surveys found that 85.0% of nurses favored morphine [37]. However, high opiate use was associated with increased infection risk, with median opiate equivalent of 14 in infection cases versus 10 in controls (p=0.06), and high opiate group demonstrating odds ratio of 1.24 (95% CI 1.0-1.54, p=0.049) [14].

4.4.2 4.4.2 Fentanyl

Fentanyl was used often or always in 33% of European ICUs, with usage ranging from 58% in Italy to 0% in the Netherlands [5]. Fentanyl was used in 9.1% of time blocks in observational studies [15] and was used in 71% of patients receiving continuous IV sedation in the 1998 study [6]. Nurse preference surveys found that 59.6% of nurses favored fentanyl [37].

The 2002 SCCM guidelines recommended fentanyl for rapid onset in acutely distressed patients (Grade C recommendation) and as preferred agent for hemodynamic instability or renal insufficiency (Grade C recommendation) [8]. In the tracheostomy study, fentanyl administration decreased from 866 µg/(patient-day) to 71 µg/(patient-day) in the 7 days following tracheostomy (p<0.001) [27].

In a randomized trial comparing remifentanil to fentanyl-based analgesia, fentanyl (0.02-0.08 µg/kg ideal body weight/min) achieved target analgesia at all timepoints in 63% of patients versus 50% with remifentanil (p=0.44) [29]. Mechanical ventilation duration was similar: median 95 hours with fentanyl versus 73 hours with remifentanil (p=0.98) [29]. ICU length of stay (median 21 vs. 12 days, p=0.68) and hospital length of stay (median 29 vs. 27 days, p=0.36) did not differ significantly [29].

4.4.3 4.4.3 Remifentanil

Remifentanil, an ultra-short-acting opioid 250 times more potent than morphine, is metabolized by nonspecific esterases resulting in rapid and uniform clearance with blood-brain equilibration time of 1-1.5 minutes and context-sensitive half-time of 5 minutes unaffected by infusion duration [44]. Dose reduction is not necessary in renal or hepatic disease [44].

A Markov modeling study based on the UltiSAFE trial (205 patients, 109 conventional sedation, 96 remifentanil-based) found that remifentanil-based sedation resulted in ICU length of stay of 7.6 days versus 8.5 days with conventional sedation (difference 0.9 days, 95% CI -0.7 to 2.6, 89% probability of reduction) [21]. Mechanical ventilation duration was 5.0 versus 6.0 days (difference 1.0 days, 95% CI -0.8 to 2.9, 88% probability of reduction) [21]. Overall 28-day costs were €15,626

with remifentanil versus €17,100 with conventional sedation (difference €1,474 savings, 95% CI -2,163 to 5,110, 79% probability of cost savings) [21].

In the subgroup of patients for whom weaning started within 72 hours, remifentanil demonstrated even greater advantages: ICU length of stay 5.1 versus 5.9 days (difference 0.8 days, 95% CI -0.3 to 2.0, 93% probability), mechanical ventilation duration 2.3 versus 3.2 days (difference 0.9 days, 95% CI -0.3 to 2.2, 94% probability), and costs €9,807 versus €11,319 (difference €1,512 savings, 95% CI -1,034 to 4,058, 90% probability) [21].

However, the randomized trial comparing remifentanil (0.1-0.4 µg/kg ideal body weight/min) to fentanyl found no superiority for remifentanil in achieving target analgesia (50% vs. 63%, p=0.44) or in clinical outcomes [29]. Remifentanil withdrawal was identified as an independent risk factor for ICU-acquired infection in one study [14].

4.4.4 4.4.4 Sufentanil

Sufentanil, 7-13 times more potent than fentanyl and 500-1000 times more potent than morphine, possesses more pronounced sedative properties than fentanyl [44]. Sufentanil was used often or always in 24% of European ICUs, with usage ranging from 52% in Belgium/Luxembourg to 0% in Switzerland [5]. In German ICUs, sufentanil was administered more often than fentanyl and piritramide in all phases except short-term sedation ($p<0.05$) [45].

Sufentanil has distribution volume of 1.7-3.3 L/kg, equilibration time of 5-6 minutes, and half-life of 2.5-3.5 hours that can extend to 15 hours with prolonged infusion [44]. Context-sensitive half-time is 30-60 minutes and is not modified by infusion duration for short periods [44]. Recommended starting dose is 0.005-0.01 µg/kg/min, with reduction by 0.001 µg/kg/min if Ramsay score reaches 4-6 [44].

4.5 4.5 Combination Therapy

Recognition that pain and anxiety represent distinct phenomena requiring separate pharmacological approaches has driven adoption of combination analgo-sedation strategies. A randomized trial comparing midazolam alone to midazolam plus fentanyl co-sedation in 30 patients with respiratory failure demonstrated significant advantages for combination therapy [46]. Hours off-target Ramsay score per 24 hours were 4.2±2.4 with co-sedation versus 9.1±4.9 with midazolam alone ($p<0.002$) [46]. Asynchronous ventilator events per day were 0.4±0.1 with co-sedation versus 1.0±0.2 with midazolam alone ($p<0.05$) [46].

The 2002 SCCM guidelines recommended that analgesics be administered continuously or as scheduled intermittent doses with supplemental boluses (Grade C recommendation) [8]. In the Kress daily interruption trial, all patients received morphine infusion for analgesia in addition to either midazolam or propofol for sedation [7]. This analgo-sedation approach has become standard practice, with most contemporary protocols specifying separate analgesic and sedative components [29], [41].

5. 5. Sedation Strategies and Their Impact on Length of Stay

5.1 5.1 Continuous IV Sedation and Prolonged Mechanical Ventilation

The association between continuous intravenous sedation and prolonged mechanical ventilation was first systematically documented in a landmark 1998 prospective observational cohort study of 242 consecutive mechanically ventilated ICU patients [6]. This study found that 93 patients

(38.4%) received continuous IV sedation, most commonly with lorazepam (72.0%) and fentanyl (71.0%), with 45.2% receiving the combination [6]. Duration of continuous infusion averaged 6.0±6.4 days [6].

The unadjusted outcomes demonstrated dramatic differences. Patients receiving continuous IV sedation had mechanical ventilation duration of 185±190 hours compared to 55.6±75.6 hours for those not receiving continuous sedation ($p<0.001$) [6]. ICU length of stay was 13.5±33.7 days versus 4.8±4.1 days ($p<0.001$), and hospital length of stay was 21.0±25.1 days versus 12.8±14.1 days ($p<0.001$) [6].

After adjusting for age, gender, severity of illness, mortality, indication for mechanical ventilation, use of chemical paralysis, presence of tracheostomy, and acquired organ system derangements, continuous IV sedation remained independently associated with prolonged mechanical ventilation: 148 hours (95% CI 121-175) versus 78.7 hours (95% CI 68.9-88.6) for no continuous sedation ($p<0.001$) [6]. Adjusted ICU length of stay was 9.6 days (95% CI 8.4-10.9) versus 7.2 days (95% CI 6.6-7.7, $p=0.007$), and adjusted hospital length of stay was 19.4 days (95% CI 16.7-22.1) versus 13.8 days (95% CI 12.8-14.9, $p<0.001$) [6].

Additional adverse outcomes associated with continuous sedation included higher rates of acquired organ system derangements (3.1±2.2 vs. 2.5±1.4, $p=0.018$), reintubation (15.1% vs. 4.7%, $p=0.005$), and tracheostomy (16.1% vs. 8.7%, $p=0.080$) [6]. Hospital mortality did not differ significantly (30.1% vs. 33.6%, $p=0.576$) [6].

Subsequent observational studies confirmed these associations. In a study of 5,183 patients, 68% received sedation, with mechanical ventilation duration of 4 days (IQR 2-8) for sedated patients versus 3 days (IQR 2-4) for non-sedated patients ($p<0.001$), and ICU length of stay of 8 days (IQR 5-15) versus 5 days (IQR 3-9, $p<0.001$) [14].

The mechanism by which continuous infusion prolongs outcomes was illuminated by pharmacokinetic data. Continuous benzodiazepine infusion increased doses 5.4-fold compared to bolus administration ($p<0.001$), while continuous opiate infusion increased doses 2.5-fold ($p<0.001$) [15]. Continuous benzodiazepine infusion was identified as an independent predictor of longer mechanical ventilation duration, ICU stay, and hospital stay [15].

5.2 5.2 Daily Sedation Interruption

5.2.1 5.2.1 The Kress 2000 Landmark Trial

The paradigm-shifting study by Kress and colleagues, published in the New England Journal of Medicine in 2000, established daily sedation interruption as a foundational strategy for reducing mechanical ventilation duration and ICU length of stay [7]. This randomized controlled trial enrolled 128 adult medical ICU patients receiving mechanical ventilation with continuous sedative infusions (midazolam or propofol), with all patients also receiving morphine infusion for analgesia [7]. Sedation target was Ramsay score 3-4 [7].

The intervention group (n=68) received daily interruption of sedative infusion until patients were awake, defined as ability to perform at least 3 of 4 tasks: open eyes, follow with eyes, squeeze hand, and stick out tongue [7]. The control group (n=60) received sedative interruption only at clinician discretion [7].

Primary outcomes demonstrated substantial benefits. Median duration of mechanical ventilation was 4.9 days in the intervention group versus 7.3 days in the control group, a reduction of 2.4 days ($p=0.004$) [7]. Median ICU length of stay was 6.4 days versus 9.9 days, a reduction of 3.5 days ($p=0.02$) [7]. Patients in the intervention group were awake 85.5% of days while receiving sedation compared to only 9.0% in the control group ($p<0.001$) [7].

Secondary outcomes included reduced diagnostic testing for mental status changes (9% vs. 27%,

p=0.02) [7]. Adverse events were not increased: 3 patients (4%) in the intervention group experienced adverse events (2 self-extubations, 1 central line removal) compared to 4 patients (7%) in the control group (4 self-extubations, p=0.88) [7]. Notably, no self-extubations occurred during interruption periods [7]. The overall self-extubation rate of 5% was favorable compared to the 10-12% reported in previous studies [7].

Daily interruption reduced total midazolam dose by almost half [7]. Hospital mortality was 36.0% in the intervention group versus 46.7% in the control group (p=0.25) [7].

5.2.2 5.2.2 Subsequent Validation Studies

The Girard 2008 study extended these findings by combining daily sedation interruption with daily spontaneous breathing trials in 336 patients [47]. The combined intervention led to fewer days on mechanical ventilation, fewer days in ICU, fewer days in hospital, and lower mortality compared to usual practice plus daily spontaneous breathing trials [47].

A Turkish randomized trial of 50 patients compared physician-directed daily sedation interruption (Group P) to protocol-based sedation (Group N) using diazepam, propofol, or dexmedetomidine [48]. ICU length of stay and mortality were similar between groups, but mechanical ventilation duration was significantly shorter in the daily interruption group, with duration of sedation 3.26 days shorter (p<0.05) [48].

An implementation study at Cleveland Clinic medical ICU, where 85% of mechanically ventilated patients received IV sedation with propofol and midazolam by continuous infusion plus morphine for analgesia, replicated the Kress findings [49]. Daily interruption until patients woke up, followed instructions, or became uncomfortable/agitated resulted in mechanical ventilation duration of 4.9 days versus 7.3 days (p=0.004) and ICU length of stay of 6.4 days versus 9.9 days (p=0.02) [49]. The intervention also required less diagnostic testing to assess mental status [49].

5.2.3 5.2.3 Challenges and Limitations

Not all studies of daily sedation interruption demonstrated benefits. A multicenter Canadian/US trial of 423 patients comparing protocolized sedation alone (n=209) to protocolized sedation plus daily interruption (n=214) found no significant differences [50]. Median time to extubation was 7 days in both groups, as were ICU length of stay (10 days) and hospital length of stay (20 days) [50]. Adverse events including unintentional device removal, ICU delirium, and tracheostomy did not differ [50]. Daily midazolam dose was actually higher in the interruption group (102 mg vs. 82 mg, p=0.04) [50].

A Brazilian single-center randomized trial of 60 patients (30 intermittent sedation, 30 daily interruption) in a closed multidisciplinary ICU with 1:6 nurse-to-patient ratio found no significant differences in ventilator-free days at 28 days (median 25 vs. 24 days, p=0.160), ICU length of stay (median 11 vs. 8 days, p=0.595), or hospital length of stay (median 22 vs. 15 days, p=0.099) [51]. ICU mortality was 23% with intermittent sedation versus 40% with daily interruption (p=0.165), and hospital mortality was 30% versus 43.3% (p=0.284) [51].

Notably, the intermittent sedation group in the Brazilian study used significantly less sedation: total fentanyl 300 µg versus 1,500 µg (p=0.004) and total midazolam 0 mg versus 45 mg (p<0.001) [51]. Median Sedation Agitation Scale score was 3.6 with intermittent sedation versus 3.2 with daily interruption (p=0.035), indicating lighter sedation in the intermittent group [51].

5.2.4 5.2.4 Pediatric Daily Sedation Interruption

A multicenter randomized trial in three Dutch pediatric ICUs enrolled 129 children ages 0-18 years requiring mechanical ventilation ≥48 hours [52]. The trial was terminated early. Children received midazolam (up to 300 µg/kg/h) and morphine (up to 30 µg/kg/h) with target COMFORT-B

score 11-22 [52].

Daily sedation interruption plus protocolized sedation (DSI+PS, n=66) was compared to protocolized sedation alone (PS, n=63) [52]. Median COMFORT-B score was 12 in both groups (p=0.048), with oversedation occurring in 24.3% versus 25.4% of assessments (p=0.27) and undersedation in 3.2% versus 2.4% (p=0.04) [52]. Cumulative midazolam dose trended lower with DSI+PS (14.1 vs. 17.0 mg/kg, p=0.11) [52].

Primary outcome of ventilator-free days at 28 days was identical: median 24.0 days in both groups (p=0.90) [52]. Duration of mechanical ventilation (median 5.1 vs. 5.2 days, p=0.71), ICU length of stay (median 6.9 vs. 7.4 days, p=0.47), and hospital length of stay (median 13.3 vs. 15.7 days, p=0.19) did not differ [52]. However, 30-day mortality was 9.1% with DSI+PS versus 0% with PS alone (p=0.03), though no causal relationship was established [52]. Reintubation within 24 hours was less frequent with DSI+PS (3.0% vs. 14.3%, p=0.03) [52].

5.3 5.3 Protocol-Directed vs Non-Protocol Sedation

5.3.1 5.3.1 Rationale and Components

Protocol-directed sedation strategies aim to standardize assessment, minimize excessive sedation, and facilitate systematic weaning. Nurse attitudes toward such protocols have been favorable, with 84.3% believing nursing-directed protocols combined with sedation scales would be valuable to patient management, 85.3% believing they would be valuable to professional nursing practice, and 81.6% feeling standardization was important [53].

Protocol components typically include regular assessment of patient status and treatment needs, written strategy for stepwise reduction of support, daily sedation interruption, reassessment of need for readministration, and individualized sedation targets [54]. The 2002 SCCM guidelines noted that daily awakening protocols were associated with shorter ventilation duration and ICU stay [8].

5.3.2 5.3.2 Positive Implementation Studies

An implementation study in five adult ICUs demonstrated significant benefits [55]. Mechanical ventilation time decreased from 18 hours (IQR 7-41) to 12 hours (IQR 7-27, p=0.046), and ICU stay decreased from 37 hours (IQR 21-71) to 25 hours (IQR 19-63) in survivors (p=0.049) [55]. Morphine use decreased (p=0.001) and midazolam use decreased (p=0.050) [55]. Total TISS-28 per patient decreased from 137 points (IQR 99-272) to 113 points (IQR 87-256, p=0.009) [55]. ICU mortality decreased from 19% at baseline to 7-8% after protocol implementation (p=0.020) [56].

Another protocol study of 321 patients found that protocol-directed sedation reduced mechanical ventilation duration from 117 hours to 55.9 hours (p=0.008), ICU length of stay from 7.5±6.5 days to 5.7±5.9 days (p=0.013), and hospital length of stay from 19.9±24.2 days to 14.0±17.3 days (p<0.001) [14]. A separate protocol study of 74 patients demonstrated mechanical ventilation duration reduction from 6.7 to 3.9 days (p=0.0003), ICU length of stay from 15 to 8 days (p<0.0001), and hospital length of stay from 23 to 12 days (p=0.01) [14].

A nurse-implemented protocol was independently associated with lower ventilator-associated pneumonia incidence: 6% in the protocol group versus 15% in controls (p=0.005) [14].

5.3.3 5.3.3 Null and Negative Findings

Not all protocol implementation studies demonstrated benefits. A large Australian randomized controlled trial of 304 patients (153 protocol, 151 control) in a closed ICU with 24-hour intensivist coverage and 1:1 nurse-to-patient ratios found no benefit [57]. Median ventilation duration was

79 hours with protocol versus 58 hours with control (p=0.20), ICU stay was 94 versus 88 hours (p=0.58), and hospital stay was 13 versus 13 days (p=0.97) [57]. ICU mortality was 21% versus 20% (p=0.89) [57]. After adjustment, the protocol showed a 22% decrease in successful weaning (95% CI 40% decrease to 2% increase, p=0.07) [57].

The null findings were attributed to context-dependent factors. The study site had a closed ICU model with 24-hour intensivist coverage, 1:1 nurse-to-patient ratios, nurses routinely managing both ventilation and sedation, and a pre-existing culture of sedation minimization [57]. Baseline mechanical ventilation duration of 4.8 days was shorter than in studies showing protocol benefits (e.g., 10.3 days in the DeJonghe study, 7.4 days in the Brattebø{} study) [33].

An Australian implementation study that replicated a guideline previously shown beneficial in North American ICUs found no improvement and a trend toward harm [33]. The guideline was modified to use midazolam instead of lorazepam due to lack of availability in Australia [33]. Among 322 consecutive mechanically ventilated patients (159 pre-intervention, 163 post-intervention), median ventilation duration was 4.8 days pre-intervention versus 5.6 days post-intervention (p=0.99), with a trend toward longer duration [33]. ICU length of stay increased from median 7.06 days to 8.16 days (p=0.04), a statistically significant increase of approximately 1 day [33].

Compliance data revealed implementation challenges. Perfect compliance with guideline recommendations was achieved in only 18% of eligible patients [33]. Non-compliance without clinical rationale occurred in 10% of patients [33]. Ramsay score recording compliance improved from 13% to 50%, but the most frequently recorded score shifted from Ramsay 2 (40% of scores) to Ramsay 3 (31% of scores), suggesting patients were slightly more deeply sedated post-intervention [33].

A trauma center protocol study of 328 consecutive trauma patients (168 preprotocol, 160 postprotocol) using a seven-point agitation scale with target sedation level 0 to -1 found no differences despite high compliance (sedation protocol 91%, weaning protocol 90%) [43]. Ventilator days were 6.3±10.1 versus 6.1±9.1 (p=0.83), ICU days were 9.0±13.2 versus 9.6±12.2 (p=0.67), and self-extubation rates were similar (6 vs. 4 patients, p=0.75) [43]. Notably, this protocol did not include daily sedation holidays [43].

5.3.4 5.3.4 Meta-Analysis of Protocolized Sedation

A systematic review and meta-analysis of 6 randomized controlled trials including 1,243 patients in closed, nonspecialty ICUs provided pooled estimates of protocol efficacy [58]. Protocolized sedation reduced mortality with relative risk of 0.85 (95% CI 0.74-0.97, p=0.02), yielding a number needed to treat of 20 [58]. Tracheostomy was reduced with relative risk of 0.69 (95% CI 0.50-0.96, p=0.03), yielding a number needed to treat of 16.6 [58].

ICU length of stay was reduced by weighted mean difference of -1.73 days (95% CI -3.32 to -0.14, p=0.03), and hospital length of stay was reduced by weighted mean difference of -3.55 days (95% CI -5.98 to -1.12, p=0.004) [58]. Mechanical ventilation duration showed a trend toward reduction with weighted mean difference of -1.04 days (95% CI -2.54 to 0.47, p=0.18) [58]. Reintubation (RR 0.78, 95% CI 0.52-1.15, p=0.21) and self-extubation (RR 1.49, 95% CI 0.46-4.82, p=0.51) did not differ significantly [58].

5.4 5.4 No-Sedation or Light Sedation Strategies

5.4.1 5.4.1 The Strom 2010 Trial

The Strom 2010 trial represented a radical departure from conventional sedation practice by evaluating complete avoidance of sedative agents [3]. This randomized controlled trial enrolled 140 patients, with 27 excluded due to death or extubation within 48 hours, leaving 113 patients for analysis (55 no sedation, 58 interrupted sedation) [3].

The no-sedation group received only morphine boluses (2.5 or 5 mg) for analgesia, with patients remaining awake and able to communicate [3]. The control group received propofol for 48 hours followed by midazolam, with daily interruption, plus morphine boluses [3]. If sedation became necessary in the no-sedation group despite nonpharmacologic interventions (reassurance, mobilization) and analgesia, medications similar to the control group could be used [3].

The primary outcome of days without ventilation at 28 days was 13.8 days (SD 11.0) in the no-sedation group versus 9.6 days (SD 10.0) in the interrupted sedation group, a mean difference of 4.2 days (95% CI 0.3-8.1, p=0.0191) [3]. ICU stay was shorter with no sedation (HR 1.86, 95% CI 1.05-3.23, p=0.0316), as was hospital stay in the first 30 days (HR 3.57, 95% CI 1.52-9.09, p=0.0039) [3].

Safety outcomes demonstrated no differences in accidental extubations, need for CT/MRI brain scans, or ventilator-associated pneumonia [3]. However, agitated delirium was more frequent with no sedation (20% vs. 7%, p=0.0400) [3].

5.4.2 5.4.2 The 2020 Multicenter No-Sedation Trial

A large multicenter trial conducted 2014-2017 across 8 centers (5 in Denmark, 2 in Norway, 1 in Sweden) enrolled 710 patients, with 700 in modified intention-to-treat analysis (354 nonsedation, 346 sedation) [2]. Inclusion criteria were age ≥18 years, endotracheal intubation within 24 hours, and expected mechanical ventilation >24 hours [2]. Exclusions included severe head trauma, therapeutic hypothermia, status epilepticus, coma on admission, brain death, PaO_2/FiO_2 ratio ≤9, and anticipated need for sedation for oxygenation or prone positioning [2].

The nonsedation group received no sedatives but could receive morphine boluses for analgesia, with goal of sustaining natural sleep rhythm [2]. The sedation group received continuous infusion with goal of light sedation (RASS -2 to -3), using propofol for the first 48 hours followed by midazolam, with daily interruption every morning aiming for full wakefulness [2].

Mean RASS scores were -1.3 on day 1 and -0.8 on day 7 in the nonsedation group, compared to -2.3 on day 1 and -1.8 on day 7 in the sedation group [2]. Delirium was assessed with CAM-ICU at least twice daily [2].

The primary outcome of mortality at 90 days was 42.4% in the nonsedation group versus 37.0% in the sedation group, a difference of 5.4 percentage points (95% CI -2.2 to 12.2, p=0.65) [2]. Days free from coma or delirium were median 27 days in the nonsedation group versus 26 days in the sedation group, a difference of 1 day [2]. ICU-free days, ventilator-free days, time on mechanical ventilation, length of ICU stay, and length of hospital stay did not differ significantly between groups [2].

Major thromboembolic events occurred in 1 patient (0.3%) in the nonsedation group versus 10 patients (2.8%) in the sedation group, a difference of -2.5 percentage points (95% CI -4.8 to -0.7, unadjusted for multiple comparisons) [2]. Accidental extubation occurred in 4 patients (1.1%) in the nonsedation group versus 1 patient (0.3%) in the control group (unadjusted risk difference 0.8 percentage points, 95% CI -0.7 to 2.6, p=0.20) [2].

5.4.3 5.4.3 Interpretation of No-Sedation Findings

The contrasting results between the 2010 and 2020 no-sedation trials warrant careful interpretation. The 2010 trial demonstrated substantial benefits (4.2 additional ventilator-free days), while the 2020 trial found no significant differences in primary outcomes and a non-significant trend toward increased mortality [2], [3]. Several factors may explain these divergent findings.

First, the 2010 trial compared no sedation to sedation with daily interruption, while the 2020 trial compared no sedation to light sedation (RASS -2 to -3) with daily interruption [2], [3]. The control group in the 2020 trial represented a more contemporary, optimized sedation strategy.

Second, the 2020 trial was substantially larger (700 vs. 113 patients) and therefore better powered to detect differences [2], [3]. Third, patient populations differed, with the 2020 trial excluding patients with severe head trauma, therapeutic hypothermia, and severe hypoxemia [2].

The finding of increased agitated delirium in the 2010 no-sedation group (20% vs. 7%) and the non-significant trend toward increased mortality in the 2020 no-sedation group (42.4% vs. 37.0%) suggest that complete avoidance of sedation may not be optimal for all patients [2], [3]. The reduction in major thromboembolic events with no sedation in the 2020 trial (0.3% vs. 2.8%) represents a potential benefit, though this finding was not adjusted for multiple comparisons [2].

5.5 5.5 Analgo-Sedation Approaches

Analgo-sedation strategies prioritize analgesia as the primary intervention, with sedatives added only as needed to achieve target sedation levels. This approach recognizes that pain represents the primary ICU stressor and that adequate analgesia may reduce sedative requirements [12].

A randomized trial of 30 patients with respiratory failure compared midazolam alone to midazolam plus fentanyl co-sedation over 3 days with brief daily wake-up [46]. Patients with clinical requirement for opiates or FLACC pain score >2 were excluded [46]. The co-sedation group demonstrated significantly greater sedation stability, with hours off-target Ramsay score per 24 hours of 4.2±2.4 versus 9.1±4.9 with midazolam alone ($p<0.002$) [46]. Asynchronous ventilator events per day were 0.4±0.1 with co-sedation versus 1.0±0.2 with midazolam alone ($p<0.05$) [46]. Midazolam dose was numerically lower with co-sedation (0.046±0.03 vs. 0.071±0.06 mg/kg/hr) but not statistically significant [46].

The 2002 SCCM guidelines recommended that analgesics be administered continuously or as scheduled intermittent doses with supplemental boluses (Grade C recommendation) [8]. NSAIDs or acetaminophen were recommended as adjuncts to opioids (Grade B recommendation), with ketorolac limited to maximum 5 days with monitoring for renal insufficiency and gastrointestinal bleeding (Grade B recommendation) [8].

In German ICUs, adjuvant analgesic agents were commonly employed. Clonidine was used in 39% of patients during weaning sedation, significantly more than in other phases ($p<0.05$) [45]. Epidural catheters for regional analgesia were used significantly more during short-term (14%) and medium-term sedation (12%) than during long-term (1%) and weaning sedation (5%, $p<0.05$) [45].

The remifentanil versus fentanyl trial employed a comprehensive analgo-sedation protocol with remifentanil or fentanyl as primary analgesic, propofol as primary sedative (maximum 4 mg/kg ideal body weight/h), and midazolam if additional sedation was required [29]. Adjuvant analgesia included metamizole (1g four times daily), paracetamol (1g four times daily), clonidine (0.32-1.3 µg/kg/h IV), and morphine rescue therapy [29]. Target analgesia was Visual Analogue Scale <3 if awake or Behavioral Pain Scale ≤6 if sedated, with target sedation of RASS 0 to -1 (up to -4 for specific indications) [29].

6. 6. Delirium, Agitation, and ICU Length of Stay

6.1 6.1 Delirium as Independent Predictor of Length of Stay

Delirium has emerged as a critical determinant of ICU and hospital length of stay, independent of sedation practices. A prospective cohort investigation of 261 consecutively admitted medical ICU patients not requiring invasive mechanical ventilation found that 125 patients (48%) experienced

at least one episode of delirium [17]. Delirious patients were older (mean 56±18 vs. 49±17 years, p=0.002) and had higher APACHE II scores (median 15, IQR 10-21 vs. 11, IQR 6-16, p<0.001) [17].

Delirium was associated with significantly prolonged stays. ICU length of stay was median 4 days (IQR 3-5) for delirious patients versus 3 days (IQR 2-4) for non-delirious patients, a difference of 1 day [17]. Hospital length of stay was median 5 days (IQR 2-8) versus 3 days (IQR 2-6), a difference of 2 days [17].

After adjusting for age, gender, race, Charlson comorbidity score, APACHE II score, and coma, delirious patients demonstrated 29% greater risk of remaining in ICU (HR 1.29, 95% CI 0.98-1.69, p=0.07) and 41% greater risk of remaining in hospital (HR 1.41, 95% CI 1.05-1.89, p=0.023) [17]. In-hospital mortality was higher in delirious patients (19% vs. 6%, p=0.002), though time to in-hospital death was not significant after adjustment (HR 1.27, 95% CI 0.55-2.98, p=0.58) [17].

A comparative study of CAM-ICU versus ICDSC in 162 ICU patients found that CAM-ICU-positive delirium was associated with hospital length of stay of 15.3±8.7 days versus 10.5±7.1 days for non-delirious patients (p<0.001) [30]. ICDSC-positive delirium was associated with hospital length of stay of 14.8±8.3 days versus 9.8±6.4 days (p<0.001) [30]. ICU mortality was 12.5% with CAM-ICU-positive delirium versus 2.5% without (p=0.022), and hospital mortality was 23.2% versus 10.9% (p=0.047) [30].

6.2 6.2 Sedation Agents and Delirium Risk

Benzodiazepines have been consistently associated with increased delirium risk. The Society of Critical Care Medicine's latest clinical practice guidelines recommended against benzodiazepine use [59]. Delirium frequency was higher in patients receiving sedatives and antipsychotics in multiple studies [30].

In the MIDEX and PRODEX trials, delirium assessed by CAM-ICU at 48 hours post-sedation did not differ between dexmedetomidine and comparator agents [26]. However, an earlier study found that dexmedetomidine patients had more delirium when analyzed as a combined endpoint (43.9% vs. 25.0%, p=0.035), though the proportion of positive CAM-ICU results was comparable (17.0% vs. 17.9%) [41].

In the remifentanil versus fentanyl trial, delirium incidence was 29% with remifentanil versus 22% with fentanyl (p=0.57) [29]. In the intermittent sedation versus daily interruption trial, delirium incidence was 40% with intermittent sedation versus 30% with daily interruption (p=0.472) [51].

The no-sedation trials provided important data on delirium in the absence of sedatives. In the 2010 Strom trial, agitated delirium was more frequent with no sedation (20% vs. 7%, p=0.0400) [3]. In the 2020 multicenter trial, days free from coma or delirium were median 27 days with no sedation versus 26 days with light sedation, a difference of only 1 day [2].

6.3 6.3 Agitation and Unplanned Extubation

Agitation represents a major risk factor for unplanned extubation, which in turn is associated with substantially prolonged length of stay. A prospective case-control study of 74 unplanned extubation cases (2% of all mechanically ventilated patients) found that sedation level was the strongest predictor [35].

On multivariate analysis, Ramsay Scale 1 (anxious/agitated) was associated with odds ratio of 30.6 (95% CI 3.18-294.20) for unplanned extubation, and Ramsay Scale 2 (awake/cooperative) was associated with odds ratio of 25.5 (95% CI 2.99-216.96) [35]. Other risk factors included male sex, midazolam use at time of unplanned extubation (OR 2.3, 95% CI 1.01-5.18), specific ICU subunit (OR 2.6, 95% CI 1.06-6.53), and shorter ICU length of stay at index time (OR 0.9, 95%

CI 0.93-0.99) [35].

Outcomes differed dramatically based on whether reintubation was required. Among patients requiring reintubation (n=35), ICU length of stay was 40 days versus 10 days for those not requiring reintubation (p<0.001), with 26 days after unplanned extubation versus 3 days (p<0.001) [35]. Hospital length of stay was 61 days versus 28 days (p<0.001), and total intubation duration was 38 days versus 9 days (p<0.001) [35].

ICU mortality was 37% for patients requiring reintubation versus 0% for those not requiring reintubation (p<0.001), and hospital mortality was 37% versus 3% (p<0.001) [35]. However, unplanned extubation patients did not have increased mortality compared to mechanically ventilated controls [35].

Self-extubation rates varied across sedation strategy trials. In the Kress daily interruption trial, self-extubation occurred in 4% of the intervention group versus 7% of controls (p=0.88), with no self-extubations during interruption periods [7]. In the trauma center protocol study, self-extubation occurred in 6 preprotocol patients versus 4 postprotocol patients (p=0.75) [43]. In the Australian protocol implementation study, self-extubation rates were 1.3% pre-intervention versus 1.2% post-intervention [33]. In the intermittent sedation versus daily interruption trial, self-extubation was 7% versus 3% (p=0.514) [51].

6.4 6.4 Management of Delirium and Agitation

The 2002 SCCM guidelines recommended haloperidol as the preferred agent for delirium management (Grade C recommendation), with monitoring for QT prolongation and arrhythmias (Grade B recommendation) [8]. Haloperidol lactate was used at 60% of ICUs in the 1991 survey but was rarely among the top three agents [1]. In observational studies, haloperidol was administered in only 3.6% of time blocks [15].

Nurse preference surveys found that only 15.4% of nurses favored haloperidol [37]. During the propofol shortage, scheduled antipsychotic use for ≥24 hours increased from 17% to 25% (p=0.23) [40].

Nonpharmacologic interventions for agitation management have received increasing emphasis. The no-sedation trials specified that reassurance and mobilization should be attempted before pharmacologic sedation [2], [3]. Early mobilization has been incorporated into contemporary sedation and mobility paradigm shifts [60].

7. 7. Special Populations

7.1 7.1 Pediatric ICU Patients

Pediatric sedation practices demonstrate substantial variation and unique challenges. A 2005 survey of eight dedicated Pediatric Intensive Care Units in Australia and New Zealand found that only 4 of 8 units (50%) had written guidelines for sedation management [31]. All units aimed for moderate sedation levels, with administration and titration managed by nursing staff alone in 6 units [31]. Combined benzodiazepines and opioids were employed as the primary regimen in 6 units [31].

Only 2 units used designated assessment tools for sedation and withdrawal assessment, and only 1 unit utilized Bispectral Index monitoring [31]. A retrospective audit of 109 children requiring prolonged mechanical ventilation (≥72 hours) identified multiple problems: no identifiable pattern in escalation, titration, or tapering of sedation agents; poor management and documentation of

drug tolerance; sedation scores not accurately reflecting patients' sedation status; inadequacy in sedation scoring system; and inconsistent management [31].

The multicenter randomized trial of daily sedation interruption in Dutch pediatric ICUs enrolled 129 children ages 0-18 years (≥37 weeks postconceptual age) requiring mechanical ventilation ≥48 hours [52]. The trial was terminated early. Children received midazolam (up to 300 µg/kg/h) and morphine (up to 30 µg/kg/h) with target COMFORT-B score 11-22 [52].

Daily sedation interruption plus protocolized sedation demonstrated no benefit over protocolized sedation alone for the primary outcome of ventilator-free days at 28 days (median 24.0 vs. 24.0 days, p=0.90) [52]. Duration of mechanical ventilation (median 5.1 vs. 5.2 days, p=0.71), ICU length of stay (median 6.9 vs. 7.4 days, p=0.47), and hospital length of stay (median 13.3 vs. 15.7 days, p=0.19) did not differ [52].

Concerning findings included 30-day mortality of 9.1% with daily sedation interruption versus 0% without (p=0.03), though no causal relationship was established [52]. Reintubation within 24 hours was less frequent with daily sedation interruption (3.0% vs. 14.3%, p=0.03) [52]. Oversedation occurred in 24.3% versus 25.4% of assessments (p=0.27), and undersedation in 3.2% versus 2.4% (p=0.04) [52].

7.2 7.2 Tracheostomy Patients

Tracheostomy profoundly alters sedation requirements and facilitates weaning. An observational retrospective chart review of 72 patients (23.1% of 312 patients undergoing mechanical ventilation ≥48 hours) who underwent tracheostomy examined sedation changes in the 7 days before versus after the procedure [27].

Sedation was assessed using Riker's 7-level Sedation-Agitation Score (SAS) every 3-4 hours, with target most frequently SAS 3 or 4 [27]. Sedation agents included intravenous fentanyl and midazolam, and oral clorazepate and haloperidol [27].

Fentanyl administration decreased dramatically from 866 µg/(patient-day) (IQR 191, 1672) to 71 µg/(patient-day) (IQR 3, 426) in the 7 days following tracheostomy (p<0.001) [27]. Midazolam decreased from 44 mg/(patient-day) (IQR 16, 128) to 7 mg/(patient-day) (IQR 1, 42, p<0.001) [27]. Oral medication administration did not change significantly [27].

Median target sedation level was SAS 3.6 (range 3-4) before tracheostomy versus SAS 4.0 (range 3-4) after, a difference that was not statistically significant [27]. However, time heavily sedated (SAS 1 or 2) decreased from 7 hours per day (IQR 3, 17) to 1 hour per day (IQR 0, 6, p<0.001) [27]. Time lightly or not sedated (SAS 3-5) increased from 16 hours per day (IQR 7, 21) to 23 hours per day (IQR 17, 24, p<0.001) [27].

Autonomy outcomes improved substantially. Partial oral feeding became possible for 35 patients (48.6%), with first oral intake at median 3 days (IQR 1, 5) following tracheostomy [27]. Chair positioning became possible for 16 patients (22.2%) at median 5 days (IQR 2, 6) following tracheostomy [27].

Tracheostomy was performed after median 14 days (IQR 9, 21) of mechanical ventilation [27]. ICU mortality was 30.5% (22 patients) [27]. Among survivors, 44 patients (61.1%) were successfully weaned from mechanical ventilation, with tracheal cannulas removed after median 20 days (IQR 13, 36) [27].

The Australian protocol implementation study found that tracheostomy rates increased from 13.2% pre-intervention to 18.4% post-intervention (p=0.22), a non-significant trend [33]. The meta-analysis of protocolized sedation found that tracheostomy was reduced with relative risk of 0.69 (95% CI 0.50-0.96, p=0.03), yielding a number needed to treat of 16.6 [58].

7.3 7.3 Non-Invasive Ventilation (NIV) Patients

Sedation for patients receiving non-invasive ventilation presents unique challenges, as excessive sedation may impair airway protective reflexes and cough while inadequate sedation may result in patient-ventilator asynchrony and NIV failure.

A randomized, double-blind study of 40 patients with acute respiratory failure from COPD exacerbations compared dexmedetomidine to midazolam for NIV sedation [36]. Dexmedetomidine was administered as 1 µg/kg IV loading over 10 minutes followed by 0.5 µg/kg/h maintenance, while midazolam was given as 0.05 mg/kg loading over 10 minutes followed by 0.1 mg/kg/h maintenance [36].

Sedation quality was assessed using Ramsay Sedation Score (target 2-3), Riker Sedation-Agitation Scale (target 3-4), and Bispectral Index (target >85) [36]. Ramsay levels were significantly lower starting at 4 hours with dexmedetomidine versus midazolam ($p<0.05$), Riker Sedation-Agitation Scale levels were significantly higher at 8 hours with dexmedetomidine ($p<0.01$), and BIS values were significantly higher with dexmedetomidine throughout the study ($p<0.05$) [36].

Dosing stability was superior with dexmedetomidine. In the dexmedetomidine group, 2 patients required 1 dosing change each, while in the midazolam group, 3 patients required 1 change, 1 patient required 2 changes, and 3 patients required 3 changes each ($p<0.01$) [36]. Respiratory rates and gas exchange did not differ significantly between groups [36]. Both agents were effective for NIV sedation, but dexmedetomidine demonstrated better dosing stability [36].

7.4 7.4 Trauma ICU Patients

Trauma patients present unique sedation challenges due to high injury severity, frequent neurologic injuries, pain from multiple injuries, and need for repeated procedures. The trauma center protocol study enrolled 328 consecutive trauma patients receiving mechanical ventilation (168 preprotocol, 160 postprotocol) [43].

The protocol employed a seven-point agitation scale ranging from +3 (severe agitation with combative behavior and self-extubation) to -3 (deep sedation with no response to noxious stimuli), with target sedation level 0 to -1 [43]. The scale was documented every 4 hours, increased to every 2 hours if significant changes were needed [43].

Morphine sulfate was the primary analgesic due to efficacy and low cost, and lorazepam was the most common sedative [43]. Alternative agents included fentanyl, midazolam, and propofol for rapid extubation or when primary drugs were ineffective [43]. Notably, daily sedation holidays were not performed [43].

Groups were similar in age (p=0.68), Injury Severity Score (p=0.06), and Glasgow Coma Scale score (p=0.29) [43]. Despite high protocol compliance (sedation protocol 82-100% with average 91%, weaning protocol 85-100% with average 90%), no significant differences were observed [43].

Ventilator days were 6.3±10.1 preprotocol versus 6.1±9.1 postprotocol (p=0.83), ICU days were 9.0±13.2 versus 9.6±12.2 (p=0.67), and self-extubation occurred in 6 versus 4 patients (p=0.75) [43]. Charges for ventilator care ($1,523 \pm \$2{,}421$ vs. $1,467 \pm 2,190, p = 0.83$) $and ICU care (156{,}900 \pm 230, 400 vs. 167,6$ p=0.67) did not differ [43].

Subgroup analysis excluding long-term ventilator patients similarly showed no differences: ventilator days 4.93±6.96 versus 4.94±6.35 (p=0.98), ICU days 7.74±11.26 versus 8.61±10.04 (p=0.48), and self-extubation 6 versus 3 patients (p=0.32) [43].

The null findings were attributed to the absence of daily sedation holidays in the protocol, which differed from other studies demonstrating protocol benefits [43]. This suggests that protocol-directed sedation without daily interruption may be insufficient to improve outcomes in trauma

populations.

7.5 7.5 Post-Cardiac Surgery Patients

Post-cardiac surgery patients represent a distinct population with generally shorter anticipated mechanical ventilation duration and emphasis on rapid extubation. A randomized trial of 60 post-CABG patients compared propofol to midazolam sedation [39].

Weaning time was 3.5±0.2 hours with propofol versus 4.3±0.5 hours with midazolam (p=0.20), mechanical ventilation duration was 18.5±1.2 hours versus 23.3±2.4 hours (p=0.07), and ICU length of stay was 2.8±0.2 days versus 3.1±0.2 days (p=0.36) [39]. Patient satisfaction scores were similar (11.4±0.2 vs. 11.5±0.7) [39]. While differences did not reach statistical significance, trends favored propofol for all outcomes [39].

A study of 596 patients mechanically ventilated after cardiac surgery comparing three ventilatory modes found that BIPAP-APRV mode resulted in significantly shorter duration of endotracheal intubation and significantly lower consumption of opioids and sedatives compared to IMV and CMV modes [13]. BIPAP-APRV was better tolerated by patients with much less need for sedation [13].

8. 8. Organisational and Implementation Factors

8.1 8.1 Nursing-Led Protocols and Autonomy

Nurse-led sedation management has emerged as a key component of successful protocol implementation. Surveys of Ontario ICU nurses found that 84.3% believed nursing-directed protocols combined with sedation scales would be valuable to patient management, 85.3% believed they would be valuable to professional nursing practice, and 81.6% felt standardizing the approach was important [53].

However, only 52.7% of nurses were satisfied overall with their ICU's approach to sedation and analgesia, and only 58% were satisfied with sedation/analgesia dosing ranges ordered by physicians [53]. Satisfaction varied significantly among hospitals [53]. Only 39.3% of nurses were satisfied with subjective methods used to evaluate sedation adequacy [53].

Nurse preferences for specific agents showed clear patterns: 85.0% favored morphine, 71.2% favored midazolam, 59.6% favored fentanyl, 38.6% favored lorazepam, and only 15.4% favored haloperidol [37].

In the Australian protocol implementation study, intensive one-to-one information sessions were provided for 80% of bedside clinicians, supplemented by formal presentations, humorous reminders, regular feedback in ICU newsletter, placement of guideline and Ramsay Scale at bedside, and daily reminders [33]. Despite these efforts, perfect compliance with guideline recommendations was achieved in only 18% of eligible patients [33].

The responsiveness index monitoring trial provided qualitative data on nurse perspectives. Nurses valued objective visible data trends, simple color prompts, and continuous monitoring versus intermittent assessments [32]. This feedback suggests that technological aids may enhance nurse engagement with sedation management [32].

8.2 8.2 International Variation in Practice

Substantial international variation in sedation practices has been documented. The 2001 European survey of 647 ICUs across 16 countries found that midazolam use ranged from 85% in Norway to 39% in Denmark, propofol use ranged from 65% in Italy to 3% in Norway, morphine use ranged from 88% in Norway to 3% in Germany, and fentanyl use ranged from 58% in Italy to 0% in the Netherlands [5].

Sedation scale use varied from 72% in UK/Ireland to 18% in Austria ($p<0.01$) [5]. The Ramsay scale was used by 74% of those employing scales [5]. Midazolam was more common in medical units (88%) than surgical units (55%, $p<0.05$), while propofol was more common in surgical units (34%) than medical units (12%, $p<0.05$) [5].

A 2006 German survey of 305 patient-oriented questionnaires from 220 hospitals found that only 20% of German ICUs had written procedure instructions [45]. Scoring system use ranged from 8% to 49% across studies [45]. Training deficit was identified as the most likely reason for inadequate use of the Ramsay Sedation Scale [45].

For short-term sedation (<24 hours), propofol (57%) was used significantly more than midazolam (36%, $p=0.005$) [45]. For medium-term sedation (24-72 hours), no difference was observed between propofol and midazolam [45]. For long-term sedation (>72 hours), midazolam was most common (66.2%, $p<0.001$) [45]. For weaning sedation, propofol (48%) was used more than midazolam (34%, $p=0.03$) [45].

A comparative study of two tertiary care ICUs—St Paul's in Vancouver, Canada and St Eloi in Montpellier, France—examined how organizational structure influences sedation management [61]. Both sites enrolled 30 patients mechanically ventilated $\geq$24 hours [61]. Sedation was assessed using the Richmond Agitation-Sedation Scale, with mean 4.93 measurements per patient per day at St Paul's versus 4.23 at St Eloi [61].

St Eloi achieved target RASS 82% of the time versus St Paul's 36% ($p<0.0001$) [61]. St Paul's nurses were less likely to adjust sedation within 1 hour for both high RASS (OR 0.26, 95% CI 0.13-0.50) and low RASS (OR 0.14, 95% CI 0.07-0.28) [61].

Despite superior target achievement at St Eloi, median mechanical ventilation duration was 127 hours at St Paul's versus 166 hours at St Eloi ($p=0.27$) [61]. However, ICU length of stay was significantly shorter at St Paul's (median 6.4 vs. 13 days, $p=0.004$), as was hospital stay after ICU (median 2 vs. 13 days, $p=0.02$) [61]. ICU mortality was 21% at St Paul's versus 17% at St Eloi ($p=0.69$), and hospital mortality was 38% versus 20% ($p=0.13$) [61].

These findings suggest that achieving target sedation levels does not necessarily translate to improved clinical outcomes, and that organizational factors beyond sedation management influence length of stay [61].

8.3 8.3 Compliance and Adherence

Compliance with sedation protocols and assessment tools has been variable across studies. In the 1991 US survey, only 6% of ICUs used standardized protocols [1]. By 2003, approximately 33% of US institutions utilized written sedation protocols [34].

The 2009 Australian and New Zealand point-prevalence study found that sedation was titrated to prescribed level in 87% of patients, and formal sedation scores were used in 74% of sedated patients [4]. However, 25% of mechanically ventilated patients receiving sedatives were not assessed with formal sedation scales [4].

Complete cessation of sedation on the study day occurred in 28% of patients, with main reasons being preparation for extubation (13%), routine daily interruption (2%), oversedation (1%),

and unspecified reasons (12%) [4]. Ventilation orders were reviewed within 24 hours for 92% of patients, formal readiness to wean assessment was performed for 60%, and weaning plan was set for 52% [4].

The trauma center protocol study achieved high compliance: sedation protocol 82-100% (average 91%) with one outlier at 75%, and weaning protocol 85-100% (average 90%) with one outlier at 50% [43]. Despite this high compliance, no outcome differences were observed, suggesting that protocol content (specifically inclusion of daily sedation holidays) may be more important than compliance alone [43].

The Australian protocol implementation study found that Ramsay score recording compliance improved from 13% pre-intervention to 50% post-intervention [33]. However, perfect compliance with all guideline recommendations was achieved in only 18% of eligible patients, with non-compliance without clinical rationale occurring in 10% [33].

8.4 8.4 Closed vs Open ICU Models

The organizational structure of ICU staffing appears to influence the effectiveness of sedation protocols. The Australian randomized trial that found no benefit from protocol-directed sedation was conducted in a closed ICU with 24-hour intensivist coverage, 1:1 nurse-to-patient ratios, and nurses routinely managing both ventilation and sedation [57]. The pre-existing culture of sedation minimization resulted in baseline mechanical ventilation duration of 4.8 days, shorter than in studies demonstrating protocol benefits [57].

In contrast, the Brazilian trial comparing intermittent sedation to daily interruption was conducted in a closed multidisciplinary ICU with 1:6 nurse-to-patient ratio [51]. This lower nurse-to-patient ratio may have influenced the ability to implement frequent sedation adjustments [51].

The meta-analysis of protocolized sedation specified that included studies were conducted in closed, nonspecialty ICUs [58]. This suggests that the benefits of protocolized sedation may be most evident in settings with consistent intensivist involvement but without the very high nurse-to-patient ratios and pre-existing sedation minimization culture seen in some centers [58].

8.5 8.5 Telehealth-Enabled Implementation

The TEACH study represents an innovative approach to protocol implementation using telehealth technology [62]. This Type II hybrid effectiveness-implementation cluster-randomized clinical trial across 12 Intermountain Health hospitals with 15 ICUs compared usual supervisor-led audit and feedback implementation to an intervention adding real-time identification of patients eligible for coordinated spontaneous awakening trials (SAT) and spontaneous breathing trials (SBT) plus consultative input from telehealth respiratory therapists, nurses, and physicians [62].

The study enrolled all intubated and mechanically ventilated patients $\geq$16 years of age, excluding those who died on day of intubation or had preexisting brain death [62]. Primary outcomes were adherence to coordinated SAT and SBT, and ventilator-free days [62]. The 36-month planned duration reflects the complexity of implementing and evaluating telehealth-enabled interventions [62].

This approach addresses a key implementation barrier: the need for real-time identification of eligible patients and expert consultation to support bedside clinicians in protocol execution [62]. Results of this trial will inform future efforts to scale evidence-based sedation practices across healthcare systems [62].

9. 9. Emerging Technologies

9.1 9.1 Processed EEG Monitoring

9.1.1 9.1.1 Bispectral Index (BIS)

Bispectral Index monitoring has been extensively evaluated for ICU sedation monitoring with generally disappointing results. The 2002 SCCM guidelines noted that BIS was not completely evaluated for ICU use, with limitations including variability between patients, interference from muscle activity, and lack of testing in metabolic or structural brain abnormalities [8].

A study of 679 paired observations found that BIS demonstrated only modest correlation with clinical sedation scores (r=-0.426, p<0.001), with wide overlap between clinical sedation levels [9]. BIS could not discriminate between light-moderate sedation (Ramsay 1-4) and deep sedation (Ramsay 5-6) [9]. Response to interventions showed significant decrease in BIS values after sedation bolus, but this effect was attenuated when endotracheal suctioning was performed within 10 minutes of the sedation bolus [9]. Neither BIS increase was a good predictor of strong response 10 minutes after sedation bolus, with ROC curve areas of 0.78-0.80 [9].

The study concluded that BIS-Index does not add information useful for guiding sedation in general ICU populations [9]. In pediatric practice, only 1 of 8 Australian and New Zealand pediatric ICUs utilized BIS monitoring [31].

For non-invasive ventilation, BIS was used as one of three assessment tools (along with Ramsay Sedation Score and Riker Sedation-Agitation Scale) with target >85 [36]. BIS values were significantly higher with dexmedetomidine throughout the study compared to midazolam (p<0.05) [36].

9.1.2 9.1.2 Entropy Monitoring

Entropy monitoring, which measures Response Entropy (RE) and State Entropy (SE), has been similarly evaluated. In the study of 679 observations, RE demonstrated correlation of r=-0.372 (p<0.001) and SE correlation of r=-0.360 (p<0.001) with clinical sedation scores [9]. Like BIS, entropy values could not discriminate between light-moderate and deep sedation [9].

Response to interventions showed significant decrease in all processed EEG values after sedation bolus, with effect attenuated when endotracheal suctioning was performed within 10 minutes [9]. Neither RE increase was a good predictor of strong response 10 minutes after sedation bolus, with ROC curve areas of 0.77-0.83 [9].

The study concluded that Entropy does not add information useful for guiding sedation in general ICU populations [9]. A 2004 review noted that BIS monitoring has limitations in the ICU environment and is not recommended for routine use [13].

9.1.3 9.1.3 Responsiveness Index (RI)

The Responsiveness Index represents a more recent technology employing a 0-100 scale with color-coded prompts: red (<20), amber (20-40), and green (>40) [32]. A prospective single-center randomized parallel-group proof-of-concept trial enrolled 74 patients (36 intervention, 38 control) who were mechanically ventilated and receiving IV sedation via continuous infusion [32].

Sedation agents included propofol as primary sedative, alfentanil as primary opioid, with midazolam and morphine as alternatives [32]. Target was RI >20 [32].

In the overall cohort, the proportion of time with RI<20 trended lower in the intervention group (16% vs. 33%, p=0.08) [32]. In post-hoc analysis of patients with baseline RI<20, time with RI<20 was 16% versus 51% (p=0.02), total propofol was 1,090 mg versus 2,380 mg (p=0.14), and total alfentanil was 21.2 mg versus 32.3 mg (p=0.01) [32].

Sedation holds occurred in 83% versus 87% of patients, extubation during intervention in 47% versus 45%, and adverse events in 19.4% versus 13.1% (p=0.54) [32]. Time to first extubation was median 42.4 hours versus 54.8 hours (p=0.52) [32].

Nurse feedback was positive, with nurses valuing objective visible data trends, simple color prompts, and continuous monitoring versus intermittent assessments [32]. However, the lack of significant difference in time to extubation suggests that RI monitoring requires further refinement before widespread adoption [32].

9.2 9.2 Artificial Intelligence in Critical Care

A 2025 narrative review examined artificial intelligence technologies in healthcare, particularly critical care [11]. AI applications include medical image analysis (X-rays, MRIs) to expedite diagnosis and treatment planning [11]. AI has potential for optimizing treatment plans and resource allocation in critical care settings [11].

However, the review noted substantial environmental concerns, as AI development has substantial environmental costs due to energy-intensive data centers, with 77% located in high-income countries [11]. The review was not a sedation study but discussed AI's potential applications broadly [11].

Specific applications of AI to sedation management have not yet been extensively studied in the literature reviewed. Potential applications could include predictive algorithms for optimal sedation depth, automated adjustment of sedation infusion rates based on continuous monitoring data, prediction of delirium risk, and identification of patients ready for sedation interruption or extubation. However, these applications remain largely theoretical pending rigorous clinical validation [11].

9.3 9.3 Weaning Assessment Technologies

The Burns Wean Assessment Program (BWAP) represents a systematic approach to identifying patients ready for weaning from mechanical ventilation [63]. This tool incorporates 26 clinical factors assessed within 24 hours before first weaning attempt [63].

A prospective descriptive study over 5 years across 5 adult ICUs obtained 1,889 BWAP scores [63]. Patients with BWAP score <50 had 74% successful weaning rate, while those with BWAP score ≥50 had 96% successful weaning rate [63]. The score of 50 remained a stable predictor across different ICU types and diagnoses [63].

Twenty of 26 BWAP factors were significantly associated with successful weaning ($p \leq 0.02$) [63]. Overall weaning success was 88% (1,669 of 1,889 attempts), with mean ventilator days of 14 (median 9), ICU length of stay mean 19 days (median 13), and hospital length of stay mean 31 days (median 23) [63].

Unit-specific differences were observed, with the neuroscience ICU deviating most (only 9 factors significant vs. 14-17 in other units) [63]. This suggests that weaning assessment tools may require customization for specific patient populations [63].

10. 10. Clinical Implications and Recommendations

10.1 10.1 Evidence-Based Recommendations for Sedation Management

The accumulated evidence from 1991 to 2025 supports several key recommendations for sedation management in mechanically ventilated critical care patients.

10.1.1 10.1.1 Assessment and Monitoring

Recommendation 1: Implement systematic sedation assessment using validated scales. The Ramsay Sedation Scale, Richmond Agitation-Sedation Scale (RASS), and Sedation-Agitation Scale (SAS) all demonstrate acceptable reliability and validity [8], [18], [25]. RASS offers advantages by separately quantifying agitation and sedation [25]. Assessment should occur at minimum every 2-4 hours and before any sedation adjustment [26], [29].

Recommendation 2: Implement systematic pain assessment using validated tools. For communicative patients, use Numeric Rating Scale or Visual Analogue Scale [8]. For non-communicative patients, use Behavioral Pain Scale or similar behavioral-physiological scales [8], [29].

Recommendation 3: Implement systematic delirium screening using CAM-ICU at least twice daily for all patients with RASS >-3 [17], [30]. CAM-ICU demonstrates superior outcome prediction compared to ICDSC [30].

Recommendation 4: Processed EEG monitoring (BIS, Entropy) should not be used routinely for sedation management in general ICU populations, as these technologies do not add clinically useful information beyond validated clinical scales [9]. Responsiveness Index monitoring shows promise but requires further validation [32].

10.1.2 10.1.2 Sedation Depth Targets

Recommendation 5: Target light sedation (RASS 0 to -2, Ramsay 2-3, or SAS 3-4) for most patients unless specific clinical indications require deeper sedation [13], [26]. Deep sedation should be reserved for specific indications including raised intracranial pressure, poor compliance with unusual ventilation modes, critical deterioration of pulmonary oxygenation, tetanus, refractory seizures, and hyperpyrexia [13].

Recommendation 6: Individualize sedation targets based on patient characteristics, clinical status, and treatment goals [54]. Recognize that optimal sedation depth may vary over the course of mechanical ventilation, with lighter targets appropriate as patients stabilize [15].

10.1.3 10.1.3 Sedation Strategies

Recommendation 7: Implement daily sedation interruption for patients receiving continuous sedative infusions, with interruption continued until patients are awake or become agitated/uncomfortable [7]. This strategy reduces mechanical ventilation duration by approximately 2.4 days and ICU length of stay by approximately 3.5 days [7]. However, daily interruption may not provide additional benefit when combined with protocol-directed sedation targeting light sedation levels [50].

Recommendation 8: Implement protocol-directed sedation with nurse-led titration based on validated assessment scales [58]. Meta-analysis demonstrates that protocolized sedation reduces ICU length of stay by 1.73 days, hospital length of stay by 3.55 days, mortality (RR 0.85), and tracheostomy (RR 0.69) [58]. Protocols should include regular assessment, written strategy for stepwise reduction, daily sedation interruption, and reassessment of need for readministration [54].

Recommendation 9: Consider no-sedation strategies (using only opioid boluses for analgesia) for selected patients in centers with appropriate staffing and expertise [3]. The 2010 Strom trial

demonstrated 4.2 additional ventilator-free days with no sedation compared to sedation with daily interruption [3]. However, the 2020 multicenter trial found no significant benefit and a non-significant trend toward increased mortality [2]. No-sedation strategies require careful patient selection, adequate nurse-to-patient ratios, and protocols for managing agitation [2], [3].

Recommendation 10: Avoid continuous benzodiazepine infusions when possible, as continuous infusion increases doses 5.4-fold compared to bolus administration and is independently associated with prolonged mechanical ventilation, ICU stay, and hospital stay [15]. When benzodiazepines are necessary, use midazolam for short-term only (<48-72 hours) or lorazepam for longer duration [8].

10.1.4 10.1.4 Agent Selection

Recommendation 11: Use an analgo-sedation approach with opioids as the foundation, adding sedatives only as needed to achieve target sedation [46]. Combination therapy with opioids plus sedatives demonstrates superior sedation stability and reduced patient-ventilator asynchrony compared to sedatives alone [46].

Recommendation 12: For short-term sedation (<72 hours) when rapid awakening is important, use propofol [8]. For long-term sedation (>72 hours), propofol demonstrates substantially shorter awakening times (0.25-2.5 hours) compared to midazolam (2.8-30 hours) [8].

Recommendation 13: Consider dexmedetomidine for light to moderate sedation, particularly when patient interaction is important [26]. Dexmedetomidine reduces mechanical ventilation duration compared to midazolam (123 vs. 164 hours, p=0.03) and time to extubation compared to both midazolam (101 vs. 147 hours, p=0.01) and propofol (69 vs. 93 hours, p=0.04) [26]. However, monitor for hypotension and bradycardia [26].

Recommendation 14: For analgesia, use fentanyl for rapid onset in acutely distressed patients or for hemodynamic instability/renal insufficiency [8]. Use morphine or hydromorphone for intermittent therapy due to longer duration [8]. Consider remifentanil for patients requiring frequent neurologic assessments or anticipated short mechanical ventilation duration, though cost-effectiveness depends on reduced ICU length of stay [21].

Recommendation 15: Avoid benzodiazepines when possible due to association with delirium and prolonged mechanical ventilation [59]. The Society of Critical Care Medicine's latest guidelines recommend against benzodiazepine use [59].

10.1.5 10.1.5 Delirium Management

Recommendation 16: Implement multicomponent strategies to prevent delirium, including light sedation targets, avoidance of benzodiazepines, maintenance of normal sleep-wake cycles, early mobilization, and minimization of unnecessary stimuli [17], [60].

Recommendation 17: For delirium management, use haloperidol as the preferred agent with monitoring for QT prolongation and arrhythmias [8]. Recognize that delirium is independently associated with 41% greater risk of prolonged hospitalization (HR 1.41, 95% CI 1.05-1.89, p=0.023) [17].

Recommendation 18: Recognize that agitation (Ramsay Scale 1-2) is the strongest predictor of unplanned extubation (OR 25.5-30.6) [35]. Implement strategies to manage agitation including adequate analgesia, reassurance, reorientation, and involvement of family members before escalating sedation [2], [3].

10.2 10.2 Special Population Considerations

Recommendation 19: For pediatric patients, implement age-appropriate sedation assessment tools such as COMFORT-B scale [52]. Recognize that daily sedation interruption has not demonstrated benefit in pediatric populations and may be associated with increased mortality [52]. Ensure written sedation guidelines are in place, as only 50% of pediatric ICUs have such guidelines [31].

Recommendation 20: For tracheostomy patients, anticipate substantial reductions in sedation requirements following tracheostomy placement, with fentanyl decreasing from 866 to 71 µg/(patient-day) and midazolam from 44 to 7 mg/(patient-day) [27]. Target lighter sedation levels (SAS 4 vs. 3.6) and facilitate early mobilization and oral intake [27].

Recommendation 21: For non-invasive ventilation patients, consider dexmedetomidine over midazolam due to superior dosing stability and lighter sedation levels [36]. Avoid excessive sedation that may impair airway protective reflexes [36].

Recommendation 22: For trauma patients, recognize that protocol-directed sedation without daily sedation interruption may be insufficient to improve outcomes [43]. Ensure protocols include daily sedation holidays and address the unique challenges of trauma populations including high injury severity and frequent neurologic injuries [43].

Recommendation 23: For post-cardiac surgery patients, consider propofol for rapid weaning and extubation [39]. Evaluate ventilator modes that reduce sedation requirements, such as BIPAP-APRV [13].

10.3 10.3 Implementation Strategies

Recommendation 24: Engage nurses as key stakeholders in sedation protocol development and implementation, as 84.3% believe nursing-directed protocols would be valuable to patient management [53]. Provide intensive education including one-to-one sessions, formal presentations, regular feedback, and bedside placement of assessment tools and protocols [33].

Recommendation 25: Recognize that protocol effectiveness is context-dependent. Centers with closed ICU models, 24-hour intensivist coverage, high nurse-to-patient ratios, and pre-existing cultures of sedation minimization may not benefit from additional protocol implementation [57]. Conversely, centers with lower nurse-to-patient ratios and less intensivist involvement may benefit substantially from protocolized approaches [58].

Recommendation 26: Monitor compliance with sedation protocols and assessment tools, targeting at least 80-90% compliance [43]. However, recognize that high compliance alone is insufficient if protocol content does not include evidence-based components such as daily sedation interruption [43].

Recommendation 27: Consider telehealth-enabled implementation strategies to provide real-time identification of patients eligible for sedation interruption and spontaneous breathing trials, plus consultative input from expert clinicians [62]. This approach may facilitate protocol adherence and improve outcomes [62].

10.4 10.4 Quality Improvement and Monitoring

Recommendation 28: Establish quality metrics for sedation management including: percentage of patients with sedation assessed using validated scales, percentage of time at target sedation level (target >85%), incidence of oversedation and undersedation, delirium incidence, unplanned extubation rate, mechanical ventilation duration, ICU length of stay, and hospital length of stay [18], [19].

Recommendation 29: Conduct regular audits of sedation practices including agent selection, dosing patterns, assessment frequency, protocol compliance, and adverse events [4]. Use audit data to provide feedback to clinicians and identify opportunities for improvement [62].

Recommendation 30: Recognize international variation in sedation practices and adapt recommendations to local context, drug availability, and regulatory environment [5], [45]. For example, lorazepam is rarely available in European practice, necessitating use of alternative agents [5].

10.5 10.5 Future Directions

Recommendation 31: Support research on artificial intelligence applications for sedation management, including predictive algorithms for optimal sedation depth, automated adjustment of infusion rates, delirium risk prediction, and identification of patients ready for weaning [11]. However, ensure rigorous clinical validation before widespread implementation [11].

Recommendation 32: Support research on novel sedation agents and strategies, including evaluation of newer alpha-2 agonists, volatile anesthetics, and combination regimens [26]. Prioritize studies with patient-centered outcomes including mechanical ventilation duration, length of stay, delirium, mortality, and long-term cognitive and functional outcomes [2].

Recommendation 33: Support implementation science research to identify effective strategies for translating evidence-based sedation practices into routine clinical care across diverse settings [62]. Recognize that implementation barriers include organizational culture, staffing models, clinician knowledge and attitudes, and availability of resources [33], [57].

10.6 10.6 SCCM PAD Guidelines Integration

The 2002 Society of Critical Care Medicine Clinical Practice Guidelines for the Sustained Use of Sedatives and Analgesics in the Critically Ill Adult provided foundational recommendations that remain relevant [8]. Key guideline recommendations include:

- Use validated sedation scales (Ramsay, SAS, MAAS, VICS) for all patients (Grade B-C evidence) [8]
- Use validated pain assessment tools (NRS, VAS, VDS, behavioral-physiological scales) (Grade B-C evidence) [8]
- Administer analgesics continuously or as scheduled intermittent doses with supplemental boluses (Grade C) [8]
- Use fentanyl for rapid onset in acutely distressed patients (Grade C) [8]
- Use fentanyl or hydromorphone for hemodynamic instability or renal insufficiency (Grade C) [8]
- Use morphine or hydromorphone for intermittent therapy (Grade C) [8]
- Use NSAIDs or acetaminophen as adjuncts to opioids (Grade B) [8]
- Use midazolam or diazepam for rapid sedation of acute agitation (Grade C) [8]
- Use propofol when rapid awakening is important (Grade B) [8]
- Use midazolam for short-term only (<48-72 hours) (Grade A) [8]
- Use lorazepam for most patients via intermittent IV or continuous infusion (Grade B) [8]
- Use haloperidol for delirium management (Grade C) with monitoring for QT prolongation (Grade B) [8]

- Implement daily awakening protocols (associated with shorter ventilation duration and ICU stay) [8]

The latest SCCM guidelines have recommended against benzodiazepine use, reflecting accumulating evidence of adverse effects including delirium and prolonged mechanical ventilation [59].

11. 11. Conclusion

This comprehensive review of 55 studies spanning 1991 to 2025 demonstrates that sedation management profoundly influences clinical outcomes for mechanically ventilated critical care patients. The evidence reveals a clear evolution from deep, continuous sedation paradigms prevalent in the early 1990s toward contemporary strategies emphasizing light sedation, protocol-driven approaches, daily interruption, and in selected cases, complete avoidance of sedative agents.

The magnitude of impact is substantial. Continuous intravenous sedation is independently associated with mechanical ventilation duration of 148 hours compared to 78.7 hours without continuous sedation ($p<0.001$), representing nearly a doubling of ventilator time [6]. Daily sedation interruption reduces median mechanical ventilation duration by 2.4 days and ICU length of stay by 3.5 days [7]. Protocol-directed sedation reduces ICU length of stay by 1.73 days and hospital length of stay by 3.55 days in meta-analysis [58]. Dexmedetomidine reduces time to extubation by 46 hours compared to midazolam and by 24 hours compared to propofol [26].

Delirium has emerged as a critical mediator of outcomes, with delirious patients experiencing 41% greater risk of prolonged hospitalization independent of sedation practices [17]. Agitation represents the strongest predictor of unplanned extubation, with odds ratios exceeding 25 for Ramsay Scale 1-2 [35]. Unplanned extubation requiring reintubation is associated with ICU length of stay of 40 days versus 10 days for those not requiring reintubation [35].

Agent selection matters. Benzodiazepines, particularly when administered by continuous infusion, are associated with prolonged mechanical ventilation, increased delirium risk, and worse outcomes [15], [59]. Propofol offers advantages for short-term sedation and rapid awakening [8]. Dexmedetomidine facilitates patient interaction and reduces time to extubation but is associated with increased hemodynamic adverse effects [26]. Analgo-sedation approaches with opioids as the foundation demonstrate superior sedation stability compared to sedatives alone [46].

Implementation factors are critical. Protocol effectiveness is context-dependent, with greatest benefits observed in centers without pre-existing cultures of sedation minimization [57]. Nurse engagement is essential, with 84.3% believing nursing-directed protocols would be valuable [53]. However, compliance remains challenging, with perfect adherence achieved in only 18% of eligible patients in one implementation study [33]. Telehealth-enabled strategies show promise for improving protocol adherence [62].

Special populations require tailored approaches. Pediatric daily sedation interruption has not demonstrated benefit and may be associated with increased mortality [52]. Tracheostomy dramatically reduces sedation requirements, with fentanyl decreasing from 866 to 71 µg/(patient-day) [27]. Trauma patients may require protocols that include daily sedation holidays to achieve benefits [43].

Emerging technologies including processed EEG monitoring (BIS, Entropy) have not demonstrated clinical utility in general ICU populations [9]. Responsiveness Index monitoring shows promise but requires further validation [32]. Artificial intelligence applications remain largely theoretical

pending rigorous clinical validation [11].

The economic implications are substantial. With ICU costs exceeding $150,000 per patient in some studies [43] and sedation strategies capable of reducing ICU length of stay by 1-3 days [7], [58], the potential for cost savings is considerable. Even agents with higher acquisition costs such as remifentanil and dexmedetomidine may be cost-effective through reductions in length of stay [21].

Looking forward, several priorities emerge. First, continued efforts to implement evidence-based sedation practices across diverse settings, recognizing that implementation strategies must be tailored to local context [62]. Second, research on novel agents and strategies, including evaluation of no-sedation approaches in broader populations [2], [3]. Third, development and validation of artificial intelligence applications for sedation management [11]. Fourth, investigation of long-term outcomes including cognitive function, psychological well-being, and quality of life [2].

The paradigm shift from deep to light sedation represents one of the most significant advances in critical care over the past three decades. However, substantial variation in practice persists, with many centers not yet implementing evidence-based strategies [4], [5]. Closing this evidence-practice gap represents a major opportunity to improve outcomes for the millions of patients who undergo mechanical ventilation in critical care units worldwide each year.

In conclusion, optimal sedation management—characterized by systematic assessment using validated tools, light sedation targets, protocol-directed approaches with daily interruption, analgo-sedation strategies, avoidance of benzodiazepines, and aggressive delirium prevention—can reduce mechanical ventilation duration by 2-4 days, ICU length of stay by 2-4 days, and hospital length of stay by 3-9 days compared to traditional deep sedation approaches. These improvements translate to reduced mortality, lower complication rates, decreased healthcare costs, and better patient experiences. Achieving these benefits requires sustained commitment to implementation of evidence-based practices, ongoing quality monitoring, and continued research to refine and optimize sedation strategies for diverse patient populations.

12. 12. References

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