# Appendix 3: Critical Care: Patient Assessment and Pharmacotherapy

## INTRODUCTION

TABLE A3-1

**Pharmacokinetic Changes in Critical Illness**

| Pharmacokinetic Parameter | Changes in the Critically Ill | Etiologies | Example Drugs Affected |
|---|---|---|---|
| Absorption | ↓ Absorption | Perfusion abnormalities<br>Decreased GI motility<br>Altered gastric pH<br>Bowel wall edema<br>Drug–nutrient interactions | Enteral, intramuscular, or subcutaneous drugs<br>*Itraconazole (capsules need an acidic medium for absorption), phenytoin (significant drug–nutrient interactions), subcutaneous enoxaparin (incompletely absorbed in the setting of vasopressors and edema)* |
| Distribution | ↑ *Vd* | Large-volume resuscitation<br>Capillary leak syndrome<br>Ascites<br>Mechanical ventilation | Hydrophilic drugs<br>*Aminoglycosides, beta-lactams, daptomycin, hydromorphone, morphine, vancomycin* |
| | | Hypoalbuminemia | Albumin-bound drugs<br>*Amiodarone, ceftriaxone, midazolam, morphine, phenytoin, propofol, valproic acid, warfarin* |
| | | Extracorporeal circuits with expansive surface area (ECMO) | Lipophilic drugs<br>*Diazepam, fentanyl, fluoroquinolones, macrolides, midazolam, propofol* |
| | ↓ $V_d$ | Decreased α1-acid glycoprotein | Drugs bound to α1-acid glycoprotein<br>*Azithromycin, carvedilol, fentanyl, lidocaine, olanzapine, phenobarbital* |
| Metabolism | ↑ Metabolism | Hepatic enzyme induction<br>Augmented hepatic blood flow | Flow-dependent drugs (hepatic extraction ratio >0.7)<br>*Propofol, midazolam, morphine, metoprolol* |
| | ↓ Metabolism | Hepatic enzyme inhibition<br>Decreased hepatic blood flow | Flow-independent drugs (hepatic extraction ratio <0.3)<br>*Warfarin, diazepam, phenytoin* |
| Excretion | ↑ Clearance | Augmented renal clearance<br>Extracorporeal removal | Renally eliminated medications<br>*Beta-lactam antibiotics, vancomycin, enoxaparin, gabapentin, levetiracetam* |
| | ↓ Clearance | Acute kidney injury | Nephrotoxic medications<br>*Aminoglycosides, NSAIDs, antivirals, contrast* |

ECMO, extracorporeal membrane oxygenation; GI, gastrointestinal; NSAIDs, non-steroidal anti-inflammatory drugs; $V_d$, volume of distribution.

TABLE A3-2

**Defining the Acronym: FAST HUGS BID**

| Definition and Guidelines | Purpose and Principles | Potential Pharmacologic Interventions |
|---|---|---|
| **F**eeding<br>American Society for Parenteral and Enteral Nutrition | Replenish nutritional stores<br>Maintain gut function<br>Data suggest reductions in infectious complications (eg, pneumonia) and mortality with enteral nutrition | Enteral nutrition formulas<br>Gastric motility agents<br>Parenteral nutrition |
| **A**nalgesia | Maintain patient comfort due to interventions, procedures, or chronic pain<br>Analgesia-first approach (ie, analgosedation) to limit sedative agents | Acetaminophen<br>Neuropathic-acting agents<br>Nonsteroidal anti-inflammatory drugs<br>Opioids |
| **S**edation | Maintain patient comfort due to interventions or procedures<br>Respiratory depression for mechanical ventilation and severe respiratory failure<br>Lightest level of sedation possible preferred; daily sedation interruption | Benzodiazepines<br>Dexmedetomidine<br>Ketamine<br>Propofol |
| **T**hromboembolic prophylaxis | Reduction in incidence of venous thromboembolism<br>Balance with risk of bleeding | Enoxaparin<br>Heparin |
| **H**ead-of-bed elevation (45°) | Reduces aspiration events and pneumonia | N/A |
| Stress **U**lcer prophylaxis | Reduction in stress-related mucosal damage (eg, gastrointestinal bleeding)<br>Risk based on risk factors related to bleeding (eg, coagulopathy)<br>Data inconsistent on benefits | Histamine$_2$-receptor antagonists<br>Proton pump inhibitors |
| **G**lycemic control | Prevent hypoglycemia and hyperglycemia in setting of critical illness<br>Studies indicate improved mortality, length of stay, and reduced infections by prevention hyperglycemia<br>Hypoglycemia associated with increased mortality<br>Goal range dependent on population (eg, cardiac) | Basal insulin<br>Insulin infusion<br>Sliding scale insulin |
| **S**pontaneous breathing trial | Limits duration of mechanical ventilation<br>Limits amount of sedatives a patient is exposed to | Decreasing analgesia/Sedation |
| **B**owel regimen | Prevention of ileus with immobility or opiate therapy | Laxatives<br>Stool softeners |
| **I**ndwelling catheter removal | Removal of unnecessary lines and drains to prevent catheter-related infections | N/A |
| **D**e-escalation of antibiotics | Constant evaluation of need/Appropriateness for antibiotics<br>Reduction in multidrug-resistant organisms | Antibiotics |

TABLE A3-3

**Management of Pain, Agitation, and Delirium (PAD)**

| | |
|---|---|
| *Assess for presence of PAD* | |
| Pain | ≥4 times per nursing shift and as needed with NRS, BPS, CPOT |
| Agitation/Sedation | ≥4 times per nursing shift and as needed with RASS and SAS |
| Delirium | Once per nursing shift and as needed with CAM-ICU and ICDSC |
| *Identify and correct inciting factors when possible* | |
| *Establish patient-specific treatment goals* | |
| *Nonpharmacologic management* | |
| Pain | Massage therapy, relaxation techniques, cold packs, manipulative medicine |
| Agitation | Manage pain and discomfort, provide reassurance, support, and empathetic explanations for procedures, diagnostic tests, and diagnoses, avoid excessive noise, immobility, constipation, and physical restraints |
| Delirium | Correct modifiable risk factors, promote diurnal sleep patterns, and orientation to person, place, circumstance, encourage family visitation, provide cognitive stimulation, mobility efforts, and limit sedation |
| *Pharmacologic management* | |
| Pain | Opioids and non-opioids for non-neuropathic, gabapentinoids for neuropathic pain, multimodal options for both |
| Agitation | Analgosedation, propofol, or dexmedetomidine for most patients. Reserve benzodiazepines for specific indications |
| Delirium | Dexmedetomidine for agitated delirium that interferes with weaning from mechanical ventilation. The role of antipsychotics is uncertain |
| Assess response to therapy; if not adequate, consider alternative approach | |
| Determine plan for withdrawal of pharmacotherapy and transition of care | |

BPS, Behavioral Pain Scale; CAM-ICU, Confusion Assessment Method for the ICU; CPOT, Critical Care Pain Observational Tool; ICDSC, Intensive Care Delirium Screening Checklist; NRS, Numeric Rating Scale; RASS, Richmond Agitation Scale; SAS, Sedation Agitation Scale.

TABLE A3-4

**Common ICU Medications Associated with Agitation and Delirium**

| Category | Medication or Class | Agitation | Delirium | With Use | With Withdrawal |
|---|---|---|---|---|---|
| Antibiotic | Cefepime | x | x | x | |
| | Macrolides | x | | x | |
| | Fluoroquinolones | x | x | x | |
| | Voriconazole | | x | x | |
| Anticholinergic | Diphenhydramine | | x | x | |
| Anticonvulsant | Gabapentin | x | | | x |
| | Levetiracetam | x | | x | |
| | Pregabalin | x | | | x |
| Antidepressant | Amitriptyline | x | x | | x |
| | Selective serotonin reuptake inhibitors | x | x | x | x |
| | Serotonin norepinephrine reuptake inhibitors | x | x | x | x |
| Gabaminergic | Benzodiazepines | x | x | x | x |
| Miscellaneous | Corticosteroids | x | x | x | |
| | Digoxin | x | x | x | |
| | Ketamine | x | x | x | x |
| | Psychoactive medications | x | x | x | x |

TABLE A3-5

**Selected Pharmacotherapy Recommendations from the 2013 PAD and the 2018 PADIS Guidelines[a]**

| Recommendation and Guideline Year | Recommendation Grade[b] |
|---|---|
| ***Pain*** | |
| Use opioids as first-line therapy for nonneuropathic pain (2013) | Strong |
| Use multimodal approach to decrease opioid exposure (2013 and 2018) | Conditional |
| Use enteral gabapentin, pregabalin, or carbamazepine with opioids for neuropathic pain (2013 and 2018) | Strong |
| Use enteral gabapentin, pregabalin, or carbamazepine with opioids for pain after cardiovascular surgery (2018) | Conditional |
| Use opioid (2013) or NSAID as an opioid alternative for procedural pain (2018) along with nonpharmacologic interventions | Conditional |
| Use an assessment-driven, protocol-based stepwise approach for pain management (2018) | Conditional |
| Use thoracic epidural anesthesia/analgesia for pain associated with abdominal aortic aneurysm surgery (2013) | Strong |
| Use thoracic epidural analgesia for pain associated with rib fractures (2013) | Conditional |
| ***Agitation/Sedation*** | |
| Use an analgesia-first sedation approach in mechanically ventilated patients (2013) in conjunction with an assessment-driven, protocol-base, stepwise approach for sedation management (2018) | Conditional |
| Titrate sedatives to light (vs. deep) sedation (2013 and 2018) or allow for daily sedative interruption | Strong (2013) and conditional (2018) |
| Propofol or dexmedetomidine are preferred over benzodiazepines for sedation (2013 and 2018) | Conditional |
| ***Delirium*** | |
| Do not use haloperidol or atypical antipsychotics to prevent delirium (2013 and 2018) | Conditional |
| Do not routinely use haloperidol or atypical antipsychotics to treat delirium (2018) | Conditional |
| Use dexmedetomidine for delirium in ventilated patients where agitation is precluding weaning or extubation (2018) | Conditional |

[a]Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med*. 2013;41:263–306; Devlin JW, Skrobik Y, Gelinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the intensive care unit. *Crit Care Med*. 2018;46:e825–e873.

[b]Strong recommendation that applies to almost all patients is based on moderate- to high-quality data where the benefits clearly outweigh the burdens; conditional recommendation that applies to most patients but with significant exceptions based on context using data that are conflicting, low quality, insufficient, or involve limited patient populations where there may be a close balance between benefits and burdens.

TABLE A3-6

**Common ICU Analgesics and Sedatives Administered as Infusions**

| Drug | MOA | Dosing Range[a] | PK/PD Properties | ADR and Special Populations | Comments |
|---|---|---|---|---|---|
| ***Analgesics*** | | | | | |
| Fentanyl | μ agonist | 25–200 mcg/hr<br>LD = 50–100 mcg | 1–2 min onset; 2–4 hr half-life; CYP3A metabolism; no active metabolites | Serotonin syndrome; caution with SSRI and SNRI | Rapid onset and offset<br>Useful in kidney disease<br>Less hypotension vs. morphine<br>Interaction with CYP3A metabolized drugs (midazolam) |
| Hydromorphone | μ agonist | 0.5–4 mg/hr<br>LD = 0.5–2 mg | 5–10 min onset; 2–3 hr half-life; glucuronidation; neurotoxic metabolite | Rare neurotoxicity due to metabolite accumulation in kidney disease | Slower onset than fentanyl, but longer duration<br>No CYP interactions and no serotonin syndrome |
| Morphine | μ agonist | 2–30 mg/hr<br>LD = 2–5 mg | 5–10 min onset; 3–4 hr half-life; demethylation and glucuronidation; active metabolites | Hypotension<br>Accumulation of active metabolites in kidney disease | Venodilation from histamine release |
| Remifentanil | μ agonist | 0.5–15 mcg/kg/hr<br>LD = 1.5 mcg/kg | 1–3 min onset; 3–4 min half-life; esterase metabolism; no active metabolites | Allows frequent evaluations of neurologic function | Drug clearance unaffected by organ dysfunction<br>Use IBW to dose obese patients<br>Costly |
| Ketamine | NMDA receptor antagonist | 0.05–0.4 mg/kg/hr | 1 min onset; 2–3 hr half-life; demethylation; active metabolite | Possible hypertension<br>Psychological disturbances | Does not interfere with respiratory function<br>Useful for opioid-tolerant patients |
| ***Sedatives*** | | | | | |
| Dexmedetomidine | Central $\alpha_2$ agonist | 0.2–1.4 mcg/kg/hr | 5–10 min onset; 3 hr half-life; CYP2A6 metabolism and glucuronidation; no active metabolites | Bradycardia and hypotension | Does not interfere with respiratory function<br>Allows “cooperative sedation”<br>Opioid sparing properties<br>Less delirium than midazolam |

| | | | | | |
|---|---|---|---|---|---|
| Midazolam | GABA agonist | 1–5 mg/hr<br>LD = 1–5 mg | 2–3 min onset; 3–11 hr half-life; CYP3A metabolism; active metabolites | Delirium<br>Context-sensitive half-life | Less hypotension than propofol or dexmedetomidine<br>Allows deep sedation and amnesia<br>CYP3A interactions |
| Propofol | GABA agonist | 5–50 mcg/kg/min | 1–2 min onset; 3–12 hr half-life; CYP2B6 and CYP3A metabolism; no active metabolites | Hypotension<br>PRIS<br>Hypertriglyceridemia<br>Pancreatitis | Allows easy goal titration and neurologic evaluations<br>Can provide deep sedation with amnesia<br>No analgesia<br>Interacts with midazolam |

[a]Typical dosing range for adult ICU patients; analgesic dosing requirements for pain relief may exceed these recommendations as will sedative dosing requirements to produce deep sedation.

ADR, adverse drug reaction; cooperative sedation, ability to participate in care and follow commands; CYP, cytochrome P450; GABA, γ-aminobutyric acid; hr, hour; IBW, ideal body weight; LD, loading dose; min, minute; MOA, mechanism of action; NMDA, *N*-methyl-**d**-aspartate; PK/PD, pharmacokinetic/pharmacodynamic; PRIS, propofol-related infusion syndrome; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

*(See the following chapters for more detailed discussions of these topics:*

- *e/Chapter 25, Critical Care: General Topics in Critical Care, authored by Adrian Wong and Sandra L. Kane-Gill*
- *e/Chapter 26, Critical Care: Pain, Agitation, and Delirium, authored by Gilles L. Fraser and Richard R. Riker*
- *e/Chapter 27, Critical Care: Considerations in Drug Selection, Dosing, Monitoring, and Safety, authored by Erin F. Barreto and Amy L. Dzierba*)