Optimizing Drug Therapy in the Surgical Intensive Care Unit

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INTRODUCTION

Drug therapy has evolved dramatically in recent decades to keep pace with the needs of evolving critical care patients. Drug therapies have become increasingly complex requiring specialized training to optimize care. Pharmacokinetic and pharmacodynamic principles are of high importance in ICUs given the heterogeneity of the patient population. Multiple variables affect the dose, route, and frequency of drug administration needed to achieve a given physiologic response (Table 1).1,2

Falling outside the therapeutic window may lead to treatment failures and/or toxicity, both of which may contribute to increased morbidity and mortality. Several organizations, including the Society of Critical Care Medicine, have endorsed an interdisciplinary model to optimize patient care in ICUs.3

This article provides a review of commonly prescribed medications in SICUs, focusing on sedatives, antipsychotics, neuromuscular blocking agents (NMBAs),

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cardiovascular agents, anticoagulants, and antibiotics. A brief overview of pharma-
cology is followed by practical considerations to aid prescribers in selecting the
best therapy within a given category of drugs to optimize patient outcomes.

SEDATIVES

The indication for pharmacologic sedation in ICUs varies but is often associated with
the need to control anxiety and agitation, especially for those patients requiring
mechanical ventilation (MV) or for procedural sedation.4 Pharmacologic sedation
should only be used after reversible causes of agitation, such as hypoxemia, hypoten-
sion, hypoglycemia, uncontrolled pain, and withdrawal from drugs or alcohol, are cor-
rected. It is imperative to ensure that the environment and analgesia are optimized,
including nonpharmacologic measures, such as frequent and continued
reorientation.5

An objective scale should be used to titrate sedation to a predefined goal, especially
in patients requiring sedation during MV. The most common validated scales used in
ICUs are the Richmond Agitation–Sedation Scale (RASS) and the Ramsay scale.6–8
Historically, sedatives have been used to achieve deep sedation (RASS −2 to −3 or
Ramsay 4–5), but contemporary practice strives to achieve a much lighter level of
sedation (RASS 0 to −1 or Ramsay 2–3), which minimizes negative consequences
of deep and prolonged sedation. Negative consequences of oversedation include
increased incidence and duration of delirium, long-term cognitive dysfunction,
increased duration of MV, and prolonged ICU and hospital length of stay (LOS). Daily
sedation vacations allow sedative drugs to clear from the patient’s system and enable

<table>
<thead>
<tr>
<th>Physiologic Variable</th>
<th>Effect on Drug</th>
<th>Dosing Modification Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic dysfunction</td>
<td>Decreased metabolism, increased risk of coagulopathy</td>
<td>Decrease dose/frequency, conservative anticoagulation</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>Decreased clearance, decreased protein binding</td>
<td>Decrease dose/frequency, avoid nephrotoxins</td>
</tr>
<tr>
<td>Advanced age</td>
<td>Decreased metabolism and clearance, increased sensitivity to drug</td>
<td>Decrease dose/frequency, avoid medications on Beers list</td>
</tr>
<tr>
<td>Malnutrition (hypoalbuminemia)</td>
<td>Decreased protein binding</td>
<td>Decrease dose/frequency</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>Decreased metabolism, intracellular electrolyte shift</td>
<td>Decrease dose/frequency, conservative electrolyte supplementation</td>
</tr>
<tr>
<td>Burns</td>
<td>Hypermetabolic state, alteration in protein binding, increased Vd</td>
<td>Increase dose/frequency</td>
</tr>
<tr>
<td>Head injury</td>
<td>Increased clearance</td>
<td>Increase dose/frequency</td>
</tr>
<tr>
<td>Obesity</td>
<td>Increased Vd for lipophilic drugs</td>
<td>Increase dose</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Increased Vd</td>
<td>Increase dose, avoid teratogens</td>
</tr>
<tr>
<td>Volume overload</td>
<td>Increased Vd, decreased SC and IM absorption</td>
<td>Increase dose, avoid SC and IM routes of administration</td>
</tr>
</tbody>
</table>

Abbreviations: SC, subcutaneous; Vd, volume distribution; IM, intramuscular.

more reliable neurologic assessment. When accompanied by protocol-driven breathing trials, sedation vacations demonstrate improved outcomes as measured by decreased duration of MV, decreased ICU LOS, and decreased mortality.9 Given that the RASS and the Ramsay scale are of no value in chemically paralyzed patients, bispectral index (BIS) monitoring, which is a numeric algorithmic analysis of an electroencephalogram, may be considered. The use of BIS is not well studied outside the operating room.

Many clinical factors affect drug selection, such as the indication for sedation, physiologic parameters that affect drug distribution, metabolism and elimination, adverse effects of the drug, institution formulary and guidelines, anticipated duration of sedation, and prescriber preference. Sedatives commonly used in ICUs are reviewed, with a focus on efficacy, safety, and variables to consider when determining the drug of choice for a given clinical circumstance (Table 2).

**Propofol**

Propofol (Diprivan) possesses hypnotic, anxiolytic, and amnestic properties but lacks analgesic effects.10,11 Additionally, it acts as an anticonvulsant, decreases cerebral oxygen consumption, and reduces intracranial pressure (ICP). As a result, propofol is particularly useful in postsurgical patients, patients in status epilepticus, and those with traumatic brain injury resulting in elevated ICP. Propofol has several proposed mechanisms of action; it acts on multiple receptors to interrupt neural transmission in the central nervous system (CNS), including γ-aminobutyric acid (GABA), N-methyl-D-aspartate (NMDA), glycine, nicotinic, and muscarinic receptors.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset of Action (IV)</th>
<th>Use</th>
<th>Dose</th>
<th>Safety Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol</td>
<td>~1 min</td>
<td>RSI, PS, short-term sedation</td>
<td>RSI, PSI: 0.5–1 mg/kg Infusion: 5–65 μg/kg/min</td>
<td>PRIS with prolonged and high dose</td>
</tr>
<tr>
<td>Midazolam</td>
<td>2–5 min</td>
<td>RSI, PS, short-term sedation</td>
<td>PRN: 0.02–0.08 mg/kg q1–2 h Infusion: 0.04–0.2 mg/kg/h</td>
<td>Accumulation with prolonged and high dose, DDIs</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>5–20 min</td>
<td>Short-term, and long-term sedation</td>
<td>PRN: 0.02–0.06 mg/kg q2–4 h Infusion: 0.01–0.1 mg/kg/h</td>
<td>PG toxicity, titrate slowly to avoid oversedation</td>
</tr>
<tr>
<td>Flumazenil</td>
<td>1–2 min</td>
<td>BZD reversal</td>
<td>0.2 mg q1–2 min</td>
<td>Over reversal may precipitate seizure</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>5–10 min</td>
<td>Short-term sedation</td>
<td>Infusion: 0.2–1.5 μg/kg/min</td>
<td>Lacks amnestic properties, hypotension</td>
</tr>
<tr>
<td>Ketamine</td>
<td>&lt;1 min</td>
<td>RSI, PS</td>
<td>PRN: 0.5–2 mg/kg</td>
<td>Emergence reaction</td>
</tr>
<tr>
<td>Etomidate</td>
<td>&lt;1 min</td>
<td>RSI, PS</td>
<td>PRN: 0.3 mg/kg</td>
<td>Adrenal suppression</td>
</tr>
</tbody>
</table>

Abbreviations: DDIs, drug-drug interactions; PRN, as-needed intermittent dosing; PRIS, propofol infusion syndrome; PS, procedural sedation; RSI, rapid sequence intubation.

The high lipid solubility of propofol allows for rapid distribution into the CNS, resulting in an onset of action of approximately 1 minute. Its rapid hepatic metabolism yields a short half-life, allowing for rapid emergence from sedation within a few minutes after a single dose. Emergence is seen within 10 to 30 minutes after a short-term (<72 hours) continuous infusion, making frequent neurologic assessment feasible when targeting light sedation. Accumulation may occur secondarily to the drug’s lipophilicity; the emergence time becomes prolonged (3–4 hours) with extended duration of infusion (>72 hours). Targeting deeper levels of sedation also yields a significantly longer emergence time and is generally discouraged. Clinical trials find propofol similar to midazolam for sedation in ICUs as measured by safety and efficacy, although time to wakefulness was consistently shorter in the propofol group.12–16 Acquisition cost for propofol is higher than with either midazolam (Versed) or lorazepam (Ativan) but less than dexmedetomidine (DEX) (Precedex). Propofol use has not yet been associated with the development of delirium.

Respiratory depression, hypotension (attributed to systemic vasodilation, especially in hypovolemic patients), arrhythmias, and hypertriglyceridemia are common dose-dependent adverse effects of propofol. Although less severe at doses used for procedural sedation (1 mg/kg) compared with those used for induction and maintenance of anesthesia or continuous sedation (2–2.5 mg/kg), they remain clinically significant. Low-dose propofol used concurrently with ketamine (Ketalar) can lessen the impact of these adverse effects (discussed later).17 Propofol is suspended in a 10% lipid emulsion containing egg lecithin and soybean oil and should be avoided in patients with known allergies to these compounds. The lipid content also results in unintentional caloric intake and should be factored into nutritional assessments accordingly.

Propofol can be administered by intravenous (IV) push for procedural sedation or as a continuous IV infusion for ongoing sedation in ICUs. Propofol infusion syndrome (PRIS) may occur with prolonged and/or high-dose infusions.18 PRIS, defined as metabolic acidosis and cardiac dysfunction, along with one of the following: rhabdomyolysis, hypertriglyceridemia, or renal failure, was reported in 1.1% of patients in one prospective trial.19 Although rare, the clinical significance is high and can be life threatening, with mortality rates ranging from 18% to 83%.19,20 Rate and duration of infusion are strong risk factors for the development of PRIS, and it is recommended that infusions greater than 65 µg/kg/min for longer than 48 hours be avoided.19 Other contributing factors include underlying mitochondrial disease or fatty acid oxidation defects, young age, critical illness of the CNS or respiratory origin, exogenous catecholamine or glucocorticoid administration, or inadequate carbohydrate intake.19 When using high-dose or prolonged infusion of propofol, it is recommended that triglycerides, pH, lactate, and creatine kinase be followed at least daily, because abnormal values are associated with the development of PRIS. Propofol should immediately be discontinued if PRIS is suspected, although complications and even death may ensue after propofol discontinuation because there is no antidote for PRIS.

**Benzodiazepines**

Benzodiazepines (BZDs) have been used for decades in ICUs. They possess anxiolytic, amnestic, sedative, and anticonvulsant properties.4,10 These actions are modulated by BZDs binding to GABA receptors, resulting in neuronal inhibition. BZDs are efficacious for rapid sequence intubation (RSI), procedural sedation, sedation during MV, and substance withdrawal. They vary by potency, duration of action, and lipid solubility, making certain BZDs more suitable for specific indications. High lipid solubility, as seen with midazolam and diazepam (Valium), yields rapid onset of action due to the increased blood-brain barrier permeability whereas the more water-soluble
lorazepam has a slower onset of effect on the CNS. Midazolam and lorazepam are commonly used for sedation in ICUs, lorazepam and diazepam for seizures or alcohol withdrawal, and diazepam for muscle spasms. Alcohol withdrawal protocols, such as the Clinical Institute Withdrawal Assessment for Alcohol, are not well validated in ICUs. They may be used in appropriate and communicative patients but should generally be avoided in most patients.

BZDs are metabolized in the liver by oxidative cytochrome P450 enzyme systems and/or by glucuronide conjugation. This is of particular importance in SICUs given that acute inflammation after elective surgery is associated with a significant decline in cytochrome P450 activity, thereby directly affecting the metabolism of BZDs. Doses should be adjusted downward accordingly.

Hypotension is a common adverse effect seen with BZDs, especially in patients who are critically ill, elderly, or have hepatic dysfunction. To minimize the impact of hemodynamic changes, initial dosing should be conservative and titrated slowly to effect. Although BZDs are effective sedatives, they are associated with increased risk for developing delirium. Delirium is associated with increased mortality. It is unclear how these data will affect future use of BZDs in ICUs.

**Midazolam**

Midazolam is a short-acting BZD commonly used in ICUs. It can be used intermittently, usually dosed 2 mg to 4 mg IV every 1 to 2 hours (0.02–0.08 mg/kg) and titrated to effect or titrated as a continuous infusion (0.04–0.2 mg/kg/h) to maintain more consistent sedation if intermittent dosing fails. Due to its high lipophilicity, it quickly and readily crosses the blood-brain barrier and rapidly induces its sedative effects but is not a desirable option as a single dose for the treatment of an acute seizure due to its rapid redistribution out of the CNS. It is useful as a continuous infusion for patients with status epileptics. Midazolam distributes extensively to adipose, leading to drug accumulation over time and an increasing duration of action with prolonged use. To prevent excessive accumulation, midazolam should only be used for short-term sedation (<72 hours) and used with caution in those with renal failure. In these patients, it is not uncommon for time to wakefulness after cessation of drug to be measured in days, not hours, if not dosed appropriately.

Midazolam is hepatically metabolized to active metabolites, which accumulate extensively in patients with renal failure. It is subjected to significant drug-drug interactions as both a substrate and inhibitor of several cytochrome P450 pathways, including 3A4. The azole antifungals, macrolides, and nondihydropyridine calcium channel blockers (CCBs) may result in increased midazolam levels, whereas carbamazepine (Tegretol) and rifampin (Rifadin) may result in reduced midazolam levels. Drug dosages need to be adjusted accordingly and more careful monitoring may be required.

**Lorazepam**

Lorazepam is a long-acting BZD with approximately 2 to 3 times the potency of midazolam. It is effective when dosed intermittently, usually at a starting dose of 1 mg to 2 mg every 2 to 4 hours as needed. If the intermittent dosing strategy fails, lorazepam may also be used as a continuous infusion after an appropriate loading dose for long-term sedation (>72 hours) but should be dosed with caution. A standard starting infusion rate is 4 mg/h. Owing to its long half-life, it is not easily titrated. Conventional frequent titration is every 5 to 15 minutes and results in an initially slow clinical response but ultimately leads to deep oversedation because the second, third, fourth, and fifth dose adjustments are made before the physiologic effects of the first dose
adjustment are fully observed. Intermittent boluses may be administered during an infusion, but the infusions should be titrated no more frequently than every 8 hours. Lorazepam remains in the CNS longer than midazolam or diazepam, making it a good agent for the acute treatment of seizures.

The IV formulation of lorazepam contains propylene glycol (PG) as a diluent that accumulates in the setting of renal failure. PG toxicity primarily manifests as an anion gap metabolic acidosis and CNS depression.\textsuperscript{27,28} Because these signs may be easily overlooked in a critically ill patient, proactive monitoring is necessary. In place of serum PG concentrations, a calculated osmol gap of greater than 10 mOsm/L to 12 mOsm/L may be used to identify patients with PG accumulation.\textsuperscript{27,28} Risk factors include infusions greater than 0.1 mg/kg/h, a history of alcohol abuse, hepatic or renal dysfunction, and concomitant metronidazole usage.\textsuperscript{28}

**Flumazenil**

Flumazenil (Romazicon) is an effective BZD antidote. It attenuates BZD sedative and respiratory depressive effects. It acts in the CNS by competitively inhibiting the BZD binding site of the GABA receptor. Flumazenil use should be avoided if at all possible and reserved for patients whose BZD toxicity is life threatening. The starting dose is 0.2 mg IV given over 30 seconds with an onset of action of 1 to 2 minutes and peak effects in about 6 minutes. Additional doses may be given every 1 minute until the desired level of consciousness is achieved, up to a maximum of 3 mg. Partial responders at 3 mg may be advanced to a maximum dosage of 5 mg. If a response is not seen at that dose, then BZD toxicity is unlikely. Some BZDs have a longer duration of action than flumazenil, necessitating redosing, which may be done safely at 20-minute intervals. Rapid BZD reversal may result in acute withdrawal for patients with BZD dependence, which may present as seizure or severe agitation.

**Dexmedetomidine**

DEX selectively stimulates centrally acting, $\alpha_2$-adrenergic receptors with sympatholytic, sedative, and analgesic properties but lacks GABA effects.\textsuperscript{29} Mechanistically, it is similar to clonidine but has a significantly higher affinity for the $\alpha_{2a}$ receptor. Adverse hemodynamic effects, however, such as bradycardia, sinus arrest, and hypotension, may occur. These effects are more pronounced in patients with labile hemodynamics at baseline or those requiring concurrent vasopressor therapy and are more likely to occur when administering a loading dose. For this reason, a loading dose is no longer routinely recommended. These effects may still be seen, however, with the maintenance infusion regardless of loading dose. A starting dose of 0.4 $\mu$g/kg/h is reasonable for most patients and should be titrated in increments of 0.1 $\mu$g/kg/h no more frequently than every 10 to 15 minutes to a maximum of 1.5 $\mu$g/kg/h.

The quality of sedation induced by DEX differs significantly from that of other sedative drugs. Patients are generally calm and sedated but arousable and even interactive, whereas BZDs and propofol often render patients sedated with limited, if any, interactive ability. DEX exhibits some analgesic properties, although concurrent use of analgesics is still indicated. More importantly, DEX lacks amnestic properties. As a result, DEX should not be used as a sole sedative in the setting of neuromuscular blockade where deeper sedation and amnesia are desired. Unlike BZDs and propofol, DEX has minimal effect on respiratory drive and does not suppress electroencephalogram. Therefore, BIS monitoring is not an appropriate means of measuring sedation for these patients.

In the critical care setting, DEX has been compared with lorazepam and midazolam in registration trials, resulting in Food and Drug Administration (FDA) approval for
short-term sedation in intubated patients.\textsuperscript{30,31} These studies suggest DEX is a safe and effective alternative and may yield shorter duration of MV and ICU LOS. In a subsequent economic analysis, the reduced duration of MV and ICU LOS were believed responsible for significantly lower total ICU costs compared with midazolam infusion.\textsuperscript{32} Controversy exists surrounding the suggestion that DEX is associated with less delirium and coma in mechanically ventilated patients. Due to poor study design and composite endpoints used, further investigation is warranted to definitively answer this question. Subsequent studies demonstrate DEX to be similar to midazolam and propofol in maintaining light to moderate sedation in patients receiving prolonged MV. Duration of MV was reduced in patients receiving DEX compared with midazolam but not compared with propofol.\textsuperscript{33} The safety and efficacy of DEX have not been established in trauma patients.\textsuperscript{34}

Current research is focused on finding the optimal population for the use of DEX, for example, defining its role for optimizing sedation while minimizing delirium and in patients at high-risk for alcohol withdrawal. Most data are limited to animal studies and human case reports, but additional human data are forthcoming.\textsuperscript{35} Additional data support the use of DEX in cardiothoracic surgery patients. The routine use of DEX as a first-line therapy for sedation in all patients, however, has been slow to evolve.

\textbf{Ketamine}

Ketamine is a nonbarbiturate anesthetic that also possesses analgesic properties.\textsuperscript{36} The precise mechanism of action is not fully elucidated, but it is believed to bind to NMDA receptors in the CNS and to interact with opiate, norepinephrine, serotonin, and muscarinic cholinergic receptors as well.\textsuperscript{36} The most common adverse effects are emergence phenomena (described as nightmares, hallucinations, delirium, and visual disturbances), transient elevations in blood pressure (BP), including ICP, and heart rate, respiratory drive stimulation, and emesis. It should be avoided in patients with elevated ICP, active myocardial ischemia, or a history of coronary artery disease when alternatives, such as etomidate or BZDs, are available. Its role in procedural sedation at a dose of 1 mg/kg IV is largely limited in the adult population due to the high incidence (10\%–20\%) of emergence phenomena, although these phenomena are less common (<2\%) in pediatrics.\textsuperscript{36,37} Ketamine may be used synergistically with propofol for procedural sedation, allowing for lower doses of each to be used (0.5 mg/kg each).\textsuperscript{17} In addition to using lower doses, it is believed that the addition of ketamine mitigates some of the hypotensive and respiratory depressive effects of propofol. Ketamine was prospectively compared with etomidate for RSI and found to have similar efficacy and safety, except for a higher percentage of etomidate patients developing adrenal insufficiency.\textsuperscript{38} The investigators concluded ketamine is a safe and valuable alternative to etomidate for endotracheal intubation in critically ill patients and should be considered in those with sepsis.

When used at lower doses as a continuous infusion (10–40 mg/h), it may be used as an adjunct to opioids for analgesia and is opioid sparing.\textsuperscript{36} This practice is of particular benefit in the perioperative setting. Although an oral formulation is not commercially available and is poorly bioavailable, it may be compounded from the IV formulation and used as a bridge to wean off a continuous infusion. Emergence phenomena are much less common at these lower doses.

\textbf{Etomidate}

Etomidate (Amidate) is a short-acting hypnotic with GABA effects. Its minimal cardiovascular and respiratory effects make it an ideal agent for RSI and induction for
anesthesia. Historically it was used as a continuous infusion for the maintenance of sedation, but it was later associated with increased mortality when used in this manner.\textsuperscript{39} It was subsequently identified that etomidate suppresses the hypothalamus-pituitary-adrenal axis, thus resulting in adrenal suppression. Its use as a continuous infusion is obsolete; however, its role for RSI is still prominent but not without controversy. Although safe and effective for most patients, some data suggest that even a single dose (0.3 mg/kg) for RSI may contribute to worse outcomes in critically ill septic patients.\textsuperscript{40,41} Conservative management dictates avoiding the drug in these patients as long as therapeutic alternatives, such as BZDs or ketamine, are available.

**PSYCHOTROPICS**

Delirium is manifested by an acute onset of fluctuating disturbances in consciousness, accompanied by inattention, disorganized thinking, and perceptual disturbances. It may be hyperactive, hypoactive, or manifest features of both.\textsuperscript{42} The development of delirium is of particular concern in ICUs because it is associated with increased morbidity, prolonged neurologic deficits, mortality, and health care cost.\textsuperscript{26,43–47} Risk factors are multifactorial and can be divided into host factors, factors of acute illness, and iatrogenic and environmental factors. Nonpharmacologic interventions focus on minimizing the impact of these factors by correcting reversible causes, optimizing the environment, and initiating early ambulation.\textsuperscript{48,49} Pharmacologic interventions are focused in 2 areas: the prevention and treatment of delirium.

A standardized tool for the detection of delirium is recommended for use in ICUs.\textsuperscript{4} The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and Intensive Care Delirium Screening Checklist (ICDSC) have been validated in ICUs and are commonly used. The CAM-ICU is a dichotomous scale simply identifying if delirium is present or not, whereas the ICDSC is a scale of 1 to 8; a score of greater than or equal to 4 has a 99% sensitivity correlation for a psychiatric diagnosis of delirium.\textsuperscript{50–53} The 2 scales were prospectively compared with each other and yielded comparable results.\textsuperscript{54} Given the numeric scale, the ICDSC may be better at determining patients trending toward and away from delirium and, therefore, may be more useful. Use of an objective tool allows for quick and reliable detection of delirium by both nurses and physicians.\textsuperscript{55} A more comprehensive look at the disease state and treatment options may be found in one of several review articles.

**Delirium Prevention**

Two approaches for the pharmacologic prevention of delirium are described. First is the avoidance of certain precipitating drugs, such as sedatives (especially BZDs) and anticholinergics.\textsuperscript{22–24} This also includes avoiding medications on the Beers list for elderly patients.\textsuperscript{56,57} Although these medications are not clearly associated with increased mortality, it is generally accepted that minimizing these medications reduces adverse drug effects.\textsuperscript{58} The second approach is to proactively administer drugs with the intent of delirium prophylaxis. A few drugs have been studied for the prevention of delirium in the perioperative setting, including the antipsychotics haloperidol (Haldol), risperidone (Risperdal), and olanzapine (Zyprexa).\textsuperscript{59–61} Although outcomes demonstrated mixed results, a Cochrane review concluded that none of these agents is generally effective for the prevention of delirium.\textsuperscript{49} Since the Cochrane review was published, a large (n = 457) prospective, double-blind, randomized, placebo-controlled trial compared haloperidol infusion to placebo for the prevention of delirium in noncardiac postoperative ICU elderly patients.\textsuperscript{62} The incidence of
delirium was 15.3% in the haloperidol group versus 23.2% in the placebo group. The impact of this study on practice is yet to be seen.

Cholinesterase inhibitors, donepezil (Aricept) and rivastigmine (Exelon) have also been studied in the prevention of delirium in ICU patients but have yielded negative results. A recent meta-analysis of 24 trials using DEX failed to show a reduction in delirium. Other pharmacologic approaches to delirium prevention have focused on minimizing sleep deprivation and optimizing the use of narcotics in the postoperative setting, but outcome data are limited.

**Delirium Treatment**

The treatment of delirium should be initiated only after underlying causes are evaluated and corrected and after analgesia and sedation are optimized. Only a few small, prospective trials have evaluated the use of typical and atypical antipsychotics for the treatment of delirium. Although it is unclear which class yields better outcomes, it is generally accepted that the atypicals, which predominately work on serotonin receptors, are at least as well tolerated as typicals, which act on dopamine receptors (Table 3). All of these agents lack FDA approval for the treatment of ICU delirium; therefore, recommended doses are based on clinical experience and clinical trials in critically ill patients rather than package inserts (Table 4). Antipsychotic agents are associated with increased mortality when used in elderly patients with pre-existing dementia, and, therefore, all now carry a black box warning to this effect.

**Typical Antipsychotics: Haloperidol and Chlorpromazine**

Haloperidol is the most commonly prescribed typical antipsychotic, largely due to the high incidence of adverse effects associated with other typical agents. Haloperidol and chlorpromazine (Thorazine) can successfully treat agitation and delirium in hospitalized patients. Haloperidol remains the drug of choice according to the Society of Critical Care Medicine, although these guidelines are more than a decade old; an update is expected later this year. Haloperidol is dosed intermittently on an as-needed basis, loaded in a stacked fashion, scheduled, and as a continuous infusion, although the optimal dosing strategy has not yet been clearly defined. QT prolongation remains a concern with haloperidol and, therefore, routine ECG monitoring is recommended. Proactive monitoring for neuroleptic malignant syndrome and extrapyramidal symptoms (EPSs) is also recommended. The drug should be immediately discontinued if these occur.

**Atypical Antipsychotics: Quetiapine, Olanzapine, Risperidone, and Ziprasidone**

With quetiapine (Seroquel), the predominantly antihistaminic mechanism of action, short half-life (which facilitates dose titration), low propensity to alter the QT interval,

<table>
<thead>
<tr>
<th>Drug</th>
<th>Anticholinergic</th>
<th>Sedation</th>
<th>EPS</th>
<th>Orthostatic Hypotension</th>
<th>Metabolic</th>
<th>QT Prolongation</th>
</tr>
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<tbody>
<tr>
<td>Haloperidol</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
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</table>

Abbreviations: +, none to minimal activity; ++, moderate activity; ++++, marked activity.
and rare reports of EPSs make it a viable option for treatment of delirium. A small placebo-controlled prospective pilot study of the treatment of ICU delirium suggests that quetiapine when added to as-needed haloperidol results in faster delirium resolution, less agitation, and a greater rate of transfer to home or rehabilitation.73 The drug is generally well tolerated, but robust efficacy and safety data are lacking. Larger studies are warranted to validate these findings.

Olanzapine is an effective alternative to haloperidol for the treatment of ICU delirium, although its undesirable sedative properties are of concern, especially in those with hypoactive delirium.74,75 Although subsequent prospective studies found no difference between olanzapine, risperidone, and haloperidol for the treatment of delirium, none of the patients were in an ICU.76,77 These results may not be applied to ICU patients; therefore, initial olanzapine findings have not been further validated.

A prospective pilot study randomized ICU patients to receive ziprasidone (Geodon), haloperidol, or placebo for the treatment of delirium.78 Treatment with either antipsychotic did not improve the number of days alive without delirium or coma nor did it increase adverse outcomes compared with placebo.

Limited outcome data are available to aid practitioners in selecting antipsychotic therapy for the treatment of ICU delirium. Haloperidol remains the standard of care for the treatment of ICU delirium, although quetiapine offers a therapeutic alternative

<table>
<thead>
<tr>
<th>Drug</th>
<th>Common ICU Dose</th>
<th>Routes Available</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>2 mg IV, increasing dose q15–20 min prn until response achieved, then scheduled q4–6 h until delirium resolved and taper off; alternatively may continue IV or po q2–4 h prn in lieu of scheduled dosing</td>
<td>IM (often used IV but not FDA approved), po, liquid</td>
<td>QTc prolongation and torsades de pointes with higher doses, neuroleptic malignant syndromes, EPS</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>25–50 mg po q6–12 h prn, increased by 25–50 mg daily to max of 400 mg/d</td>
<td>po</td>
<td>Sedation, hypotension</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.25–1 mg po q6–12 h prn, increased by 0.5–1 mg every 2–3 d to max dose 6 mg/d</td>
<td>po, liquid, ODT</td>
<td>EPS</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2.5–5 mg po q6–12 h prn, increased by 2.5–5 mg daily to max dose 20 mg/d</td>
<td>IM, po, ODT</td>
<td>Sedation</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>20–40 mg po q6–12 h prn, increased by 20 mg daily to max dose of 160 mg/d</td>
<td>IM, po</td>
<td>QTc prolongation</td>
</tr>
</tbody>
</table>

**Abbreviations:** IM, intramuscular; EPS, extrapyramidal; max, maximum; ODT, orally disintegrating tablet.

a Based on clinical experience and clinical trials in critically ill (nonelderly, nonpsychiatric, non-demented) patients, doses should be reduced by at least 50% when used in elderly patients. Regularly reassess for de-escalation to an as needed basis and discontinue once no longer clinically indicated.
with potentially fewer adverse drug effects. Olanzapine may be considered an alternative to haloperidol and quetiapine, although concerns regarding sedation are legitimate and must be considered. Risperidone’s role may be similar to olanzapine’s, although concerns for EPSs and hypotension may limit its use. The role of ziprasidone in ICUs has not yet been defined, and concerns for ECG changes are legitimate. Once delirium has resolved, drug treatment is no longer indicated and should be discontinued. Minimizing patients’ exposure to antipsychotic therapy is preferred, regardless of which agent is used.

**NEUROMUSCULAR BLOCKING AGENTS**

NMBAs have been used for many years in ICUs. As the name implies, these agents disrupt the transmission of impulses to the motor endplate, resulting in muscle paralysis. Single doses may be used for procedures, including RSI, line placement, and dressing changes. Short-term use during transport between and within health care facilities is described, which provides an element of safety when providers have limited access to patients, such as in an elevator, ambulance, or helicopter. This practice is the standard of care for critically wounded military personnel during aeromedical evacuation. Commonly cited indications for long-term use are facilitating MV, ablation of muscle spasms (tetanus), control of ICP, and decreasing oxygen demand. Placebo-controlled randomized trials are generally lacking for these agents. Most studies make the assumption that NMBAs are indicated and, therefore, compare one agent to another, or are dose-finding studies comparing different dosing strategies of the same agent. Given that the use of sustained NMBAs poses significant risks, it should only be considered after efforts to provide adequate sedation have failed to achieve the desired therapeutic goals. During NMBAs use, clinicians should regularly assess for the opportunity to discontinue therapy. The adverse effects associated with the use of NMBAs are discussed.

**Depolarizing Agent: Succinylcholine**

NMBAs are divided into 2 main groups: depolarizing agents and nondepolarizing agents. Depolarizing agents mimic acetylcholine (ACh) at the neuromuscular junction (NMJ), yielding sustained depolarization and prevention of muscle contractions. The depolarization of the postsynaptic membrane causes repetitive excitation of the motor end plate, resulting in fasciculation. Succinylcholine (Anectine) is the only available depolarizing agent in the United States. Its primary use is for RSI and it is used for this indication more than any other NMBA due to its rapid onset and short duration of action (Table 5). Because succinylcholine is metabolized more slowly than ACh, its prolonged effect on muscle cells results in an extracellular shift of potassium, which may lead to dysrhythmias or even cardiac arrest. On average, the rise in serum potassium is modest, at 0.5 meq/L, although it can be higher in patients predisposed to hyperkalemia (renal failure, burns, crush injury, and severe infection). Succinylcholine should be avoided in these patients. It should also be avoided in patients with a family history of malignant hyperthermia. Other adverse effects include bradycardia, hypotension, and elevated intraocular pressure, but the drug is generally well tolerated.

**Nondepolarizing Agents: Atracurium, Cisatracurium, Rocuronium, Vecuronium, and Pancuronium**

Nondepolarizing agents, which resemble ACh, competitively inhibit ACh receptors in the NMJ; the prevention of ACh binding results in blockade of muscle contraction.
Although these agents vary in onset and duration of action, they are generally too slow acting for routine RSI (Table 6). The only exception to this is rocuronium (Zemuron), which exhibits an onset of action nearly as rapid as succinylcholine. Route of elimination and adverse effects are of highest importance when selecting an agent to be used as a continuous infusion, the primary role of nondepolarizing agents. The nondepolarizing agents are further divided in 2 subgroups, the benzylisoquinoliniums and the aminosteroidals.

The benzylisoquinoliniums, atracurium (Tracrium) and cisatracurium (Nimbex), are eliminated via Hofmann elimination, a spontaneous degradation in plasma and tissue at normal body pH and temperature, and by ester hydrolysis. Elimination is not dependent on renal or hepatic function. Atracurium yields the active metabolite laudanosine, which may accumulate and induce seizures. It also causes mast cell degranulation, which releases histamine resulting in vasodilation and hypotension. This hypotensive effect has largely limited its use, especially in the critically ill patient population. These effects are also seen with cisatracurium but they are significantly less pronounced, thereby making it the preferred agent, especially in hemodynamically unstable patients. Tachyphylaxis is associated with prolonged use of both agents, whereby progressive upward dose titration is required to maintain neuromuscular blockade. Upward dose titration, especially in prolonged use, can have a significant impact on ICU drug costs.

The remaining NMBAs comprise the aminosteroidal group. With the exception of tubocurarine (Curare), Pancuronium (Pavulon) is the oldest N MBA and was the mainstay of therapy from the 1970s through the early 1980s because therapeutic alternatives were lacking. Although effective, pancuronium is poorly tolerated because of its vagolytic activity, which results in tachycardia, hypertension, and increased myocardial oxygen demand. Its long duration of action (60–100 minutes) makes it a difficult agent to effectively titrate. Vecuronium (Norcuon) became the mainstay of therapy with its introduction in 1984 and remains widely used today. It lacks vagolytic activity and, therefore, exerts minimal hemodynamic effects. In addition, its shorter duration of

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg)</th>
<th>Onset (s)</th>
<th>Duration (min)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinylcholine</td>
<td>1.5</td>
<td>&lt;60</td>
<td>10</td>
<td>Preferred agent; contraindicated in malignant hyperthermia; avoid in patients predisposed to hyperkalemia; higher doses needed in patients with myasthenia gravis</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>0.6–1.2</td>
<td>60–90</td>
<td>25–50</td>
<td>Preferred agent when unable to use succinylcholine; may require a subsequent dose of sedative to outlast paralytic effects</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>Avoid due to slow onset of action</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>Avoid due to slow onset of action</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atracurium</td>
<td>Avoid due to histamine release (hypotension) and slow onset of action</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancuronium</td>
<td>Avoid due to vagolytic action (hypertension and tachycardia) and long duration of action</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Table 5  
Neuromuscular blockers used for rapid sequence intubation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg)</th>
<th>Onset (s)</th>
<th>Duration (min)</th>
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<td>Preferred agent when unable to use succinylcholine; may require a subsequent dose of sedative to outlast paralytic effects</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>Avoid due to slow onset of action</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>Avoid due to slow onset of action</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atracurium</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancuronium</td>
<td>Avoid due to vagolytic action (hypertension and tachycardia) and long duration of action</td>
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<td></td>
<td></td>
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<table>
<thead>
<tr>
<th>Drug</th>
<th>Loading Dose (mg/kg)</th>
<th>Continuous Dose (µg/kg/min)</th>
<th>Onset of Action (min)</th>
<th>Duration of Action (min)</th>
<th>Elimination</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atracurium</td>
<td>0.4–0.5</td>
<td>2–15</td>
<td>2–3</td>
<td>20–35</td>
<td>Hofmann elimination (dependent on pH and temperature)</td>
<td>Tachyphylaxis associated with prolonged use; seizure risk due to accumulation of active metabolite laudanosine; histamine release results in hypotension</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>0.1</td>
<td>0.5–10</td>
<td>1.5–2</td>
<td>20–35</td>
<td>Hofmann elimination (dependent on pH and temperature)</td>
<td>Tachyphylaxis associated with prolonged use</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>0.04–0.1</td>
<td>1–2</td>
<td>2–3</td>
<td>60–100</td>
<td>Renal 57%–89%; hepatic 15%; biliary (11%)</td>
<td>Vagolytic activity causes tachycardia, hypertension, and increased CO; significant accumulation in renal failure</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>0.1</td>
<td>1–2</td>
<td>2.4–3.8</td>
<td>25–60</td>
<td>Biliary 30%–50%; hepatic 30%; renal 15%–30%</td>
<td>Accumulation seen in renal and hepatic failure</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>0.4–0.5</td>
<td>4–16</td>
<td>1–1.5</td>
<td>25–50</td>
<td>Biliary extensive; renal up to 30%</td>
<td>Accumulation seen in renal failure</td>
</tr>
</tbody>
</table>

action (35–45 minutes) allows for easier dose titration. It is primarily eliminated via the bile, although hepatic and renal elimination play a significant role. Accumulation with continued administration may result in a prolonged effect in the setting of renal or hepatic failure. Rocuronium is similar to vecuronium with regard to tolerability and accumulation seen in the setting of renal failure. Its onset of action, however, is more rapid than any other nondepolarizing agent, making it a feasible option for RSI.

**Adverse Drug Effects**

The use of NMBAs is not without adverse effects. The most common complication is prolonged recovery, defined as a 50% to 100% longer time to recovery than predicted by pharmacologic parameters. This phenomenon is more commonly reported with pancuronium and vecuronium due to accumulation of NMBAs and/or active metabolites; however, this observation may be due in part to these agents having longer use in clinical practice compared with the newer benzylisoquinoliniums.85 Another, more sinister, complication is acute quadruplegic myopathy syndrome. It is characterized by the triad of acute paresis, myonecrosis, and increased creatine kinase.86,87 Caution should be used in the setting of concomitant corticosteroid administration due to its association with increased risk of developing acute quadruplegic myopathy syndrome.79 Acceptor upregulation, as seen in spinal cord injury, results in resistance to nondepolarizing agents but increased sensitivity to depolarizing agents. Conversely, down-regulation, as seen in myasthenia gravis, leads to increased sensitivity to nondepolarizing agents. Several medications may affect the action of NMBAs (Box 1). Most medications that interact have a potentiating effect on the action of NBMA, whereas fewer inhibit NMBA activity.79,88

**Monitoring**

Patients should be closely monitored during NMBA administration to assess the degree of neuromuscular blockade.79,89 Peripheral nerve stimulation, as used in the operating room, is the most common method. Train-of-four of 1 to 2 out of 4, along with clinical assessment, is recommended for monitoring patients receiving NMBA.79 Dosing of NMBA guided by train-of-four monitoring may yield faster recovery after paralysis, result in fewer adverse effects, and provide some pharmacoeconomic

<table>
<thead>
<tr>
<th>Potentiate</th>
<th>Antagonize</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmics: procainamide, quinidine, verapamil</td>
<td>Antiepileptics: carbamazepine, phenytoin</td>
</tr>
<tr>
<td>Antibiotics: aminoglycosides, tetracyclines, clindamycin</td>
<td>Other: ranitidine, theophylline</td>
</tr>
<tr>
<td>Cardiovascular medications: β-blockers, CCBs</td>
<td></td>
</tr>
<tr>
<td>Cations: calcium, magnesium</td>
<td></td>
</tr>
<tr>
<td>Immunosuppressants: cyclophosphamide, cyclosporine</td>
<td></td>
</tr>
<tr>
<td>Inhaled anesthetics: desflurane, sevoflurane, isoflurane, halothane</td>
<td></td>
</tr>
<tr>
<td>Local anesthetics</td>
<td></td>
</tr>
<tr>
<td>Other: dantrolene, diuretics, lithium</td>
<td></td>
</tr>
</tbody>
</table>

benefits; however, data are conflicting. It is suggested that good clinical assessment alone may yield similar outcomes to those associated with train-of-four use. Given the increased sophistication of mechanical ventilator processors, spontaneous respiration could be used as an indication of incomplete blockade and titrate NMBA accordingly irrespective of train-of-four results.

**Sedation**

NMBA s lack analgesic, sedative, and amnestic properties and, therefore, require concurrent use of a sedative agent possessing amnestic properties, such as propofol or BZDs. DEX lacks amnestic properties and should be avoided in these patients. The RASS and the Ramsay scale are not validated in paralyzed patients and should be avoided. The popularity of BIS has increased in recent years in patients receiving NMBA, although strong data are lacking. Its role remains controversial in ICUs. Some practitioners have suggested BIS only be used to increase sedation during paralysis but not to reduce sedation. Clinical assessment and thorough physical examination remain the standard for monitoring sedation in paralyzed patients.

**Reversal Agents**

The need for reversal of nondepolarizing NMBA is common, especially in the perioperative setting. The primary goal is to maximize nicotinic transmission while minimizing muscarinic side effects. Therapy consists of an acetylcholinesterase inhibitor and an anticholinergic agent. Acetylcholinesterase inhibitors, such as neostigmine (Prostigmin), pyridostigmine (Mestinon), physostigmine, (Antilirium), and edrophonium (Reversol), act at the NMJ, allowing for more ACh to compete for binding with the NMBA. Neostigmine is most commonly used because of its less severe adverse effect profile compared with other agents. Unfortunately, the cholinesterase inhibitors are not specific for the NMJ and act at cholinergic receptors in other organ systems. The most prominent effects are on the cardiovascular system, which result in decreased heart rate and dysrhythmias, but the pulmonary, cerebral, gastrointestinal, genitourinary, and ophthalmologic systems may also be affected. These muscarinic actions may be attenuated or prevented by the coadministration of an anticholinergic agent, such as glycopyrrolate (Robinul) or atropine (Atreza). These agents are administered at a fixed dose relative to the ACh inhibitor. A common combination is neostigmine (2.5 mg) administered with glycopyrrolate (0.5 mg; 0.2 mg glycopyrrolate per 1 mg neostigmine). The anticholinergic (glycopyrrolate) should be given before the acetylcholinesterase inhibitor (neostigmine) to minimize the adverse effects manifested on the muscarinic receptors.

**CARDIOVASCULAR AGENTS**

Catecholamines, or sympathomimetics, exert their cardiovascular effects through their actions on $\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$ and dopaminergic receptors. The type of physiologic effect that is elucidated from these agents is determined by the location of the receptor (Table 7) and the affinity of the agent for the specific adrenoceptor subtypes (Table 8). The use of these catecholamines in the critical care setting is dictated by the underlying disease state and desired clinical effect; therefore, it is important to determine the cause of the shock state to appropriately choose a vasopressor or inotrope. Vasopressors should not be used in a hypovolemic patient until proper fluid resuscitation has been achieved to minimize potential toxicity from these agents (Table 9) and, in some situations, vasopressors should not be used at all. The use of vasopressors in hemorrhagic shock may lead to increased mortality and the
The mainstay of therapy for these patients remains blood and fluid resuscitation. Common vasopressors and inotropes and their appropriate use are discussed.

### Vasopressors

**Phenylephrine**

Phenylephrine (Neo-Synephrine) is a direct-acting, predominately \(\alpha_1\)-adrenergic receptor agonist with minimal affinity for \(\beta\)-adrenergic receptors. The vasoconstriction caused by \(\alpha_1\)-adrenergic stimulation results in an increase in...
systemic vascular resistance (SVR) and ultimately a dose-dependent increase in BP. In the presence of normal cardiovascular reflexes, this rise in BP elicits a baroreceptor-mediated increase in vagal tone leading to a slowing of the heart rate HR. The resulting decrease in HR does not necessarily result in a lowering of cardiac output (CO).91,93,94 The increased venous return related to phenylephrine use can lead to an increase in stroke volume; however, the effects on CO remain controversial in the literature.95,96 These physiologic effects, along with its rapid onset and short duration of action, make phenylephrine a useful medication in the setting of hypotension, although it is not a first-line treatment for most types of shock due to limited outcome data.91,97,98 Phenylephrine is specifically not recommended as a first-line agent for septic shock, and its use is not addressed in the cardiogenic shock guidelines.97,98 Due to its alpha selectivity, however, the drug can be useful in certain patient populations. Phenylephrine is a good agent for neurogenic shock in the setting of normocardi and in patients with hypotension and concomitant aortic stenosis and is also an option in shock states when tachyarrhythmias limit the use of other vasopressors.99

**Epinephrine**

Epinephrine (ADRENALIN) is an endogenous catecholamine with high affinity for α-adrenergic and β-adrenergic receptors in cardiac and vascular smooth muscle. The β-adrenergic effects are more pronounced at lower doses (1–10 μg/min) whereas the

<table>
<thead>
<tr>
<th>Table 9: Inotropic and vasopressor clinical indication, dose range and major side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td>Phenylephrine</td>
</tr>
<tr>
<td>Epinephrine</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
</tr>
<tr>
<td>Dopamine</td>
</tr>
<tr>
<td>Vasopressin</td>
</tr>
<tr>
<td>Dobutamine</td>
</tr>
<tr>
<td>Milrinone</td>
</tr>
</tbody>
</table>

Data from Refs. 91,93,94,100
$\alpha_1$-adrenergic effects are seen more with higher dosages (>10 $\mu$g/min).\textsuperscript{91,93,94} The increase in systolic BP seen with epinephrine is a result of its positive inotropic and chronotropic actions on the heart ($\beta_1$ effects) and the vasoconstriction ($\alpha_1$ effects) actions on blood vessels. Epinephrine also acts on $\beta_2$-adrenergic receptors in the vasculature leading to vasodilation, balancing the drugs overall effect on SVR. These physiologic effects make epinephrine an effective drug for shock states; however, the undesirable side effects of tachyarrhythmias, ischemia related to increased oxygen consumption, lactic acidosis, and hypoglycemia can limit its use.\textsuperscript{100} Similar to phenylephrine, epinephrine is recommended as a second-line agent in patient’s failing to respond to first-line therapies for septic shock.\textsuperscript{98} Its use is not recommended in cardiogenic shock management outside of advanced cardiac life support (ACLS) where bolus dosing increases blood flow to the heart and brain during cardiopulmonary resuscitation and makes VF more susceptible to defibrillation.\textsuperscript{97,101} In patients with neurogenic shock, epinephrine is an option for the treatment of symptomatic bradycardia.\textsuperscript{99}

**Norepinephrine**

Norepinephrine (Levophed) is an agonist with similar potency to epinephrine at $\alpha_1$-adrenergic and $\alpha_2$-adrenergic receptors with less pronounced $\beta$-adrenergic receptor effects. Consequently, norepinephrine can cause potent vasoconstriction leading to increased BP and also produces a small (10%–15%) increase in CO and stroke volume.\textsuperscript{100} Similar to other catecholamines, its vasoconstrictive effects have the potential to cause a decrease in renal, splanchnic, or peripheral blood flow, particularly in patients not adequately fluid resuscitated.\textsuperscript{102} Norepinephrine is well studied in septic shock where it increases BP without causing deterioration of cardiac index and organ function.\textsuperscript{103,104} The largest randomized trial to date showed no significant difference in 28-day mortality between norepinephrine and dopamine for the treatment of shock, rendering either agent a first-line vasopressor for septic shock.\textsuperscript{98,105} Norepinephrine is also an option for the management of hypotension accompanying spinal cord injury as well as cardiogenic shock.\textsuperscript{97,99}

**Dopamine**

Dopamine (Intropin), the natural precursor of norepinephrine, acts on dopaminergic and adrenergic receptors to varying degrees in a dose-dependent fashion (see Table 8). At lower doses (0.5–5 $\mu$g/kg/min) it stimulates mostly dopaminergic receptors leading to vasodilation of mesenteric and renal tissues and increased blood flow to these areas. The increase in blood flow caused by low-dose dopamine does not translate into a clinical benefit and its use is not recommended for protection from renal failure.\textsuperscript{106} Moderate doses (5–10 $\mu$g/kg/min) stimulate $\beta_1$-adrenergic receptors resulting in an increase in HR and contractility. The $\alpha_1$-adrenergic effects of dopamine predominate at high doses (>10 $\mu$g/kg/min), leading to vasoconstriction and an increase in BP.\textsuperscript{100} Dopamine increases in BP and CO primarily due to its increase in stroke volume and HR; therefore, it is often an option in the setting of hypotension and cardiac compromise. These effects also lead to tachycardia and arrhythmias, a major limitation of dopamine therapy. Dopamine continues to be recommended along with norepinephrine as a first-line therapy for the treatment of septic shock.\textsuperscript{98} It is also recommended as a potential agent for the management of hypotension along with bradycardia in spinal cord injury and for increasing CO in the setting of hypotension for patients in cardiogenic shock.\textsuperscript{97,99}

**Vasopressin**

Vasopressin (Pitressin) is a peptide hormone that is synthesized in the hypothalamus, stored in the pituitary gland, and released in response to hypotension or increased
plasma osmolality. It stimulates vasopressin (V\textsubscript{1a}) receptors, causing smooth muscle contraction and vasoconstriction, and vasopressin (V\textsubscript{2}) receptors, enhancing renal collecting duct permeability and water reabsorption, leading to an increase in SVR and a reflexive increase in vagal tone. Vasopressin also increases responsiveness of the vasculature to catecholamines. The addition of low doses of vasopressin (0.01–0.04 units/min) to catecholamine therapy in patients with vasopressor-refractory septic shock decreases catecholamine requirements. Vasopressin remains effective in the setting of acidosis, whereas catecholamines do not. A fixed dose of vasopressin (0.03–0.04 units/min) is a safe and effective adjunctive therapy to norepinephrine in fluid-resuscitated patients with septic shock and this therapy is recommended in the surviving sepsis guidelines. Vasopressin is typically not titrated and is given as a fixed dose because higher doses of vasopressin are associated with splanchnic, digital, and cardiac ischemia. Its use should be reserved for situations where alternative vaspressors have failed. Vasopressin is not recommended in the treatment of cardiogenic shock outside the setting of ACLS.

**Inotropes**

**Dobutamine**

Dobutamine (Dobutrex) is a synthetic catecholamine with a strong affinity for both β\textsubscript{1}-adrenergic receptors and β\textsubscript{2}-adrenergic receptors. It binds in a 3:1 ratio to the β\textsubscript{1}-adrenergic receptors and β\textsubscript{2}-adrenergic receptors leading to its inotropic effects. It has a variable effect on BP secondary to its modest effects on the α\textsubscript{2}-adrenergic and β\textsubscript{2}-adrenergic receptors, usually leading to a net vasodilation. Vasoconstriction increasingly dominates at higher infusion rates. Monitoring CO and other clinical measures of tissue perfusion are typically used to guide dosing. Dobutamine is the drug of choice in patients with a low-output syndrome with reasonable BP. However, it can significantly increase myocardial oxygen consumption and therefore, can potentially induce ischemia. Dobutamine also has a role in the treatment of septic shock as the first-line therapy for patients with a low-output state but adequate filling pressures. Reference is not made to dobutamine in the spinal cord injury guidelines.

**Milrinone**

Milrinone (Primacor) is a phosphodiesterase inhibitor whose inotropic activity is caused by the prevention of the breakdown of intercellular cyclic adenosine monophosphate. Due to its mechanism of action, milrinone tends to have fewer chronotropic and arrhythmogenic effects compared with the catecholamines; however, its effects on vascular smooth muscle cells can cause vasodilation leading to an exacerbation of hypotension. The side effect of hypotension and its long half-life (2–4 hours) limits its use in ICUs to patients whose adrenergic receptors are downregulated or desensitized due to chronic heart failure (HF) or chronic β-agonist administration. The use of milrinone is not commented on in any of the current consensus guidelines for the treatment of septic, cardiogenic, or neurogenic shock.

**Acute Hypertension**

Acute hypertension in ICUs is common, often iatrogenic in nature, and is associated with a high risk of acute end-organ damage and bleeding, especially in the perioperative setting. Hypertensive emergencies are defined by severe elevations in BP, typically systolic BP greater than 180mmHg or diastolic BP greater than 120 mm Hg, in the presence of end-organ damage, such as neurologic changes, hypertensive encephalopathy, myocardial ischemia or infarction, renal insufficiency, and so
The therapeutic goal for these patients is to lower the mean arterial pressure by 20% to 25% within 60 minutes, avoiding a precipitous or excessive decrease in BP. If a patient remains stable, the BP can further be reduced to systolic BP 160 mm Hg and diastolic BP of 100 mm Hg to 110 mm Hg over the next 2 to 6 hours. The ultimate goal is to be at a patient’s baseline BP in 24 to 48 hours. To reduce BP in a controlled and predictable manner, it is important to understand the IV drug options available. The agent of choice depends on the clinical presentation (Box 2, Table 10). Hypertensive urgencies also require therapeutic intervention; however, they can often be managed with oral therapy and do not necessarily require admission to an ICU. The pharmacology of common IV antihypertensives and their appropriate use are discussed.

**Nicardipine**

Nicardipine (Cardene), a second-generation dihydropyridine CCB, is highly selective for vascular smooth muscle and causes vasodilation, leading to a reduction in BP and a decrease in afterload. It has strong selectivity for cerebral and coronary vessels and, therefore, is useful in the setting of cerebral and cardiac ischemia. Nicardipine has demonstrated ability to increase stroke volume and coronary blood flow with a favorable effect on myocardial oxygen balance; however, it is contraindicated in patients with advanced aortic stenosis. It has similar efficacy to sodium nitroprusside (Nipride) for perioperative BP control and the treatment of hypertensive emergencies and it is safe for patients with renal and hepatic disease (see Box 2). The most common adverse effects associated with nicardipine are headache, nausea, vomiting, hypotension, and reflex tachycardia.

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Preferred Agent(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute aortic dissection</td>
<td>Esmolol (may add nicardipine or nitroprusside to IV β-blocker)</td>
</tr>
<tr>
<td>Acute HF</td>
<td>Nitroprusside, nitroglycerin</td>
</tr>
<tr>
<td>Acute intracerebral hemorrhage/acute ischemic stroke</td>
<td>Labetalol, nicardipine</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>β-Blocker in combination with nitroglycerine</td>
</tr>
<tr>
<td></td>
<td>(if HR &lt;70 beats/min, nicardipine or clevidipine)</td>
</tr>
<tr>
<td>Acute pulmonary edema</td>
<td>Nitroprusside, nitroglycerin</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>Fenoldopam, nicardipine, clevidipine</td>
</tr>
<tr>
<td>Eclampsia or preeclampsia</td>
<td>Hydralazine, labetalol, nicardipine</td>
</tr>
<tr>
<td>Perioperative hypertension</td>
<td>Clevidipine, esmolol, nicardipine, nitroglycerin, nitroprusside</td>
</tr>
<tr>
<td>Sympathetic crisis or catecholamine toxicity</td>
<td>Nicardipine, fenoldopam, clevidipine (avoid unopposed β-blockade)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Onset, Duration</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicardipine</td>
<td>5–15 mg/h (max 15 mg/h)</td>
<td>5–10 min, 4–6 h (longer with prolonged infusion)</td>
<td>Headache, hypotension, nausea, vomiting, reflex tachycardia</td>
</tr>
<tr>
<td></td>
<td>Titration: 2.5 mg/h every 5 min</td>
<td></td>
<td>Contraindications: aortic stenosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Caution: angina/MI, acute HF</td>
</tr>
<tr>
<td>Clevidipine</td>
<td>1–2 mg/h (max 21 mg/h, short-term experience with 32 mg/h)</td>
<td>2–4 min, 5–15 min</td>
<td>Headache, AF, nausea, vomiting, acute renal failure</td>
</tr>
<tr>
<td></td>
<td>Titration: double dose every 90 s</td>
<td></td>
<td>Contraindications: soy/egg allergies, severe aortic stenosis, defective lipid metabolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Caution: HF, reflex tachycardia, rebound HTN</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>0.3–0.5 μg/kg/min (max 3 μg/kg/min)</td>
<td>Immediate, 2–3 min</td>
<td>Cyanide toxicity, methemoglobinemia</td>
</tr>
<tr>
<td></td>
<td>Titration: 0.5 μg/kg/min</td>
<td></td>
<td>Contraindications: renal, hepatic failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Caution: increased ICP</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>5–10 μg/min (max 200 μg/min)</td>
<td>2–5 min, 5–10 min</td>
<td>Headache, tachyphylaxis, methemoglobinemia</td>
</tr>
<tr>
<td></td>
<td>Titration: 5 μg/min every 3–5 min</td>
<td></td>
<td>Contraindications: concomitant use of phosphodiesterase inhibitors</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>5–10 mg IV every 4–6 h (max 20 mg/dose)</td>
<td>5–30 min, 1–4 h</td>
<td>Reflex tachycardia, headache, flushing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Caution: angina/MI, increased ICP, aortic dissection</td>
</tr>
<tr>
<td>Esmolol</td>
<td>0.5–1 mg/kg loading dose, 25–50 μg/kg/min (max 300 μg/kg/min)</td>
<td>1–2 min, 10–30 min</td>
<td>Bradycardia/heart block, bronchospasm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Caution: concurrent β-blocker therapy, HF</td>
</tr>
<tr>
<td>Labetalol</td>
<td>20–80 mg IV every 15 min OR 0.5–2 mg/min (max 300 mg/24 h)</td>
<td>5–10 min, 3–6 h</td>
<td>Bradycardia/heart block, bronchospasm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Caution: concurrent β-blocker therapy, HF</td>
</tr>
<tr>
<td>Fenoldopam</td>
<td>0.1 μg/kg/min (max 1.6 μg/kg/min)</td>
<td>&lt;5 min, 30 min</td>
<td>Headache, flushing, tachycardia, dizziness, increased intraocular pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Caution: glaucoma, sulfite allergy</td>
</tr>
<tr>
<td>Enalaprilat</td>
<td>0.625–1.25 mg IV every 4–6 h (max 5 mg every 6 h)</td>
<td>Within 30 min, 12–24 h</td>
<td>Renal insufficiency/failure, hyperkalemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Contraindications: pregnancy, renal artery stenosis</td>
</tr>
</tbody>
</table>

**Abbreviations:** HF, heart failure; HTN, hypertension; MI, myocardial infarction.

*Data from Refs.112–116*
Clevidipine
Clevidipine (Cleviprex), a third-generation dihydropyridine CCB, acts specifically to vasodilate the arterioles and can reduce afterload without affecting cardiac-filling pressures or causing reflex tachycardia. Due to its rapid onset and offset of action, clevidipine is useful when tight BP control is critical and has been studied most in the perioperative setting. Clevidipine is rapidly metabolized by esterases in the blood, and, therefore, its metabolism is not affected by renal or hepatic function. It is commercially available in a lipid emulsion, which carries limitations with regard to allergies, total dosage, triglyceride monitoring, and risk of microbial growth.

Sodium nitroprusside
Sodium nitroprusside is an arterial and venous vasodilator that decreases preload and afterload. Unlike CCBs, sodium nitroprusside dilates large-capacitance vessels. It decreases cerebral blood flow while increasing ICPs and is not recommended in patients with hypertensive encephalopathy or after a cerebrovascular accident. In patients with coronary artery disease, there is the potential that sodium nitroprusside can cause a reduced coronary perfusion pressure due to the theorized coronary steal mechanism and is not recommended in the setting of acute myocardial infarction. It has a short onset and offset of action and is useful when rapid BP reduction is needed, such as the perioperative setting. Intra-arterial BP monitoring is strongly recommended with the use of sodium nitroprusside due to the drug’s potency, rapid onset of action, and the development of tachyphylaxis. There is a risk of cyanide toxicity when the drug is used in patients with renal or hepatic disease, at higher doses and for long periods of time; however, the coadministration of thiosulfate can help avoid toxicity.

Nitroglycerin
Nitroglycerin (Nitro-Bid) is a potent venodilator and can cause arterial smooth muscle dilation at high doses. It reduces BP by decreasing preload and in volume-depleted patients, and reduced preload can decrease CO. This is an undesirable effect in patients with compromised myocardial, cerebral, or renal perfusion. Severe hypotension and reflex tachycardia are reported with nitroglycerin use in volume-depleted patients. Administration of low doses of nitroglycerin (approximately 60 μg/min) can be beneficial as adjunct therapy for patients with hypertensive emergencies associated with acute coronary syndromes or acute pulmonary edema.

Hydralazine
Hydralazine (Apresoline) causes relaxation of arteriolar smooth muscle leading to peripheral vasodilation and reduced cardiac afterload. There is some evidence that hydralazine can cause reflex sympathetic stimulation leading to increases in HR and ICP; however, this effect can be blunted by coadministration of a β-receptor antagonist. Hydralazine is administered as intermittent IV or intramuscular (IM) bolus doses. A single dose has an onset of action of up to 30 minutes and a prolonged pharmacologic effect on BP, up to 12 hours in some reports. The unpredictability of the dose response as well as the prolonged duration of action limits the drug’s utility as a first-line option for the treatment of hypertensive emergencies.

Esmolol
Esmolol (Brevibloc) is a short-acting, selective β1-adrenergic receptor antagonist. Due to its pharmacokinetic properties, esmolol is a good medication for heart rate control in the critically ill and is useful in decreasing the sympathetic discharge seen with severe postoperative hypertension accompanied by increased
HR, CO, and BP.\textsuperscript{141–143} Esmolol is indicated for perioperative BP management and can be safely used in the setting of myocardial ischemia or infarction, although caution should be used in the setting of HF.\textsuperscript{112,144}

**Labetalol**
Labetalol (Trandate) is a combined selective $\alpha_1$-adrenergic and nonselective $\beta$-adrenergic antagonist. It blocks $\alpha$-receptor to $\beta$-receptor activity in a ratio of 1:7 when given IV and because of the $\alpha$-adrenergic activity, the decrease in CO related to the $\beta$-receptor blockade is minimized.\textsuperscript{145,146} Cerebral, renal, and coronary blood flow are maintained with labetalol use and it is a drug of choice in the setting of pregnancy-induced hypertensive emergency due to limited placental drug transfer.\textsuperscript{146} Caution should be used in the setting of reactive airway disease, decompensated HF, and second-degree or third-degree atrioventricular (AV) block.\textsuperscript{112}

**Fenoldopam**
Fenoldopam (Corlopam) is a selective peripheral D$_1$-agonist causing vasodilation of peripheral arteries and the renal and mesenteric vasculature. It lowers BP and SVR while maintaining renal blood flow.\textsuperscript{147} It is associated with a lower risk of the need for renal replacement therapy in patients at risk for acute renal impairment; however, the data for prophylaxis of contrast-induced nephropathy are not robust.\textsuperscript{148,149} There is a dose-related increase in intraocular pressure with the drug and it should be avoided in patients with glaucoma.\textsuperscript{147}

**Enalaprilat**
Enalaprilat (Vasotec) is an IV angiotensin-converting enzyme inhibitor that causes vasodilation due to decreased production of angiontensin II, a potent vasoconstrictor.\textsuperscript{113} Enalaprilat is not commonly used in critically ill patients with hypertensive emergencies due to its variable onset and long duration of action. It should also be avoided in patients with acute MI, bilateral renal artery stenosis, and pregnancy.

**Antiarrhythmic Agents**
Atrial arrhythmias occur frequently in ICUs, whereas ventricular arrhythmias are less common but often much more serious and life threatening.\textsuperscript{150} Arrhythmias in ICUs are often related to catecholamine excess (endogenous or exogenous), hypoxia, infections, cardiac ischemia, or electrolyte disturbances. Management of arrhythmia should focus on correction of underlying causes as well as drug therapy directed at the arrhythmia itself. In the setting of hemodynamic compromise due to arrhythmia, however, cardioversion should be performed.\textsuperscript{101} This discussion focuses on the drug therapy options for the most commonly encountered arrhythmias in ICUs.

**Atrial fibrillation**
Atrial fibrillation (AF) is the most common narrow complex tachyarrhythmia encountered in ICUs and is particularly prevalent in surgical patients.\textsuperscript{150,151} AF occurs in 20% to 50% of postcardiac surgery patients with a peak incidence on postoperative day 2.\textsuperscript{152} Appropriate preoperative prophylaxis with $\beta$-blockers or amiodarone is recommended for the prevention of postoperative AF. There are 2 treatment strategies for rapid onset of new AF in hemodynamically stable patients: rate control, and cardioversion. Rate control can be achieved with $\beta$-blockers, CCBs, or digoxin, and the most common agent for chemical cardioversion is amiodarone.\textsuperscript{150,152} Other antiarrhythmic agents, such as procainamide (Pronestyl), sotalol (Betapace), and ibutilide (Corvert), convert AF to sinus rhythm, but their safety profiles limit their use outside of expert consultation.\textsuperscript{152} When using either strategy, it is important to consider the patient’s
anticoagulation needs in the setting of AF. Anticoagulation is usually initiated if AF persists greater than 48 hours.\textsuperscript{152}

\textbf{β-Blockers} β-Blockers work to slow ventricular rate in AF and are particularly useful in the setting of increased adrenergic tone.\textsuperscript{152} There is some evidence that these agents are superior to CCB for establishing rate control.\textsuperscript{141,153} Metoprolol (Lopressor) and esmolol are most commonly used in ICUs due to their IV formulations. Metoprolol is typically dosed 2.5 mg to 5 mg IV every 5 to 10 minutes for a total of 15 mg as BP tolerates. Esmolol can be a good option in more unstable patients due to its rapid onset and offset of action.\textsuperscript{150}

\textbf{Calcium channel blockers} The nondihydropyridine CCBs, diltiazem (Cardizem) and verapamil (Calan), are also effective AV nodal blockers used for rate control in AF.\textsuperscript{154–156} Both of these agents have a negative inotropic effect and should be used cautiously in HF.\textsuperscript{157} Diltiazem is available in an IV formulation and is commonly used as a continuous infusion of 5 mg/h to 15 mg/h. IV diltiazem may cause hypotension, so caution should be used in hemodynamically unstable patients.

\textbf{Digoxin} Digoxin (Lanxin) controls ventricular response through a centrally mediated vagal mechanism as well as via direct action on the AV node, leading to HR control at rest. It has limited use in ICUs given the higher level of circulating catecholamines and the longer onset of action (at least 60 minutes).\textsuperscript{152} For the treatment of AF, a loading dose of digoxin (0.25 mg every 2 hours up to a maximum of 1.5 mg) is recommended. Digoxin use is also limited by drug interactions and potential for arrhythmias, especially in elderly patients with compromised renal function.\textsuperscript{158}

\textbf{Amiodarone} Amiodarone is considered a class III antiarrhythmic drug due to its potassium channel blockade; however, the drug also acts on sodium channels and calcium channels and has a negative chronotropic effect on cardiac nodal tissue.\textsuperscript{159} The drug is used for both atrial and ventricular arrhythmias and is effective for conversion of AF as well as ventricular rate control in AF when other agents are ineffective, although the latter indications carry less evidence.\textsuperscript{152,160} Amiodarone is not superior to other antiarrhythmic drugs for successful conversion of recent-onset AF, although it is relatively safe in patients with structural heart disease and left ventricular dysfunction.\textsuperscript{152} Acute adverse effects of amiodarone include bradycardia, hypotension, and phlebitis. Concerns with thyroid, liver, lung, and ocular toxicity occur with long-term use.

\textbf{Ventricular arrhythmias} Ventricular arrhythmias include ventricular tachycardia (VT), ventricular fibrillation (VF), and torsades de pointes. These arrhythmias are often life threatening and appropriate ACLS guidelines should be followed when they are encountered. As with atrial arrhythmias, unstable patients presenting with a ventricular arrhythmia should be candidates for immediate cardioversion.\textsuperscript{101} In the setting of VF or pulseless VT, epinephrine (1 mg IV/intraosseous) may be given after the first defibrillation effort and high-quality cardiopulmonary resuscitation. Amiodarone (300 mg IV push) is also part of the ACLS VF/pulseless VT algorithm if defibrillation, cardiopulmonary resuscitation, and a vasopressor fail to produce a perfusing rhythm.\textsuperscript{101} Amiodarone improves the rate of return of spontaneous circulation and hospital admission in refractory VF/pulseless VT. If torsades de pointes are encountered at any time, magnesium sulfate (2 g IV bolus) should be considered. In the setting of a stable, monomorphic VT, there are additional drug therapy options.
Adenosine Adenosine (Adenocard) directly inhibits that AV nodal refractory period and is indicated for regular narrow complex supraventricular tachycardias as well as regular wide complex tachycardias, if the cause of the latter cannot be determined.\textsuperscript{101,159} Adenosine 6 mg to 12 mg IV push is relatively safe for both treatment and diagnosis of regular wide-complex tachycardias. In the setting of supraventricular tachycardias with aberrancy, adenosine converts the tachycardia into a sinus rhythm.\textsuperscript{161,162} If the underlying rhythm is VT, there is no effect on the rhythm with adenosine administration and patients are then candidates for IV antiarrhythmic drugs or elective cardioversion.\textsuperscript{101}

Procainamide Procainamide, a class Ia antiarrhythmic, is the first-line therapy for patients with stable, monomorphic VT due to its conversion rates compared with lidocaine (Xylocaine).\textsuperscript{163} The side effects of QT prolongation and hypotension limit its use. Also, procainamide is contraindicated in patients with HF.\textsuperscript{101} For this reason as well as its side effects, amiodarone is often used in its place.

Sotalol Sotalol has both β-adrenergic receptor activity and the ability to prolong the action potential.\textsuperscript{159} Sotalol (100 mg IV over 5 minutes) is more effective at the conversion of a stable, monomorphic VT compared with lidocaine and is recommended with the same level of evidence as amiodarone for this indication.\textsuperscript{101,164} Sotalol should be avoided in patients with prolonged QT interval and should be used cautiously in patients with HF due to its β-blocking activity.

ANTICOAGULANTS

Intravenous and Subcutaneous Anticoagulants

Unfractionated heparin Unfractionated heparin (UFH) is an indirect parenteral anticoagulant often indicated for venous thromboembolism (VTE) prophylaxis as well as therapeutic anticoagulation.\textsuperscript{165} The half-life of UFH is approximately 1.5 hours, allowing for frequent monitoring and rapid titration. This, along with rapid elimination from the body, makes UFH an attractive agent for use in critically ill patients. When dosed therapeutically, the anticoagulant effect of UFH is monitored using the activated partial prothrombin time to a goal of 1.5 to 2.5 times control.\textsuperscript{165} Although this therapeutic goal is based on retrospective data from the 1970s, it is widely accepted today.\textsuperscript{166} Activated clotting time is used to monitor the higher UFH doses given to patients undergoing cardiopulmonary bypass surgery, percutaneous coronary interventions, and extracorporeal membrane oxygenation. The dose of UFH can vary based on indication and the presence of thrombosis. Evidence suggests that patients with an active venous thrombosis require higher doses of UFH compared with patients requiring UFH infusions for prophylaxis of clot formation or for the treatments of acute coronary syndrome.\textsuperscript{167,168} The use of an institution specific protocol for dosing and monitoring UFH is recommended to assure appropriate safety and efficacy. Patients requiring unusually high doses of UFH may be heparin resistant due to antithrombin III (AT III) deficiency or increased UFH clearance; the use of alternative anticoagulants may be indicated in these situations.

The use of UFH can be limited by hemorrhagic complications and its ability to induce heparin-induced thrombocytopenia (HIT). Fortunately, protamine sulfate can rapidly reverse the anticoagulant effects of heparin in the setting of hemorrhagic complications (Table 11). There is a slight risk of hypotension and bradycardia with protamine sulfate administration that can be minimized by slow administration over 10 minutes. HIT is an immune-mediated drug reaction related to heparin exposure that is associated with a high risk of thrombosis.\textsuperscript{169} HIT is characterized by
<table>
<thead>
<tr>
<th>Drug</th>
<th>Reversal Agents</th>
<th>Dose</th>
<th>Onset of Action</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH</td>
<td>Protamine sulfate</td>
<td>1 mg Protamine IV/100 units of UFH (max of 50 mg over 10 min)</td>
<td>5 min</td>
<td>Hypotension and bronchoconstriction</td>
</tr>
<tr>
<td>LMWH</td>
<td>Protamine sulfate</td>
<td>If LMWH given within 8 h: 1 mg of protamine IV/100 anti-Xa units of LWMH</td>
<td>5 min</td>
<td></td>
</tr>
<tr>
<td>Fundaparinux</td>
<td>No antidote: hemodialysis slightly reduces plasma levels by (\sim 20%); rFVIIa is option</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTI</td>
<td>No antidote: rFVIIa and PCC likely ineffective; hemodialysis may remove (\sim 60%) of dabigatran</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>Vitamin K (Phytonadione)</td>
<td>po: 1–10 mg po: (\sim 24) h po: 1–10 mg over 10–20 min IV: 12–16 h</td>
<td></td>
<td>Anaphylaxis with IV formulation Volume sensitive patients; risk of TRALI Thrombosis</td>
</tr>
<tr>
<td>FFP</td>
<td></td>
<td>Variable (10–15 mL/kg IV) Temporary effect (4–6 h)</td>
<td></td>
<td>Volume sensitive patients; risk of TRALI Thrombosis</td>
</tr>
<tr>
<td>PCC</td>
<td></td>
<td>25–50 units/kg* IV (not exceeding rate of 10 mL/min) Immediate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rFVIIa</td>
<td></td>
<td>30–90 (\mu)g/kg IV bolus over 2–5 min 10–20 min</td>
<td></td>
<td>Thrombosis</td>
</tr>
</tbody>
</table>

Abbreviations: FFP, fresh frozen plasma; TRALI, transfusion-related acute lung injury.
* Various other dosing strategies available (INR based and factor level based).

Data from Refs.\(^{180,186,191,192,229-234}\)
a thrombocytopenia (platelet count <150 \times 10^9/L) typically presenting 5 to 10 days after the initiation of UFH, with or without thrombosis. The 4Ts scoring tool is used to help practitioners predict the presence of HIT by looking for the timing of thrombocytopenia, the timing of the drop in platelet count, presence of thrombosis, and other potential causes of thrombocytopenia.\textsuperscript{170,171} The diagnosis of HIT is confirmed by the presence of platelet-activating antiplatelet factor 4 antibodies and, occasionally, the serotonin release assay is used if additional confirmation is warranted.\textsuperscript{169} Alternative anticoagulants, typically direct thrombin inhibitors (DTIs), are indicated in the setting of HIT.

**Low-molecular-weight heparins**

Low-molecular-weight heparins (LMWHs) are derived from UFH and have a more predictable dose response curve compared with UFH. Similar to UFH, they are used for thromboprophylaxis as well as therapeutic anticoagulation. LMWHs are dosed as a subcutaneous injection daily or twice daily depending on the indication and patient specific factors, such as weight and renal function. Monitoring with anti-Xa levels is not routinely recommended outside of LMWH use in obese patients, pregnancy, and in the setting of renal insufficiency.\textsuperscript{172–174} The half-life of LMWHs of 3 to 6 hours is dose dependent and prolonged in patients with renal failure, which may limit the utility of these drugs in certain critical care populations.\textsuperscript{165} Optimal dosing of LMWHs in patients with renal insufficiency is uncertain and use in this patient population is linked with increased bleeding risk.\textsuperscript{25} For these reasons, UFH is the preferred agent when therapeutic anticoagulation is indicated in the setting of renal insufficiency.\textsuperscript{165} There are some data, specifically for enoxaparin (Lovenox) and dalteparin (Fragmin), suggesting no increased bleeding risk with prophylactic LMWH dosing in patients with a creatinine clearance (CrCl) of less than 30 mL/min.\textsuperscript{175–177} The dosing of LMWHs in obese patients is also controversial. Data that are available suggest dosing based on total body weight up to a weight of 144 kg with enoxaparin and 190 kg with dalteparin is appropriate.\textsuperscript{178,179}

LMWHs carry a similar risk of bleeding complications compared with UFH; however, their use is associated with lower rates of nonhemorrhagic complications, such as HIT and osteoporosis.\textsuperscript{165,180} There is not a proved method for neutralizing the anticoagulant effects of LMWH. Protamine sulfate administration is recommended for its partial neutralization activity of LMWH if given within an 8-hour window of the last LMWH dose.\textsuperscript{165}

**Fondaparinux**

Fondaparinux (Arixtra) is a synthetic analog of the AT III–binding portion of UFH and LMWH that has an increased affinity for AT III. Similar to LMWH, fondaparinux has a predictable dose-response curve and is administered once daily in fixed doses. It has a half-life of approximately 17 hours and this can be extended up to 21 hours in elderly patients, which can limit its use in critically ill patients.\textsuperscript{181} Fondaparinux is indicated for thromboprophylaxis as well as for the treatment of acute coronary syndromes, deep vein thrombosis, and pulmonary embolism.\textsuperscript{165} The dosing is based on indication, patient weight, and renal function. Elimination of fondaparinux is almost completely dependent on renal clearance and, therefore, it is contraindicated in patients with a CrCl of less than 30 mL/min. Routine coagulation monitoring is not recommended; however, when determining the anticoagulant activity of fondaparinux, a fondaparinux-specific anti-Xa assay is used.

Fondaparinux carries a similar bleeding risk to UFH and LMWH. Protamine sulfate is ineffective in neutralizing its anticoagulant activity.\textsuperscript{180} If uncontrolled bleeding does
occur with fondaparinux therapy, administration of recombinant factor VIIa (rFVIIa) may be effective.\textsuperscript{182} Fondaparinux is unlikely to cause HIT and there are case reports suggesting it can be used for HIT treatment, but additional safety and efficacy studies are needed.\textsuperscript{169,183}

**Direct thrombin inhibitors**

Lepirudin (Refludan), bivalirudin (Angiomax), and argatroban are parenteral DTIs used for the treatment of HIT. Lepirudin has a half-life of approximately 60 minutes and it is renally eliminated. Dose reductions are required if CrCl less than 60 mL/min. It is contraindicated in renal failure. It is a good therapeutic option in patients with hepatic dysfunction.\textsuperscript{184} Lepirudin can cause antibodies to develop in up to 40% of patients exposed to the drug. Anaphylaxis can occur if patients are re-exposed to the drug; therefore, alternatives should be considered in patients who have previously received lepirudin.\textsuperscript{165}

In addition to HIT, bivalirudin is indicated for anticoagulation in patients undergoing percutaneous interventions for acute coronary syndrome. Bivalirudin has a short half-life of 25 minutes and is partially eliminated by the kidneys; dose reduction is recommended in patients to moderate to severe renal dysfunction.\textsuperscript{165}

Argatroban is indicated for the treatment of HIT and can be used during percutaneous interventions when UFH is contraindicated due to recent history of HIT. It is primarily metabolized by the liver and must be used cautiously in patients with hepatic dysfunction. Conversely, it is a good option for patients with severe renal impairment.\textsuperscript{165} Lower empiric dosing is recommended for critically ill patients to prevent prolonged or exaggerated anticoagulant effects. The half-life is 45 minutes and, as with all parenteral DTIs, activated partial prothrombin time is recommended for monitoring of the anticoagulant effect. All DTIs can interact with the laboratory assay for the international normalized ratio (INR), causing a falsely elevated INR.\textsuperscript{165} This is seen especially with argatroban, and specific recommendations are available on how to appropriately transition to a vitamin K antagonist, such as warfarin (Coumadin).

There are no specific antidotes for DTIs should hemorrhagic complications arise. rFVIIa has been studied as a reversal agent in healthy volunteers; its use in bleeding patients is not established.\textsuperscript{185} Hemodialysis can be an effective way to remove DTIs.

**Oral Anticoagulants**

**Warfarin**

Warfarin, a vitamin K antagonist, has been the only oral anticoagulant for the treatment and prevention of thromboembolic events until the recent addition of an oral DTI and a direct factor Xa inhibitor to the market. Of the oral anticoagulant options, warfarin has the most efficacy and safety data available, but the monitoring requirements and drug, food, and genetic interactions often complicate therapy. Owing to its half-life of 36 to 42 hours, warfarin can take up to a week for onset and offset of action, deeming the drug difficult to use in the critical care setting.\textsuperscript{186} Fortunately, warfarin has several reversal options (see Table 11). The reversal strategy for warfarin depends on the indication for reversal and the urgency of the situation. Therapeutic reversal options include administration of vitamin K and blood derivatives, such as fresh frozen plasma, prothrombin complex concentrates (PCCs), and rFVIIa.\textsuperscript{187–189}

**Dabigatran**

Dabigatran (Pradaxa) is approved for the prevention of stroke or systemic embolism in nonvalvular AF.\textsuperscript{186} It is also used for prevention of VTE in the setting of total knee or hip arthroplasty although this indication is lacking in the United States. Compared with warfarin, dabigatran has a short half-life, 12 to 17 hours, and, therefore, bridging is
not recommended with the initiation of therapy. No therapeutic monitoring is recommended with dabigatran therapy and determining the degree of anticoagulation with the drug can be challenging.\textsuperscript{186} Measuring the ecarin clotting time is likely the most promising measure of dabigatran effect; however, this test is not readily available.\textsuperscript{190} As with other DTIs, there is no antidote for dabigatran. The limited data available with using rFVIIa and PCCs suggest that these agents are ineffective in reversing bleeding related to dabigatran use. Hemodialysis may be effective in removing up to 60\% of the drug.\textsuperscript{191,192}

Rivaroxaban
Rivaroxaban (Xarelto) is a direct factor Xa inhibitor approved for VTE prophylaxis in patients undergoing total hip or knee replacement surgery and for stroke and VTE prevention in patients with nonvalvular AF. Compared with warfarin and dabigatran, rivaroxaban has a short half-life of 6 to 7 hours; however, factor Xa activity may not return to normal until up to 24 hours after the dose is given.\textsuperscript{193} No antidote for rivaroxaban exists and due to its high protein binding, it is unlikely that the drug is dialyzable.\textsuperscript{186} There are limited data evaluating the role of PCCs and rFVIIa in the setting of rivaroxaban use. One study showed restoration of prolonged PT and normalization of thrombin generation after PCC administration in healthy volunteers who had received rivaroxaban; however, the clinical implications of these findings are unknown.\textsuperscript{192}

ANTIBIOTICS
Antibiotic therapies are of tremendous importance to ICU care. Inappropriate empiric therapy and delayed initiation of therapy contribute to increased mortality, development of resistance, increased health care costs, and lack of compliance with national standards.\textsuperscript{98,194–201} Lack of compliance with national standards results in financial penalties on reimbursement. Antimicrobial drug development has been declining for years and the future does not look promising. Therefore, appropriate use of currently available antibiotics, referred to as antimicrobial stewardship, is imperative.\textsuperscript{202,203} Although beyond the scope of this article, stewardship can be summarized as appropriate drug selection based on patient-specific risk factors, such as appropriate dose, route, and frequency; de-escalation based on culture and sensitivity reports; and duration of therapy compliant with evidence-based treatment guidelines. Following these stewardship principles, along with source control, yields optimal outcomes while minimizing unnecessary resistance and health care cost.\textsuperscript{202} To aid prescribers, the Infectious Diseases Society of America has published treatment guidelines for major disease states available free of charge at www.idsociety.org. For appropriate dosing information, drug package inserts should be consulted.

\textbf{\textit{\textbeta-\textit{Lactams}}}
\textbeta-Lactam (BL) antibiotic is a general term used to describe antibiotics that contain a BL ring in their molecular structure.\textsuperscript{204,205} BL antibiotics include penicillins, cephalosporins, \textbeta-lactam/\textbeta-lactamases (BLase) inhibitors. Each of these antibiotic classes manifests their activity on the bacterial cell wall, resulting in time-depending killing. Extended infusions may increase efficacy and reduce treatment costs. Patients with allergies to a specific BL should be considered at risk for allergic reactions to other BL antibiotics. In general, BL antibiotics are well tolerated. Potential adverse effects include hypersensitivity reactions, interstitial nephritis, drug fever, thrombocytopenia, possibly hemorrhagic complications as a result of disturbing synthesis of vitamin
K–dependent clotting factors, and biliary sludging for those that concentrate in the bile. The BL subgroups are discussed in more detail later.

**Cephalosporins**

The cephalosporin drug class has a reported allergic cross-reactivity of 5% to 10% to penicillin. Cephalosporins should be avoided in those with serious or immediate reactions (anaphylaxis or bronchospasm) but may be tried in patients with mild or delayed reactions, although drug desensitization would be a safer approach. Moving from first-generation to third-generation cephalosporins, the gram-negative activity is enhanced at the expense of some gram-positive activity, although all generations (including fourth) lack activity against enterococci. Cephalosporins have good tissue penetration and distribute well to organs. First-generation cephalosporins, such as cefazolin (Ancef), are commonly used for perioperative prophylaxis owing to their activity against skin flora, such as methicillin-sensitive Staphylococcus aureus (MSSA) and \( \text{S epidermidis} \). Cefazolin may also be used therapeutically for routine gram-positive pathogens and has some activity against anaerobes associated with mouth flora. The term, cephamycin, is sometimes used to describe a subset of cephalosporins that have enhanced activity against anaerobes, including mouth and colon flora, such as second-generation cefoxoitin (Mefoxin) and cefotetan (Cefotan). Although second-generation cephalosporins have less gram-positive activity than first generations, they are good options for a mixed infection or perioperative prophylaxis for bowel surgery. Third-generations, such as ceftriaxone (Rocephin), can be used in combination with the antianaerobic metronidazole (Flagyl) to broaden the spectrum of activity. This combination is efficacious for uncomplicated and complicated intra-abdominal infections when multidrug-resistant pathogens are not suspected. Fourth-generation cefepime (Maxipime) has the broadest spectrum of gram-negative activity and maintains activity against \( \text{Pseudomonas aeruginosa} \), as does the third generation, ceftazidime (Fortaz), making them viable options for nosocomial infections, including pneumonia. The recently developed fifth-generation ceftobiprole (Zeftera) and ceftaroline (Teflaro) retained activity against methicillin-resistant \( \text{S aureus} \) (MRSA), including exotoxin-producing strains. Of the 2, only ceftobiprole maintains activity against \( \text{P aeruginosa} \). Both agents have marginal activity against enterococci.

**\( \beta \)-Lactam/\( \beta \)-Lactamase Inhibitors**

Piperacillin/tazobactam (Zosyn) and ticarcillin/clavulanate (Timentin) offer an enhanced spectrum of activity compared with cefepime, particularly against anaerobes and gram-negative pathogens, like \( \text{P aeruginosa} \). Ampicillin/sulbactam (Unasyn) has a narrower spectrum as a result of the less potent BLase inhibitor sulbactam, which results in less gram-negative activity. All agents maintain activity against resistant organisms that are cephalosporinase producing and BLase producing, which would otherwise render cephalosporins ineffective. Only patients previously exposed to antibiotics and those at risk for resistant pathogens should receive these drugs empirically. These agents must be avoided in patients with BL allergies. Amoxicillin/clavulanate (Augmentin) is an oral option that allows for step-down therapy.

**Carbapenems**

Carbapenems maintain activity against a wide spectrum of bacteria, including those harboring resistance to other drug classes, such as cephalosporinases and extended-spectrum BLase. As a result, this drug class should not be routinely used first line but reserved for complicated and resistant infections, similar to BL/BLase inhibitors. Cross-reactivity with penicillin allergy is less defined as compared
### Table 12
Antimicrobial activity against select pathogens

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>G(+)</th>
<th>G(−)</th>
<th>Anaerobes</th>
<th>Enterococcus</th>
<th>MRSA</th>
<th>Pseudomonas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime, cefepime</td>
<td>IV</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Ceftaroline, ceftobiprole</td>
<td>IV</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>Ceftobiprole only</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>po, IV</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>−</td>
</tr>
<tr>
<td>Ciprofloxacin, levofloxacin</td>
<td>po, IV</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>IV</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Meropenem, imipenem-cilastatin, doripenem</td>
<td>IV</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Ampicillin-sulbactam</td>
<td>IV</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>po</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Piperacillin-tazobactam, ticarcillin-clavulanate</td>
<td>IV</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Gentamicin, tobramycin, amikacin</td>
<td>IV</td>
<td>+</td>
<td>−</td>
<td>±</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>IV</td>
<td>+</td>
<td>−</td>
<td>±</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Linezolid</td>
<td>po, IV</td>
<td>+</td>
<td>−</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>IV</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>IV</td>
<td>+</td>
<td>−</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
</tbody>
</table>

**Abbreviations:** +, reliable activity; ±, somewhat reliable activity; −, lack of activity; G(+), gram-positive pathogens; G(−), gram-negative pathogens; po, oral.
with cephalosporins but is estimated as 10% or more.211 Meropenem (Merrem), imipenem-cilastatin (Primaxin), and doripenem (Doribax) have similar spectrums of activity and are generally interchangeable. They maintain activity against most clinically significant gram-positive and gram-negative pathogens (including MSSA, enterococci, and \( P. \) aeruginosa), and anaerobes. Ertapenem (Invanz) has a narrower spectrum, which lacks activity against enterococci and \( P. \) aeruginosa. Its use may select out for these pathogens in clinical practice.

Carbapenems may reduce seizure threshold and should be avoided in high-risk patients. It has been suggested that meropenem may have the lowest risk of seizure in the drug class and is often used for infections related to the CNS.

**Fluoroquinolones**

Fluoroquinolones (FQs) most often used in practice are moxifloxacin (Avelox), levofloxacin (Levaquin), and ciprofloxacin (Cipro).212 They have good tissue penetration and serve as empiric therapy for most infections when multidrug resistance is not suspected. Moxifloxacin has strong gram-positive activity, good gram-negative activity, and strong anaerobic activity but lacks urine penetration and should not be used for urinary tract infections. It lacks activity against \( C. \) difficile infection (CDI) outbreaks as a result of killing competitive flora in the bowel. Levofloxacin maintains good activity against most bacteria, whereas ciprofloxacin has strong gram-negative activity at the expense of only moderate gram-positive and anaerobic activity. These traits make ciprofloxacin a nice formulary complement to moxifloxacin. FQs often maintain in vitro activity against MSSA and MRSA but yield a high incidence of treatment failure and resistance; FQ use should be avoided for the treatment of these bacteria. Ciprofloxacin can treat \( E. \) Enterococcus in the urine where it achieves concentrations but should be avoided in other sites of infection. FQ should be avoided in patients at risk for seizures because they may reduce the seizure threshold. FQs have multiple drug interactions, in particular, in SICUs, warfarin (Coumadin), theophylline (Uniphyl), and specifically ciprofloxacin with tizanidine (Zanaflex); concurrent use should be avoided. They also prolong QTc interval and should be used cautiously with drugs with similar effects, such as fluconazole (Diflucan) and amiodarone (Cordarone).

**Aminoglycosides**

Aminoglycosides are among the most potent gram-negative antimicrobials available and have been used effectively for decades.213 Resistance rates decrease from gentamicin (Garamycin) to tobramycin (Nebcin) to amikacin (Amikin) having the most robust activity profile. They remain the gold standard for gram-negative bacteremia owing to potency and concentration in the serum, although their empiric use has diminished as a result of less toxic therapeutic alternatives.214 Aminoglycosides remain a reliable drug class for many multi-drug resistant pathogens. They may be used synergistically with BL antibiotics for resistant strains of \( S. \) aureus and Enterococcus; the BL antibiotic disrupts the bacterial cell wall, allowing the aminoglycoside to penetrate the bacteria and manifest its activity. Dosing has evolved to extended interval, usually 5 mg/kg/d to 7 mg/kg/d (15–21 mg/kg/d for amikacin), to optimize the concentration-dependent killing.215–217 A peak to minimal inhibitory concentration ratio of 10:1 has yielded increased survival.214 Nephrotoxicity is common with a reported incidence as high as 20%; renal function should be closely monitored. Ototoxicity may also occur. Nephrotoxicity and ototoxicity may not be reversible. Pharmacist consultation has demonstrated increased efficacy with decreased toxicity and should routinely be considered.
**MRSA Treatment Options**

Infections caused by MRSA are associated with increased morbidity, mortality, and health care costs. Fortunately, several treatment options are available. Vancomycin, a glycopeptide with a broad gram-positive spectrum, has been the cornerstone of MRSA treatment for decades. Over time, the minimal inhibitory concentration has risen, but true resistance is rare. It also has activity against enterococci, but its use has induced the development of vancomycin-resistant enterococci (VRE), which is on the rise. For both staphylococci and enterococci, BL antibiotics should always be used if possible based on susceptibility results because their efficacy is greater than that of vancomycin for these bacteria. Nephrotoxicity associated with vancomycin is concerning; dosing should be patient-specific to minimize potential risk. Most institutions have pharmacokinetic consult services that can optimize dosing to achieve evidence-based troughs (ranging from 10 to 20 µg/mL depending on indication) while minimizing adverse effects.

Linezolid is well established for the treatment of nosocomial pneumonia and complicated skin and skin structure infections (SSTI). It also maintains activity against VRE, although similar to vancomycin, resistance is on the rise. Limited data suggest superiority of linezolid over vancomycin for the treatment of pneumonia, but this remains controversial. The oral formulation is well absorbed and offers a useful option for patients able to tolerate oral medications. The drug’s weak monoamine oxidase inhibition increases the risk of serotonin syndrome, a rare but fatal complication, when used concurrently with other serotonergic agents. This combination should be avoided if possible. Adverse effects include optic neuropathy, peripheral neuropathy, and pancytopenia, commonly manifested as thrombocytopenia. Limiting the duration of treatment to less than 14 days reduces the likelihood of these complications.

Tigecycline (Tygacil) is a broad-spectrum glycycycline approved for complicated intra-abdominal infections and SSTI infections. It maintains activity against MRSA, VRE, and extended-spectrum BLase-producing pathogens. It lacks activity against *P. aeruginosa*, however, which greatly limits its role as monotherapy. Owing to its similarities to tetracycline, it has been slow to gain acceptance for the treatment of serious life-threatening infections. An unexplained increase in all-cause mortality is observed in patients receiving tigecycline in both phase 3 and 4 studies. Also, tigecycline monotherapy should be avoided in patients with perforated bowel due to poorer outcomes reported in phase 3 trials. Its use is often limited to treating patients with BL allergies, intolerant to conventional therapy, or with polymicrobial infections. Side effects are minimal compared with other agents, most commonly manifested as nausea and vomiting.

Daptomycin (Cubicin) has good activity against MRSA but has little role in SICUs except for treatment of endocarditis or for complicated SSTI where other therapies have failed or are contraindicated. Daptomycin is inactivated by pulmonary surfactant and should not be used to treat bacterial pneumonia. The most common serious adverse effects are myopathy and rhabdomyolysis for which baseline and weekly creatine kinase measurement is recommended. It is associated with the development of eosinophilic pneumonia. If any of these is observed, daptomycin should be immediately discontinued.

In addition to the previously discussed agents there are several other oral options with activity against community-associated MRSA, including Sulfamethoxazole-trimethoprim (Bactrim and Septra), doxycycline (Vibramycin), and clindamycin (Cleocin) (Box 3). These agents are not usually used for severe nosocomial MRSA infection but are often used for community-acquired MRSA infections, usually SSTI.
Clostridium difficile Treatment Options

CDI is an increasingly common complication in health care, including ICUs. Treatment is determined by both episode (initial vs recurrent) and severity of infection (Table 13).\textsuperscript{226} Metronidazole is the drug of choice for the initial episode of mild-to-moderate CDI and has the lowest acquisition cost of all treatment. Both IV and oral metronidazole are effective treatment options. Oral vancomycin is generally reserved for more severe infections due to demonstrated superiority compared with metronidazole. IV vancomycin is not effective for CDI; rectal therapy may be considered when oral therapy is not an option. Combination therapy may be considered in severe or complicated CDI.

Fungal Treatment Options

Fluconazole (Diflucan), an azole antifungal, remains the standard of care for most uncomplicated Candida infections in ICUs, but local susceptibility patterns must also be considered.\textsuperscript{227} It maintains good activity against Candida albicans, the most prevalent species in ICUs, although its activity has decreased against C glabrata over the years, the second most prevalent species. Voriconazole (Vfend), another azole, has slightly enhanced activity against Candida species but not enough to warrant routine use beyond treatment of Aspergillus species.\textsuperscript{227,228} Both agents are associated with elevations in liver enzymes and QTc prolongation but are generally well tolerated. For moderately severe to severe illness or in patients with recent azole exposure, empiric therapy should consist of an echinocandin rather than an azole.\textsuperscript{227} Echinocandins have more potent activity against Candida than azoles and maintain activity against some Aspergillus species. Caspofungin (Cancidas), micafungin (Mycamine), and anidulafungin (Eraxis) are generally considered interchangeable in terms of activity spectrum and side-effect profile. They are generally well tolerated although they can be associated with elevation in liver enzymes.

DRUG SHORTAGES

In recent years, drug shortages have had an increasing impact on patient care; ICUs are not immune to these effects. Several organizations, such as the American Society of Health-System Pharmacists and the American Medical Association, have worked...
closely with legislators and the FDA to promote sustained production of drugs and minimize or prevent future shortages. This process is slow and does not address immediate needs. It is recommended that prescribers work closely with clinical pharmacists to prospectively address and manage potential shortages. Clinical pharmacists should be used to help estimate drug supply, recommend alternative therapies, and provide education to prescribers when formulary changes are made to accommodate shortages.

**SUMMARY**

In summary, appropriate pharmacotherapy, as a supplement to surgical intervention, can improve patient outcomes in SICUs. Given the multiple variables in ICUs that affect pharmacokinetics and pharmacodynamics, however, an understanding of drug properties and pharmacotherapy is essential to optimize care. Collaboration between a clinical pharmacist and intensivist can help improve patient outcomes and provide delivery of safe and cost-effective drug therapy.
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