17.8 Sedation and analgesia in the ICU 3898 Michae

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ESSENTIALS Patients undergoing mechanical ventilation or other forms of inva- sive organ support in an intensive care unit should ideally be free of pain, anxiety, and delirium, sufficiently cooperative or sedated to en- able safe delivery of essential aspects of their care, sufficiently awake such that tracheal extubation is not unnecessarily delayed, and left with few or no unpleasant memories of their illness and treatment. This ideal is often not achieved. Management should be based on an analgesia-first, delirium- control, sedation-minimization approach. Identifying intensive care unit-associated delirium is not straightforward: most delirious pa- tients are not agitated, and 'hypoactive' delirium can mask substan- tial psychological distress. Various assessment scales can be used to quantitate, monitor and communicate sedation and sedation goals, and similar tools can be employed to identify delirium. The most common choice of drugs for pain control, delirium control and sed- ation varies markedly around the world, and is determined more by familiarity and traditional local practice than by evidence from com- parative effectiveness trials. However, the widespread application of a systematic approach offers a significant prospect of patient and hospital efficiency benefit compared to current practice in many in- tensive care units. Introduction Patients undergoing mechanical ventilation or other forms of inva- sive organ support in an intensive care unit (ICU) should ideally be: • free of pain, anxiety and delirium; • sufficiently cooperative or sedated to enable safe delivery of essen- tial aspects of their care, in particular with a low risk of removal of their endotracheal tube or intravascular catheters; • sufficiently awake such that tracheal extubation is not unneces- sarily delayed; and • left with few or no unpleasant memories of their illness and treatment. When properly applied, modern pharmacotherapy along with nonpharmaceutical techniques should be able to achieve these goals in most patients. This is helped considerably by technical advances in organ-support technologies such as microprocessor- controlled ventilators that are sensitive to the patient's respiratory effort, minimally-invasive cardiovascular monitoring, and better use of regional analgesia that acts

without affecting cognitive function. Where patients were once thought to require deep sed- ation to tolerate various aspects of ICU care, most can now remain interactive and indeed begin their physical and psychological re- habilitation while still requiring mechanical ventilation and other invasive organ support. Very few patients require deep sedation, which is indicated only to reduce intracranial pressure, control seizures, or prevent awareness during neuromuscular blockade. However, despite this optimistic outlook, contemporary observa- tional studies consistently find that most critically ill patients re- call substantial pain and anxiety, often accentuated by distressing hallucinations. Clearly there is a gap between optimal and actual practice. Central to optimizing 'sedation and analgesia in the ICU' is understanding the interplay of causes of pain, agitation (and un- pleasant awareness) and delirium in a particular patient, and also the interactions of drugs used for each of these indications. Much like the 'triad of anaesthesia' (hypnosis, analgesia, and muscle re- laxation) reminds anaesthetists that a balanced anaesthetic using specific drugs reduces the adverse effects of 'overdosing' any one drug category, the 'ICU triad' (Fig. 17.8.1) emphasizes the benefit of targeted treatment. Drug choices for sedation, analgesia,
and delirium control Drugs in common use are listed in Table 17.8.1. The most common choice in each drug category varies markedly around the world, and is determined more by familiarity and trad- itional local practice than by evidence from comparative effective- ness trials. Analgesics The principal reason for treating pain is to relieve the patient's dis- tress. Pain also intensifies the hormonal and cytokine stress response, worsens delirium, and may interfere with essential patient care. 17.8 Sedation and analgesia in the ICU Michael C. Reade

17.8 Sedation and analgesia in the ICU 3899 Pain Endotracheal tube Tissue injury (e.g. surgery, trauma, pressure areas) Vascular access Affective component (e.g. 'this pain means I'm more likely to die') Elements of routine ICU care (e.g. turning, physical therapy) Advanced age Severity of illness Medical co-morbidity Pre-existing mental impairment Neurologic diagnosis (e.g., head injury) Observable and occult metabolic abnormalities Withdrawal from chronic psychoactive medications (e.g. benzo- diazepines, opioids) Sleep deprivation Substance abuse or withdrawal Noise Sedatives Delirium Agitation; unpleasant awareness Anxiety (appropriate or pathologic) Frustration Lack of homeostasis (e.g. thirst, hunger, dyspnoea) Ventilator dyssynchrony Inability to communicate Physical restraint Fig. 17.8.1 The 'ICU triad' highlighting interactions of the causes of pain, agitation/unpleasant awareness, and delirium in the management of critical illness. From New England Journal of Medicine. Reade M.C. and Finfer S., Sedation and Delirium in the Intensive Care Unit, 370, 444–454. Copyright © 2014 Massachusetts Medical Society. Reprinted with permission. Table 17.8.1 Sedatives, analgesics, and antidelirium drugs in common use in the ICU Drug Mechanism Typical adult dose Pharmacokinetics Adverse effects 1. Sedatives Midazolam GABAA agonist Bolus 1–5 mg; infusion
1–5 mg/hr Half-life 3–11 hours. Active metabolite accumulates with prolonged infusion. Metabolized by hepatic oxidation, with renal excretion of active metabolite Possibly a higher risk of delirium and tolerance than nonbenzodiazepine sedatives Hypotension (less than propofol) Respiratory depression Lorazepam GABAA agonist Bolus 1–4 mg; infusion
1–5 mg/hr Slower onset (5–20 mins, compared to 2–5 mins with midazolam and diazepam). Half-life 8–15 hours Metabolized by hepatic glucuronidation, with no active metabolites. Offset is more predictable than midazolam in critical illness Possibly a higher risk of delirium and tolerance than nonbenzodiazepine sedatives Hypotension (less than propofol) Respiratory depression Propofol GABAA agonist, with other effects including on glutamate and cannabinoid receptors 50–200 mg/hr

(or 1–3 mg/kg/hr) Half-life 30–60 minutes after infusion; longer after prolonged infusion due to redistribution from fat stores. Metabolized by hepatic glucuronidation and hydroxylation Vasodilatation/negative inotropy causing hypotension/bradycardia. Propofol infusion syndrome (lactic acidosis, arrhythmia, and cardiac arrest), mostly associated with prolonged infusion rates

> 4–5 mg/kg/hr Respiratory depression Hypertriglyceridemia (due to carrier solution) Pancreatitis (continued)

Section 17 Critical care medicine 3900 Drug Mechanism Typical adult dose Pharmacokinetics Adverse effects Dexmedetomidine α-2 agonist 0.2–1.5 mcg/kg/hr Half-life 2 hours. Does not accumulate with prolonged infusion. Metabolized by hepatic glucuronidation and oxidation, with no active metabolites Transient hypertension, then hypotension Bradycardia (may be profound) Dry mouth Nausea Remifentanil Mu agoinst (also with kappa agonist effects). NB: Typically considered an 'analagosedative' as at typical doses has a sedating as well as analgesic effect 0.05–2 mcg/kg/hr Loading doses of
0.4–0.8 mcg/kg may be considered Half-life 3–4 minutes. Does not accumulate with prolonged infusion. Metabolized by plasma esterases and so unaffected by organ function Nausea Constipation Respiratory depression Bradycardia 2. Analgesics Fentanyl Mu agoinst (also with kappa agonist effects) 20–100 mcg/hr Loading dose of 50–100 mcg may be considered Half-life 1.5–6 hours. Highly fat-soluble, so rapid onset but accumulates with prolonged infusion. Metabolized by hepatic oxidation. No active metabolite Nausea Constipation Respiratory depression Skeletal muscle rigidity with large bolus doses Morphine Mu agoinst (also with kappa and
δ-agonist effects) 1–5 mg/hr
Loading dose of 2–5 mg may be considered Half-life 3–7 hours. More water soluble, so slower onset than fentanyl with less accumulation. Metabolized by hepatic glucuronidation to M-6-glucuronide (10%) (20× as active as parent drug) and M-3- glucuronide (90%) (inactive as an analgesic, but causes neuroexcitation, at least in animal models), glucuronides excreted via kidney Nausea Constipation Respiratory depression Histamine release and consequent vasodilation and hypotension (with large doses) and pruritus Hydromorphone Mu agoinst (also with kappa and δ-agonist effects) 0.04–0.4 mg/hr Loading dose of 0.4–1.5 mg may be considered Half-life 1.5–3.5 hours. 7–11 times more potent than morphine. Metabolized by hepatic glucuronidation to H-3-glucuronide, with similar effects to M-3-glucuronide Nausea Constipation Respiratory depression Ketamine NMDA antagonist, with weak mu and kappa agonist action and inhibition of reuptake of serotonin, dopamine, and noradrenaline 5–15 mg/hr Half-life 2.5 hours. Hepatic metabolism to a variety of compounds, one of which (norketamine) which is 1/6 as active as ketamine Hallucinations Delirium Hyper- or hypotension (but little effect at analgesic doses) Paracetamol Mechanism of action is not fully understood, but in part acts by inhibition of cyclooxygenase-2 1 g q6hr IV or PO Half-life 2.7 hours. Hepatic metabolism to inactive metabolites. Notably, one metabolite (N-acetyl-p-benzoquinone imine; NAPQI) irreversibly conjugates with glutathione, which in overdose can cause potentially fatal hepatic damage by oxidative stress Gastrointestinal (GI) upset Increased liver function tests (LFTs), with hepatotoxicity at high doses or prolonged regular use (especially in malnourished patients). Pyroglutamic acidosis (thought to be rare) Nonsteroidal

anti-inflammatory drugs Cyclooxygenase- 2 inhibition (thereby reducing prostaglandins and thromboxanes and producing anti-inflammatory, analgesic and antipyrectic effect) +/- cyclooxygenase- 1 inhibition (producing gastrointenstinal ulceration) Varies by drug (e.g. ibuprofen, 400 mg PO q6hr) Varies by drug (e.g. ibuprofen 2 hours. Hepatic metabolism to inactive metabolites) GI ulceration Renal impairment Bronchospasm Bleeding though an antiplatelet effect Tinnitus Rebound headache Table 17.8.1 Continued

17.8 Sedation and analgesia in the ICU 3901 Adequate treatment of pain can avoid the need for any other drug therapy. A multimodal approach to analgesia is best, beginning with • reducing painful stimuli (e.g. reducing needless dressing changes); • continuous regional or neuraxial analgesia (now substantially fa- cilitated by ultrasound-guidance of catheter placement), specific treatment of neuropathic pain; and • nonopioid analgesic drugs. ■ Regular (rather than as-required) paracetamol should be given to every patient without contraindications requiring treatment of somatic pain. ■ Nonsteroidal anti-inflammatory drugs are often contraindi- cated in critical illness due to their renal, coagulation, and gastrointestinal effects, but are nonetheless useful in patients at otherwise low risk of these complications. ■ Ketamine is usually thought of as a cardiovascularly stable an- aesthetic induction agent and retains this utility in the ICU; however at the doses required for continuous sedation it usu- ally causes problematic hallucinations and so is not used for this indication. However, low-dose ketamine by continuous infu- sion is a very effective opioid-sparing analgesic that is thought to work mainly by modulating transmission of pain at the level of the dorsal horn of the spinal cord. At low doses, problem- atic hallucinations are uncommon, and if present can usually be treated with low-dose benzodiazepines. Notwithstanding, opioids are the main analgesics used in the ICU. Virtually no mechanically ventilated ICU patients should receive sedative drugs without also receiving opioid analgesia. In one ran- domized trial, properly addressing analgesia with opioids was found to remove entirely the requirement for sedation in 82% of patients. Attempting such a ‘no sedation’ strategy, compared to conventional sedation, was also associated with a shorter ICU stay and a near- significant trend to reduced ICU mortality with no increase in adverse events such as self-extubation. There is little evidence to guide choice of opioid, but pharmacokinetic and pharmacodynamic rationale suggest that any differences would be clinically insignificant. Sedatives Several observational studies have found associations between benzodiazepine-based sedation, delirium, and longer ICU admis- sion, but these associations are confounded by indication with benzodiazepines typically being chosen for less haemodynamically stable patients, who are expected to need more prolonged ventila- tion. Several large comparative trials have found dexmedetomidine to be superior to benzodiazepines in terms of delirium and length of mechanical ventilation, while these differences were not evident in a comparison of dexmedetomidine to propofol. Despite more than 90 other comparative trials, no sedative is clearly superior for all patients. Antidelirium agents Delirium should be sought actively in all ICU patients. The evidence underpinning specific drug treatment of delirium is less robust than that for the other arms of the ‘ICU triad’, but optimized drug selec- tion and dosing have nonetheless been associated with better out- comes. The term ‘antidelirium agent’ is preferable to ‘antipsychotic’ when using the drugs in Table 17.8.1 to treat ICU-acquired delirium, which has similarities to but is distinct from psychosis. Nonetheless, all these drugs were originally described as antipsychotics for use in the chronic treatment of mental illness. Options for delirium con- trol vary markedly in their pharmacokinetic and dynamic proper- ties. Quetiapine is the most sedating option, and was found superior to placebo in a randomized trial. Dexmedetomidine has also been found to be superior to placebo in the management of patients who cannot be extubated due to

agitated delirium. Small antidelirium drug/drug comparative trials are essentially inconclusive. A major Drug Mechanism Typical adult dose Pharmacokinetics Adverse effects 3. Antidelirium agents Haloperidol Predominant dopamine-2 receptor antagonist 0.5–2.5 mg IV bolus repeated as required; typical maximum 50 mg/day Half-life 12–38 hours. Metabolized by hepatic oxidative N-dealkylation to inactive metabolites Somnolence Neuroleptic malignant syndrome Extrapyramidal effects (more common with PO administration) QT prolongation/torsades de pointes Quetiapine Predominant histamine-1 receptor antagonist, with very little antidopaminergic effect 25–100 mg PO bd Half-life 7 hours. Metabolized by hepatic cytochrome p450 to inactive metabolites Somnolence Dizziness Dry mouth Extrapyramidal effects QT prolongation in very high doses/ overdose Risperidone Predominant 5HT2A receptor antagonist 1–3 mg PO bd (also available as an orally disintegrating tablet) Half-life 3–17 hours, determined in part by genetic variation Metabolized by hepatic cytochrome p450 partly to active metabolites Insomnia Agitation Extrapyramidal effects Neuroleptic malignant syndrome Olanzapine Predominant muscarinic receptor antagonist with moderate anti- 5HT2A action 5–10 mg PO daily (also available as an orally disintegrating tablet) Half-life 33 hours Metabolized by hepatic conjugation and oxidation to largely inactive metabolites Somnolence Anticholinergic effects (dry mouth, urinary retention, constipation, fever) Extrapyramidal effects Table 17.8.1 Continued

Section 17 Critical care medicine 3902 flaw of many such trials is the grouping together of patients with both hyper and hypoactive delirium, a factor that logically would be expected to influence response to drugs with different sedating properties. Dosing targets and strategies The goal of minimizing sedation and optimizing analgesia and delirium control has been pursued using several dosing strat- egies (Fig. 17.8.2). Compared to conventional physician-directed dosing, a strategy of daily interruption of all sedatives (+/- spon- taneous breathing trials) resulted in shorter ventilation and ICU stay, and in one trial, increased survival. However, daily sedative interruption was found not superior to a protocol that minim- ized sedation by giving bedside nurses substantial autonomy in ti- trating sedatives to agreed goals. The best choice for each ICU will rest on factors such as nurse:patient ratios, physician availability, and the autonomy with which nurses are permitted to act. In many ICUs, communicating and monitoring sedation goals is facilitated by the use of sedation monitoring scales, such as those listed in Table 17.8.2. Identifying ICU-associated delirium is complex, as by definition the condition fluctuates and has protean manifestations. Most deli- rious ICU patients are not agitated, and this ‘hypoactive’ delirium can produce a misleading appearance of calm that masks substan- tial psychological distress. The two diagnostic tools in commonest use are the Confusion Assessment Method for the ICU (CAM- ICU), which involves an active assessment of the patient at a single time point, and the Intensive Care Delirium Screening Checklist (ICDSC), which asks the clinician to observe several features of delirium over a period of time (Table 17.8.3). As defined and con- ventionally used, both scales dichotomize delirium as ‘present’ or ‘absent’, and neither distinguish hypo- from hyper- active delirium. Status epilepticus intracranial hypertension severe respiratory failure with or without neuromuscular blockade Assess pain and treat with opioid or other drug or technique Assess pain and treat with opioid or other drug or technique Specific indication for sedation Pain controlled Pain controlled Assess for delirium Mainly hypoactive delirium No delirium Mainly hyperactive delirium Yes Treat with antidelirium medication (or nonpharmacologic measures) Treat with nonpharmacologic measures (e.g. physical therapy, earplugs or quiet room, cognitive stimulation, repeated reorientation) Delirium controlled Yes Assess need for sedative medication to achieve target RASS score of –2 to 0 (lightly sedated but responsive at least to voice) Reassess analgesic, antidelirium, and sedative requirement

regularly (e.g. every 4 hr or with observed change) Do not use sedative medication Target sedation to RASS score of –2 to 0 Yes No No Yes No No Yes Target sedation to indication: Seizure control Acceptable intracranial pressure Tolerance of hypercarbia or necessary ventilator settings No awareness when being treated with neuromuscular blocking agent Regularly assess the need for this level of sedation The target sedation level is likely to be best communicated using the RASS scale Fig. 17.8.2 A suggested algorithm that implements the analgesia-first, delirium-control, sedation-minimization approach supported by modern ICU clinical trials. From New England Journal of Medicine. Reade M.C. and Finfer S., Sedation and Delirium in the Intensive Care Unit, 370, 444–454. Copyright © 2014 Massachusetts Medical Society. Reprinted with permission.

17.8 Sedation and analgesia in the ICU 3903 Another major concern with delirium detection is the interaction of sedative medications with assessment. Deeply sedated patients cannot be assessed, but light or recently discontinued sedation can produce a positive test result that does not portend the adverse con- sequences associated with persistent delirium. Having identified delirium, a logical dosing strategy (supported by some trial evidence) is quickly to gain control of delirium using an as- required prescription (most commonly of the only commonly-used drug available in parenteral form, haloperidol) along with institu- tion of a regularly scheduled low-dose (but titratable) enteral longer- acting drug: in theory quetiapine or olanzapine for agitated delirium and respiridone for hypoactive delirium. Recently, a large trial tested the hypothesis that prophylactic low dose haloperidol would reduce mortality in ICU patients considered at high risk of delirium. The trial also examined the effect of haloperidol on 15 secondary outcomes including incidence of delirium, and duration of ICU treatment and Table 17.8.2 ICU sedation scales Riker Sedation Agitation Scale (‘Riker’ or ‘SAS’) 7 Dangerous agitation Pulling at endotracheal tube (ETT) tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side-to-side 6 Very agitated Requiring restraint and frequent verbal reminding of limits, biting ETT 5 Agitated Anxious or physically agitated, calms to verbal instructions 4 Calm and cooperative Calm, easily rousable, follows commands 3 Sedated Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again 2 Very sedated Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously 1 Unarousable Minimal or no response to noxious stimuli, does not communicate or follow commands Richmond Agitation-Sedation Scale (RASS) +4 Combative Overtly combative, violent, immediate danger to staff +3 Very agitated Pulls or removes tube(s) or catheter(s); aggressive +2 Agitated Frequent nonpurposeful movement, fights ventilator +1 Restless Anxious but movements not aggressive vigorous 0 Alert and calm Alert and calm –1 Drowsy Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (>10 seconds) –2 Light sedation Briefly awakens with eye contact to voice (<10 seconds) –3 Moderate sedation Movement or eye-opening to voice (but no eye contact) –4 Deep sedation No response to voice, but movement or eye-opening to physical stimulation –5 Unrousable No response to voice or physical stimulation Table 17.8.3 ICU delirium identification tools Confusion assessment method for the ICU (CAM-ICU) Patient must be sufficiently awake (RASS score ≥–3) to be able to be assessed. The following criteria are assessed: Positive or negative

1. an acute change from mental status baseline OR fluctuating mental status during the past 24 hours (must be true to be CAM-ICU positive);
2. more than 2 errors in a 10-point test of attention to voice or pictures (must be true to be CAM-ICU positive);

3. If the RASS is not 0 and the previous two criteria are positive, the patient is delirious.
4. If the RASS = 0 and the previous two criteria are positive, test for disorganized thinking using 4 yes/no questions and a 2-step command. >1 error means the patient is delirious; ≤1 error excludes delirium. Intensive Care Delirium screening Checklist (ICDSC) Patient must show at least a ‘response to mild or moderate stimulation’. Then score one point for each of the following features observed, as assessed in the manner thought appropriate by the clinician: A score of ≥ 4 is positive for delirium (scores of 1–3 are ‘subsyndromal delirium’)
5. Anything other than ‘normal wakefulness’
6. Inattention
7. Disorientation
8. Hallucination
9. Psychomotor agitation
10. Inappropriate speech or mood
11. Sleep/wake cycle disturbance
12. Symptom fluctuation

Section 17 Critical care medicine 3904 mechanical ventilation. The trial reported no detectable beneficial ef- fect from the prophylactic administration of haloperidol. While the diagnosis of delirium is associated with worse outcomes for ICU pa- tients, a causal relationship has not been established and the assump- tion that treating delirium, particularly hypoactive delirium, leads to improved outcome is not yet proven. Monitoring of brain electrical activity Various simplified forms of electroencephalogram (EEG) moni- toring have become established methods for monitoring depth of anaesthesia, which is particularly useful for patients requiring neuromuscular blockade as paralysis can mask signs of awareness. However, such devices have not been adopted in most ICUs as depth-of-sedation monitors, for several reasons. First, prevention of awareness is not the goal in most ICU patients and at lighter levels of sedation the processed EEG signal correlates poorly with observed clinical signs. Second, muscle relaxants are rarely indicated in the ICU, and the muscle activity of nonparalysed and lightly sedated pa- tients interferes with the EEG signal. Third, of the small trials that have been performed, most have found no suggestion of patient benefit when sedatives are titrated to an EEG signal rather than con- ventional clinical endpoints. Nonpharmacological techniques and ‘complex interventions’ addressing pain, agitation, and delirium Optimizing patient comfort (by positioning, frequent turning, and min- imizing painful procedures), minimizing sleep disruption, facilitating environmental stimulation (for example, with windows, lighting, spec- tacles, and hearing aids) but not overstimulation (e.g. by reducing am- bient noise or using earplugs or headphones), repeated reorientation, maximizing the presence of familiar trusted people, addressing meta- bolic derangements, and of course addressing the underlying critical illness are all low-risk, low-cost components of good holistic care that at least some evidence suggests reduce the need for pharmacological control of pain, agitation, and delirium. The most robust evidence sup- ports a strategy of early mobilization, even for patients still dependent on mechanical ventilation. In comparison to standard care, this has re- sulted in less delirium and less time mechanically ventilated, with more patients functionally independent at the time of hospital discharge, none of which came at the cost of more adverse events. Combining nonpharmacologic techniques with both tailored drug selection that recognizes the importance of very early interven- tions adjusted as required by illness progression (rather than policy- based drug A vs. drug B trials) and a dosing strategy that facilitates maximum drug titratibility in the

physician/nursing/organizational context is a ‘complex intervention’ that is only recently starting to be tested in clinical trials. Special circumstances Substance abuse or dependence on medically indicated psycho- active medications is common in patients admitted to an ICU. Even patients who were previously drug-naive can manifest with- drawal syndromes after discontinuation of ICU sedatives and other medications. The commonest withdrawal syndromes are from alcohol, nicotine, GABA-agonists, and opioids. Classic fea- tures of withdrawal from sedating drugs include agitation, sym- pathetic activation, and delirium. Somnolence might be expected during withdrawal from nicotine but is often overshadowed by irritability and anxiety. • Benzodiazepines are the time-honoured treatment for both al- cohol and GABA-agonist withdrawal, but the association of benzodiazepines used as an ICU sedative with delirium suggests that other agents might be superior. Very little trial evidence sup- ports the theoretical advantages of alternatives. • Clonidine (an α-2 receptor agonist) is the popular choice for opioid withdrawal, combining reduction of sympathetic activity with a sedative action similar to that of dexmedetomidine. • Nicotine withdrawal is typically treated with transcutaneous nico- tine replacement. However, the evidence underpinning each of these strategies is largely anecdotal, with few comparative trials. One pivotal trial found that early severe acute respiratory distress syndrome is a special circumstance that should be the exception to the modern approach of light or no ICU sedation. Patients random- ized to receive muscle relaxation for the first 48 hours of their ICU stay had a significantly lower 28-day mortality than those treated according to usual care. Most clinicians feel that muscle relax- ation without sufficient sedation to prevent awareness is needlessly distressing to the patient. Prognosis/outcome There is substantial evidence from observational studies and clin- ical trials that selection of drugs to provide sedation, analgesia, and delirium control, along with optimizing their mode of delivery and concurrent use of nonpharmacological interventions, affects both hospital efficiency (e.g. duration of mechanical ventilation and ICU length of stay) and patient-centred outcomes (e.g. time spent in pain or with dysphoric delirium, long-term cognitive, and functional outcomes and mortality). Early concerns that a light- or no- sedation strategy in mechanically ventilated patients might produce more adverse events (such as self-extubation or removal of vascular access catheters) or more long-term psychological morbidity (such as post-traumatic stress disorder) have proved unfounded. Guidelines Several research groups and professional societies have published evidence-based guidelines for the management of cognitive func- tion in the ICU. Principal among these are the ‘Clinical practice guidelines for the management of pain, agitation and delirium in adult patients in the intensive care unit’, published by the American College of Critical Care Medicine in 2013. This document, with 472 references (the result of reviewing over 19 000 references) contains 54 statements and recommendations.

17.8 Sedation and analgesia in the ICU 3905 Likely future developments The key to optimal sedation, analgesia, and antidelirium practice is almost certainly the type of ‘complex intervention’ described here, but several (easier to test) hypotheses and questions are likely to be answered over the coming years: • Understanding the importance of very early (i.e. immediately after intubation to 24–48hrs) sedation/analgesia strategy in influencing later outcomes; • Evaluating established sedative drugs in use in anaesthesia in well- designed pragmatic comparative effectiveness trials (including remifentanil, inhaled halogenated anaesthetic vapours and xenon); • Evaluating patient-controlled sedation and other novel approaches to mode of administration of sedative/analgesic/antidelirium agents, such as better communication and modification of goals and the optimal degree of autonomy that should be held by the bedside nurse; • Describing a delirium detection tool that accounts for the fluctuating nature of the condition, its hypo and hyperactive manifestations, and the influence of sedating medications; then validating the utility of

this tool in guiding treatment that im- proves outcomes; and • Better comparison of the clinical effects of the various antidelirium drug options, taking into account their different sedative properties and thus likely different effects on hyper and hypoactive delirium. Benefits associated with these points are likely to be incremental rather than revolutionary, but widespread application of the well- founded recommendations listed in this chapter offers a significant prospect of patient and hospital efficiency benefit compared to what appears to be current practice in many ICUs.

FURTHER READING Barr J, et al. (2013). Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med, 41, 278–80. Devlin JW, et al. (2011). Impact of quetiapine on resolution of indi- vidual delirium symptoms in critically ill patients with delirium: a post-hoc analysis of a double-blind, randomized, placebo-controlled study. Crit Care, 15, R215. Girard TD, et al. (2008). Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a ran- domised controlled trial. Lancet, 371, 126–34. Mehta S, et al. (2012). Daily sedation interruption in mechanically ven- tilated critically ill patients cared for with a sedation protocol: a ran- domized controlled trial. JAMA, 308, 1985–92. Papazian L, et al. (2010). Neuromuscular blockers in early acute re- spiratory distress syndrome. N Engl J Med, 363, 1107–16. Reade MC, Finfer S (2014). Sedation and delirium in the intensive care unit. N Engl J Med, 370, 444–54. Reade MC, et al. (2016). Effect of dexmedetomidine added to standard care on ventilator-free time in patients with agitated delirium: a ran- domized clinical trial. JAMA, 315, 1460–8. Riker RR, et al. (2009). Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA, 301, 489–99. Schweickert WD, et al. (2009). Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised con- trolled trial. Lancet, 373, 1874–82. Strom T, Martinussen T, Toft P (2010). A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. Lancet, 375, 475–80. van den Boogaard M, et al. (2018). Effect of haloperidol on survival among critically ill adults with a high risk of delirium: the REDUCE randomized clinical trial. JAMA, 319, 680–90.

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