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36th edition

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To Emily, Papa and Mama Heudebert, Goose, and Jota.

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Chairman's Note

Clinical medicine continues to evolve based on the rapid advances in medical research. It has become more important than ever for physicians to commit to lifelong learning and continuing medical education and use new evidence to guide clinical practice. Tremendous advances in science have led to new biomarkers, better diagnostics, and novel therapies that improve patient outcomes. The *Washington Manual® of Medical Therapeutics* provides an outstanding source of current information focusing on practical clinical approaches to the diagnosis, investigation, and treatment of common medical conditions regularly encountered by internists. The online version and the pocket-book size of the *Washington Manual®* ensure that it will continue to be of enormous assistance to interns, residents, medical students, and other practitioners. The *Washington Manual®* provides an important resource to optimize learning and transfer learning into evidenced-based patient care.

I am very appreciative of the authors, who include outstanding house officers, fellows, and attendings at Washington University/Barnes-Jewish Hospital. Their efforts and exceptional skills are evident in the quality of the final product. In particular, I am proud of our editors: Zachary Crees, Cassandra Fritz, Alonso Heudebert, Jonas Noé, Arvind Rengarajan, and Xiaowen Wang, and series editors Drs. Tom De Fer and Thomas Ciesielski, who have worked tirelessly to produce another outstanding edition of the *Washington Manual® of Medical Therapeutics*. I also thank Dr. Melvin Blanchard, Chief of the Division of Medical Education in the Department of Medicine at Washington University, for his outstanding commitment to our residency training program and his excellent bedside teaching. I am confident that this edition will meet its desired goal of providing practical knowledge that will be directly applied to improving patient care.

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Preface

It is our privilege and honor to introduce the 36th edition of *The Washington Manual® of Medical Therapeutics*. This edition marks the 75th anniversary of *The Manual* and gives opportunity for both celebration and reflection.

In drafting the first edition of *The Manual* in 1943 as a local resource for the Washington University house staff, Wayland MacFarlane likely had little idea he was laying the foundation stone of one of the most successful medical reference manuals in the history of medicine. During the mid-1960s *The Manual* grew in popularity with the publishing of 4,000 copies of the 16th edition by Robert Packman, MD, making it available to numerous medical schools across in the United States for the first time. The subsequent edition grew to 25,000 sold copies. *The Manual* has since expanded to incorporate the broad depth of medical knowledge in its increasing complexity. Seventy-five years after Dr. MacFarlane first put pen to paper, *The Manual* has sold more than 1 million electronic and print copies worldwide and has been translated into over 20 languages, without losing sight of the initial mission of providing relevant, evidence-based clinical support to physicians at the bedside and positively impacting patient care.

This enormous work has been made possible by the tireless efforts of generations of physicians. The well-known quote, "If I have seen a little further, it is by standing on the shoulders of giants" accurately reflects the constant progress of the series, each edition advancing by building on the work of those who have gone before us.

This edition is foremost a tribute to the Washington University medicine house staff, fellows, medical students, and attendings with whom we work daily. Their role modeling, mentoring, compassion, teaching, brilliance, and hard work are an unlimited source of enthusiasm, inspiration, and dedication. We consider ourselves very lucky and grateful to have trained alongside them, in service to our patients.

We have great appreciation for the substantial support and direction that Dr. Thomas De Fer and Dr. Thomas Ciesielski, the series editors, provided in the creation of this edition. We also sincerely thank Katie Sharp and the editorial staff at Wolters Kluwer for their assistance and guidance in this effort.

We have had the distinction of serving as chief residents in the Department of Medicine at Washington University School of Medicine in St. Louis. Our firm chiefs, Drs. Megan Wren, Emily Fondahn, Geoffrey Cislo, Dominique Cosco, Amber Deptola, and Patricia Kao, have been instrumental over the course of the year, serving as mentors and role models. Our program director, Dr. Melvin Blanchard, provided guidance and support in the production of *The Manual*. Our Chairman of Medicine, Dr. Vicky Fraser, has served as wonderful role model and mentor and holds our sincere admiration.

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1 Inpatient Care in Internal Medicine

Mark Thoelke, Eric Johnson, and Crystal Atwood

General Care of the Hospitalized Patient

GENERAL PRINCIPLES

- Although a general approach to common problems can be outlined, **therapy must be individualized**. All diagnostic and therapeutic procedures should be explained carefully to the patient, including the potential risks, benefits, and alternatives.
- The period of hospitalization represents a complex interplay of multiple caregivers that subjects the patient to potential harm by **medical errors and iatrogenic complications**. Every effort must be made to minimize these risks. Basic measures include the following:
  - Use of standardized abbreviations and dose designations
  - Excellent communication between physicians and other caregivers
  - Institution of appropriate prophylactic precautions
  - Prevention of nosocomial infections, including attention to hygiene and discontinuation of unnecessary catheters
  - Medicine reconciliation at all transfers of care
- **Hospital orders**
  - Computer order entry offers admission order sets that should be entered promptly after evaluation of a patient. A contact number should be made available.
  - Daily rounds should include assessment for ongoing need of IV fluids, telemetry, catheters, and supplemental oxygen, all of which can limit mobility.
  - Routine daily labs, such as CBC and BMP, should be discouraged because significant iatrogenic anemia may develop.
- **Discharge**
  - **Discharge planning** begins at the time of admission. Assessment of the patient's social situation and potential discharge needs should be made at this time.
  - **Early coordination** with nursing, social work, and case coordinators/managers facilitates efficient discharge and a complete post discharge plan.
  - **Patient education** should occur regarding changes in medications and other new therapies. Compliance with treatment is influenced by the patient's understanding of that treatment.
  - **Prescriptions** should be written for all new medication, and the patient should be provided with a complete medication list including instructions and indications.
  - **Communication** with physicians who will be resuming care of the patient is important for optimal follow-up care and should be a component of the discharge process.

PROPHYLACTIC MEASURES

Venous Thromboembolism Prophylaxis

GENERAL PRINCIPLES

Epidemiology

Venous thromboembolism (VTE) is a preventable cause of death in hospitalized patients. In the largest observational study to date attempting to risk-stratify medical patients, 1.2%

of medical patients developed VTE within 90 days of admission. A total of 10%–31% of patients were deemed to be at high risk for VTE, defined as having **two or more points** by weighted risk factors below.[1]

- three points: previous VTE, thrombophilia
- one point: cancer, age >60

Prevention

- **Ambulation** several times a day should be encouraged.
- **Pharmacologic prophylaxis** results in a 50% decrease in VTE risk, although this includes many asymptomatic calf vein thromboses that do not progress. No overall mortality benefit from prophylaxis has been demonstrated.
- Acutely ill patients at high risk of VTE, without bleeding or high risk of bleeding, should be treated with low-dose unfractionated heparin (UFH), 5000 units SC q12h or q8, or low-molecular-weight heparin (LMWH); enoxaparin, 40 mg SC daily, or dalteparin, 5000 units SC daily; or fondaparinux, 2.5 mg SC daily.
- Betrixaban is the only direct oral anticoagulant approved for DVT prophylaxis in hospitalized patients. Betrixaban reduced the composite outcome of asymptomatic and symptomatic VTE plus VTE-related deaths when compared with enoxaparin.[2]
- Aspirin alone is not sufficient for prophylaxis in hospitalized patients.[3]
- At-risk patients with contraindications to anticoagulation prophylaxis may receive mechanical prophylaxis with intermittent pneumatic compression or graded compression stockings, although evidence of benefit is lacking.[4]

Decubitus Ulcers

GENERAL PRINCIPLES

Epidemiology

Decubitus ulcers typically occur within the first 2 weeks of hospitalization and can develop within 2–6 hours. Once they develop, decubitus ulcers are difficult to heal and have been associated with increased mortality.[5] More than 100 risk factors for the development of decubitus ulcers have been identified; the most important include immobility, malnutrition, reduced skin perfusion, and sensory loss.[6]

Prevention

Prevention is the key to management of decubitus ulcers. It is recognized that not all decubitus ulcers are avoidable.[7] Preventative measures include the following:

- **Risk prediction** using the Norton or Braden scales scores immobility, activity levels, incontinence, impaired nutritional status, impaired circulation, and altered level of consciousness to identify patients at risk for pressure injury.
- **Advanced static mattresses or** overlays should be used in at-risk patients.[8]
- **Skin care,** including daily inspection with particular attention to bony prominences including heels, minimizing exposure to moisture, and applying moisturizers to dry sacral skin.
- **Nutritional supplements** may be provided to patients at risk.
- **Frequent repositioning** (minimum of every 2 h, or every 1 h for wheelchair-bound patients) is suggested.
- **Multilayer foam dressings** have been shown to reduce the rates of pressure injuries.[9]

DIAGNOSIS

National Pressure Ulcer Advisory Panel Staging:

- **Suspected deep tissue injury:** Purple or maroon localized area of discolored intact skin or blood-filled blister because of damage of underlying soft tissue from pressure and/or

shear. The area may be preceded by tissue that is painful, firm, mushy, boggy, warmer, or cooler as compared with adjacent tissue.

- **Stage I:** Intact skin with nonblanchable redness of a localized area usually over a bony prominence. Darkly pigmented skin may obscure findings.
- **Stage II:** Partial thickness loss of dermis presenting as a shallow open ulcer with a red pink wound bed without slough. May also present as a blister.
- **Stage III:** Full thickness tissue loss. Subcutaneous fat may be visible, but the bone, tendon, or muscle is not exposed. Slough may be present but does not obscure the depth of tissue loss. May include undermining and tunneling.
- **Stage IV:** Full thickness tissue loss with exposed bone, tendon, or muscle. Slough or eschar may be present on some parts of the wound bed. Often includes undermining and tunneling.
- **Unstageable:** Full thickness tissue loss in which the base of the ulcer is covered by slough (yellow, tan, gray, green, or brown) and/or eschar (tan, brown, or black) in the wound bed.

TREATMENT

Optimal treatment of pressure ulcers remains poorly defined. There is evidence to support the following:[10]

- **Hydrocolloid or foam** dressings may reduce wound size.
- **Protein or amino acid supplementation** is recommended, although there are insufficient data to recommend a specific supplement regimen.[11]
- **Electrical stimulation** may accelerate healing.
- **Other adjunctive therapies** with less supporting evidence include radiant heat, negative pressure, and platelet-derived growth factor. Topical agents (silver sulfadiazine) may optimizing healing or lead to minor slough debridement (Santyl, Xenaderm).
- There is no role for antibiotics to aid healing of a noninfected ulcer.

OTHER PRECAUTIONS

- **Fall precautions** should be written for patients who have a history of falls or are at high risk of a fall (e.g., dementia, weakness, orthostasis). Falls are the most common accident in hospitalized patients, frequently leading to injury. **Fall risk should not be equated with bed rest,** which may lead to debilitation and higher risk of future falls.
- **Seizure precautions,** which include padded bed rails and an oral airway at the bedside, should be considered for patients with a history of seizures or those at risk of seizing.
- **Restraint orders** are written for patients who are at risk of injuring themselves or interfering with their treatment because of disruptive or dangerous behaviors. Physical restraints may exacerbate agitation. Bed alarms, sitters, and sedatives are alternatives in appropriate settings.

ACUTE INPATIENT CARE

An approach to selected common complaints is presented in this section. An evaluation should generally include a directed history and physical examination, review of the medical problem list (including chronic conditions), review of medications with attention to recent medication changes, and consideration of recent procedures.

Chest Pain

GENERAL PRINCIPLES

Common causes of chest pain range from life-threatening causes such as myocardial infarction (MI) and pulmonary embolism to other causes including esophageal reflux, peptic ulcer disease, pneumonia, costochondritis, shingles, trauma, and anxiety.

DIAGNOSIS

History and Physical Examination

- History should include previous cardiac or vascular disease history, cardiac risk factors, and factors that would predispose the patient to a pulmonary embolus.
- Physical examination is ideally conducted during an episode of pain and includes vital signs (bilateral blood pressure [BP] measurements if considering aortic dissection), cardiopulmonary and abdominal examination, and inspection and palpation of the chest.

Diagnostic Testing

Assessment of oxygenation status, chest radiography, and ECG is appropriate in most patients. Serial cardiac biomarkers should be obtained if there is suspicion of ischemia. Spiral CT and ventilation/perfusion scans are employed to diagnose pulmonary embolus.

TREATMENT

- If cardiac ischemia is a concern, see Chapter 4, Ischemic Heart Disease, for details.
- If a gastrointestinal (GI) source is suspected, Maalox, viscous lidocaine, and hyoscyamine (1:1:1 mix) can be administered.
- Musculoskeletal pain typically responds to acetaminophen or NSAID therapy.
- Prompt empiric anticoagulation if there is high suspicion for MI or pulmonary embolism.

Dyspnea

GENERAL PRINCIPLES

Dyspnea is most commonly caused by a cardiopulmonary abnormality, such as congestive heart failure (CHF), cardiac ischemia, bronchospasm, pulmonary embolus, infection, mucus plugging, and aspiration. Dyspnea must be promptly and carefully evaluated.

DIAGNOSIS

History and Physical Examination

- Initial evaluation should include a review of the medical history for underlying pulmonary or cardiovascular disease and a directed history.
- A detailed cardiopulmonary examination should take place, including vital signs.

Diagnostic Testing

- Oxygen assessment by pulse oximetry or arterial blood gas and chest radiography are useful in most patients.
- Other diagnostic measures should be directed by the findings in the initial evaluation.

TREATMENT

Oxygen should be administered promptly if needed. Other therapeutic measures should be directed by the findings in the initial evaluation.

Acute Hypertensive Episodes

GENERAL PRINCIPLES

- Acute hypertensive episodes in the hospital are most often caused by inadequately treated essential hypertension. If there is evidence of end-organ damage, IV medications are

indicated. Oral agents are more appropriate for hypertensive urgency without end-organ damage.
- Hypertension associated with withdrawal syndromes (e.g., alcohol, cocaine) and rebound hypertension associated with sudden withdrawal of antihypertensive medications (i.e., clonidine, α-adrenergic antagonists) should be considered. These entities should be treated as discussed in Chapter 3, Preventive Cardiology.
- Volume overload and pain may exacerbate hypertension and should be recognized appropriately and treated.

Fever

GENERAL PRINCIPLES

Fever accompanies many illnesses and is a valuable marker of disease activity. Infection is a primary concern. Drug reaction, malignancy, VTE, vasculitis, central fever, and tissue infarction are other possibilities but are diagnoses of exclusion.

DIAGNOSIS

History and Physical Examination

- History should include chronology of the fever and associated symptoms, medications, potential exposures, and a complete social and travel history.
- Physical examination should include oral or rectal temperature. In the hospitalized patient, special attention should be paid to any IV lines, asymmetric edema, a thorough skin exam, and indwelling devices such as urinary catheters.
- For management of neutropenic fever see Chapter 22, Cancer.

Diagnostic Testing

- Testing includes blood and urine cultures, complete blood count (CBC) with differential, serum chemistries with liver function tests, urinalysis, and stool cultures if appropriate.
- Diagnostic evaluation generally includes chest radiography.
- Cultures of abnormal fluid collections, sputum, cerebrospinal fluid, and stool should be sent if clinically indicated. Cultures are ideally obtained prior to initiation of antibiotics; however, antibiotics should not be delayed if serious infection is suspected.

TREATMENT

- Antipyretic drugs may be given to decrease associated discomfort. Aspirin, 325 mg, and acetaminophen, 325–650 mg PO or PR q4h, are the drugs of choice.
- Empiric antibiotics should be considered in hemodynamically unstable patients in whom infection is a primary concern, as well as in neutropenic and asplenic patients.
- Heat stroke and malignant hyperthermia are medical emergencies that require prompt recognition and treatment (see Chapter 26, Medical Emergencies).

Pain

GENERAL PRINCIPLES

Pain is subjective, and therapy must be individualized. Chronic pain may not be associated with any objective physical findings. Pain scales can be employed for quantitation.

TREATMENT

- Acute pain usually requires short term therapy.
- **Chronic pain requires multimodality management to keep opioid use to a minimum to prevent risk of dependence and subsequent escalation of opioid doses.** Higher doses of opioids have been shown to increase the risk of overdose without providing increased pain relief.[12]
- If pain is refractory to medical therapy, then nonpharmacologic modalities, such as nerve blocks, sympathectomy, and cognitive behavioral therapy, may be appropriate.

Nonopioid Analgesics

- Acetaminophen
  - Effects: Antipyretic and analgesic actions; no antiinflammatory or antiplatelet properties.
  - Dosage: 325–1000 mg q4–6h (maximum dose, 4 g/d), available in oral, IV, and rectal suppository. Dosage in patients with liver disease should not exceed 2 g/d.
  - Adverse effects: The principal *advantage* of acetaminophen is its lack of gastric toxicity. Hepatic toxicity may be serious, and acute overdose with 10–15 g can cause fatal hepatic necrosis (see Chapter 19, Liver Diseases, and Chapter 26, Medical Emergencies).
- Aspirin
  - Effects: Aspirin has analgesic, antipyretic, antiinflammatory, and antiplatelet effects. Aspirin should be used with caution in patients with hepatic or renal disease or bleeding disorders, those who are pregnant, and those who are receiving anticoagulation therapy. Antiplatelet effects may last for up to 1 week after a single dose.
  - Dosage: 325–650 mg q4h PRN (maximum dose, 4 g/d), available in oral and rectal suppository. Enteric coated formulation may minimize GI side effects.
  - Adverse effects: Dose-related side effects include tinnitus, dizziness, and hearing loss. Dyspepsia and GI bleeding can develop and may be severe. Hypersensitivity reactions, including bronchospasm, laryngeal edema, and urticaria, are uncommon, but patients with asthma and nasal polyps are more susceptible. Chronic use can result in interstitial nephritis and papillary necrosis.
- NSAIDs
  - Effects: NSAIDs have analgesic, antipyretic, and antiinflammatory properties mediated by inhibition of cyclooxygenase. All NSAIDs have similar efficacy and toxicities, with a side effect profile similar to that of aspirin. Patients with allergic or bronchospastic reactions to aspirin should not be given NSAIDs. See Chapter 25, Arthritis and Rheumatologic Diseases, for further information on NSAIDs.
- Anticonvulsants (e.g., gabapentin, pregabalin, carbamazepine, oxcarbazepine), tricyclic antidepressants (e.g., amitriptyline), and duloxetine are PO agents that can be used to treat neuropathic pain.
- Topical anesthetics (e.g., lidocaine) may provide analgesia to a localized region (e.g., postherpetic neuralgia).

Opioid Analgesics

Effects: Opioid analgesics are pharmacologically similar to opium or morphine and are indicated for moderate to severe pain, particularly when there is a contraindication to NSAIDS.

- Dosage: Table 1-1 lists equianalgesic dosages.
- For acute pain management, the **lowest effective dose of immediate-release opioids** should be given. Use of nonopioid pain medications and nonpharmacological pain management strategies to minimize opioid needs is encouraged.
- When changing to a new narcotic because of poor response or patient intolerance, the new medication should be started at 50% the equianalgesic dose to account for incomplete cross-tolerance.

TABLE 1-1 Equipotent Doses of Opioid Analgesics

Drug	Onset (min)	Duration (h)	IM/IV/SC (mg)	PO (mg)
Fentanyl	7–8	1–2	0.1	NA
Levorphanol	30–90	4–6	2	4
Hydromorphone	15–30	2–4	1.5–2.0	7.5
Methadone	30–60	4–12	10	20
Morphine	15–30	2–4	10	30[a]
Oxycodone	15–30	3–4	NA	20
Codeine	15–30	4–6	120	200

[a]An IM:PO ratio of 1:2 to 1:3 used for repetitive dosing.
Note: Equivalences are based on single-dose studies.
NA, not applicable.

- Parenteral and transdermal administration are useful in the setting of dysphagia, emesis, or decreased GI absorption.
- Agents with short half-lives, such as morphine, should be used. Narcotic-naïve patients should be started on the lowest possible doses, whereas patients with demonstrated tolerance will require higher doses.
- Patient-controlled analgesia often is used to control pain in a postoperative or terminally ill patient. Opioid-naïve patients should not have basal rates prescribed because of risk of overdose.
- If a patient requires continuous (basal) analgesia, supplementary PRN doses for breakthrough pain at doses of roughly 5%–15% of the daily basal dose can be provided. If frequent PRN doses are required, the maintenance dose should be increased, or the dosing interval should be decreased.
- Severe pain uncontrolled with large doses of opiates, particularly while using patient-controlled analgesia with basal rates, may warrant consultation with a pain specialist.
- Selected opiates
  - **Tramadol** is an opioid agonist and a centrally acting nonopioid analgesic that acts on pain processing pathways.
    - Dosage: 50–100 mg PO q4–6h can be used for acute pain. For elderly patients and those with renal or liver dysfunction, dosage reduction is recommended.
    - Adverse effects: Concomitant use of alcohol, sedatives, or narcotics should be avoided. Nausea, dizziness, constipation, and headache may also occur. Respiratory depression has not been described at prescribed dosages but may occur with overdose. Tramadol should not be used in patients who are taking a monoamine oxidase inhibitor, as it can contribute to serotonin syndrome.
  - Codeine is usually given in combination with aspirin or acetaminophen.
  - Oxycodone and hydrocodone are both available orally in combination with acetaminophen; oxycodone is available without acetaminophen in immediate-release and sustained-release formulations. Care should be taken to avoid acetaminophen overdose with these formulations.
  - Morphine sulfate preparations include both immediate release and sustained release. The liquid form can be useful in patients who have difficulty in swallowing pills. Morphine should be used with caution in renal insufficiency.
  - Methadone is very effective when administered orally and suppresses the symptoms of withdrawal from other opioids because of its extended half-life. Despite its long elimination half-life, its analgesic duration of action is much shorter.

- Hydromorphone is a potent morphine derivative, five to seven times the strength of morphine, and caution should be used when ordering this medication.
- Fentanyl is available in a transdermal patch with sustained release over 72 hours. Initial onset of action is delayed. Respiratory depression may occur more frequently with fentanyl.

• Precautions
- Opioids are relatively contraindicated in acute disease states in which the pattern and degree of pain are important diagnostic signs (e.g., head injuries). They also may increase intracranial pressure.
- Opioids should be used with caution in patients with hypothyroidism, Addison disease, hypopituitarism, anemia, respiratory disease (e.g., chronic obstructive pulmonary disease [COPD], asthma, kyphoscoliosis, severe obesity), severe malnutrition, debilitation, or chronic cor pulmonale.
- Opioid dosage should be adjusted for patients with impaired hepatic or renal function.
- Drugs that potentiate the adverse effects of opioids include phenothiazines, antidepressants, benzodiazepines, and alcohol.
- Tolerance develops with chronic use and coincides with the development of physical dependence, which is characterized by a withdrawal syndrome (anxiety, irritability, diaphoresis, tachycardia, GI distress, and temperature instability) when the drug is stopped abruptly. It may occur after only 2 weeks of therapy.
- Administration of an opioid antagonist may precipitate withdrawal after only 3 days of therapy. Tapering the medication slowly over several days can minimize withdrawal.
- The quantity of opioid tablets prescribed at discharge should not exceed the expected duration of pain. A quantity to cover 3 days or less should be sufficient. **Prescribing a quantity at discharge to cover more than 7 days duration of pain should not be necessary and is discouraged.**[12]

• Adverse and toxic effects
- Central nervous system (CNS) effects include sedation, euphoria, and pupillary constriction.
- **Respiratory depression** is dose related and pronounced after IV administration.
- Cardiovascular effects include **peripheral vasodilation** and hypotension.
- GI effects include **constipation**, **nausea**, and **vomiting**. Stool softeners and laxatives should be prescribed to prevent constipation. Opioids may precipitate toxic megacolon in patients with inflammatory bowel disease.
- Genitourinary effects include **urinary retention.**
- **Pruritus** occurs most commonly with spinal administration.
- **Opioid overdose**
  - Naloxone, an opioid antagonist, should be readily available for administration in the case of accidental or intentional overdose. For details of administration, see Chapter 26, Medical Emergencies.
  - Naloxone home rescue kits have been shown to reduce opioid overdose mortality.[13] **Patients being discharged home on more than 50 morphine milligram equivalents per day have a higher risk of overdose** and may benefit from a prescription for intranasal naloxone at discharge.

Altered Mental Status

GENERAL PRINCIPLES

Mental status changes have a broad differential diagnosis that includes neurologic (e.g., stroke, seizure, delirium), metabolic (e.g., hypoxemia, hypoglycemia), toxic (e.g., drug

effects, alcohol withdrawal), and other etiologies. Infection (e.g., urinary tract infections, pneumonia) is a common cause of mental status changes in the elderly and in patients with underlying neurologic disease. Sundown syndrome refers to the appearance of worsening confusion in the evening and is associated with dementia, delirium, and unfamiliar environments.

DIAGNOSIS

History and Physical Examination

- Focus particularly on medications, underlying dementia, cognitive impairment, neurologic or psychiatric disorders, and a history of alcohol and/or drug use.
- Family and nursing personnel may be able to provide additional details.
- Physical examination generally includes vital signs, a search for sites of infection, a complete cardiopulmonary examination, and a detailed neurologic examination including mental status evaluation.

Diagnostic Testing

- Testing includes blood glucose, serum electrolytes, creatinine, CBC, urinalysis, and oxygen assessment.
- Other evaluation, including lumbar puncture, toxicology screen, cultures, thyroid function tests, noncontrast head CT, electroencephalogram, chest radiograph, or ECG should be directed by initial findings.

TREATMENT

Management of specific disorders is discussed in Chapter 27, Neurologic Disorders, available in the online version.

Medications

Agitation and psychosis may be features of a change in mental status. The antipsychotic haloperidol and the benzodiazepine lorazepam are commonly used in the acute management of these symptoms. Second-generation antipsychotics (risperidone, olanzapine, quetiapine, clozapine, ziprasidone, aripiprazole, paliperidone) are alternative agents that may lead to decreased incidence of extrapyramidal symptoms. All of these agents pose risks to elderly patients and those with dementia if given long term.

- Haloperidol is the initial drug of choice for acute management of agitation and psychosis. The initial dose of 0.5–5 mg (0.25 mg in elderly patients) PO and 2–10 mg IM/IV can be repeated every 30–60 minutes. Haloperidol has fewer active metabolites and fewer anticholinergic, sedative, and hypotensive effects than other antipsychotics but may have more extrapyramidal side effects. In low dosages, haloperidol rarely causes hypotension, cardiovascular compromise, or excessive sedation.
- Prolongation of the QT interval. Use should be discontinued with prolongation of QTc >450 ms or 25% above baseline.
- Postural hypotension may occasionally be acute and severe after administration. IV fluids should be given initially for treatment. If vasopressors are required, dopamine should be avoided because it may exacerbate the psychotic state.
- Neuroleptic malignant syndrome (see Chapter 27, Neurologic Disorders).
- Lorazepam is a benzodiazepine that is useful for agitation and psychosis in the setting of hepatic dysfunction and sedative or alcohol withdrawal. The initial dose is 0.5–1 mg IV. Lorazepam has a short duration of action and few active metabolites. Excessive sedation and respiratory depression can occur.

Nonpharmacologic Therapies

Patients with delirium of any etiology often respond to frequent reorientation, observance of the day–night light cycle, and maintenance of a familiar environment.

Insomnia and Anxiety

GENERAL PRINCIPLES

- Insomnia and anxiety may be attributed to a variety of underlying medical or psychiatric disorders, and symptoms may be exacerbated by hospitalization.
- Causes of insomnia include environmental disruptions, mood and anxiety disorders, substance abuse disorders, common medications (i.e., β-blockers, steroids, bronchodilators), sleep apnea, hyperthyroidism, and nocturnal myoclonus.
- Anxiety may be seen in anxiety disorder, depression, substance abuse disorders, hyperthyroidism, and complex partial seizures.

DIAGNOSIS

The diagnosis of insomnia and anxiety is a clinical one. No laboratory or imaging tests help in establishing the diagnosis; however, they can help to rule out other etiologies.

TREATMENT

Benzodiazepines

Benzodiazepines are frequently used in management of anxiety and insomnia. Table 1-2 provides a list of selected benzodiazepines and their common uses and dosages.

- Pharmacology: Most benzodiazepines undergo oxidation to active metabolites in the liver. Lorazepam, oxazepam, and temazepam undergo glucuronidation to inactive metabolites; therefore, these agents may be particularly useful in the elderly and in those with liver disease. Benzodiazepines with long half-lives may accumulate substantially in the elderly, in whom the half-life may be increased manyfold.
- Dosages: Relief of anxiety and insomnia is achieved at the doses outlined in Table 1-2. Therapy should be started at the lowest recommended dosage with intermittent dosing schedules.
- Side effects include drowsiness, dizziness, fatigue, psychomotor impairment, and anterograde amnesia. Benzodiazepine toxicity is heightened by malnutrition, advanced age, hepatic disease and concomitant use of alcohol, other CNS depressants, and CYP3A4 inhibitors. The elderly may experience falls, paradoxical agitation, and delirium.
  - IV administration of diazepam and midazolam can be associated with hypotension, bradycardia, and respiratory or cardiac arrest.
  - Respiratory depression can occur even with oral administration in patients with respiratory compromise.
  - Tolerance to benzodiazepines can develop and dependence may develop after only 2–4 weeks of therapy.
  - Seizures and delirium may also occur with sudden discontinuation of benzodiazepines. A *withdrawal syndrome* consisting of agitation, irritability, insomnia, tremor, palpitations, headache, GI distress, and perceptual disturbance begins 1–10 days after a rapid decrease in dosage or abrupt cessation of therapy. Short-acting and intermediate-acting drugs should be decreased by 10%–20% every 5 days, with a slower taper in the final few weeks. Long-acting preparations can be tapered more quickly.
- Overdose: **Flumazenil**, a benzodiazepine antagonist, should be readily available in case of accidental or intentional overdose. For details of administration, see Chapter 26, Medical Emergencies.

TABLE 1-2 Characteristics of Selected Benzodiazepines

Drug	Route	Common Uses	Usual Dosage	Half-Life (h)[a]
Alprazolam	PO	Anxiety disorders	0.75–4.0 mg/24 h (in three doses)	12–15
Chlordiazepoxide	PO	Anxiety disorders, alcohol withdrawal	15–100 mg/24 h(in divided doses)	5–30
Clonazepam	PO	Anxiety disorders, seizure disorders	0.5–4.0 mg/24 h (in two doses)	18–28
Diazepam	PO	Anxiety disorders, seizure disorders, preanesthesia	6–40 mg/24 h (in one to four doses)	20–50
	IV		2.5–20.0 mg (slow IV push)	20–50
Flurazepam	PO	Insomnia	15–30 mg at bedtime	50–100
Lorazepam[b]	PO	Anxiety disorders	1–10 mg/24 h (in two to three doses)	10–20
	IV or IM	Preanesthetic medication	0.05 mg/kg (4 mg max)	10–20
Midazolam	IV	Preanesthetic and intraoperative medication	0.01–0.05 mg/kg	1–12
	IM		0.08 mg/kg	1–12
Oxazepam[b]	PO	Anxiety disorders	10–30 mg/24 h (in three to four doses)	5–10
Temazepam[b]	PO	Insomnia	15–30 mg at bedtime	8–12
Triazolam	PO	Insomnia	0.125–0.250 mg at bedtime	2–5

[a]Half-life of active metabolites may differ.
[b]Metabolites are inactive.

Trazodone

- Trazodone is a serotonin receptor antagonist antidepressant that may be useful for the treatment of severe anxiety or insomnia. Common dosing is 50–100 mg at bedtime.
- It is highly sedating and can cause postural hypotension. It is rarely associated with priapism.
- Levels may be substantially increased when used with CYP3A4 inhibitors.

Nonbenzodiazepine Hypnotics

These agents appear to act on the benzodiazepine receptor and have been shown to be safe and effective for initiating sleep. All should be used with caution in patients with impaired respiratory function.

- Zolpidem is an imidazopyridine hypnotic agent that is useful for the treatment of insomnia. It has no withdrawal syndrome, rebound insomnia, or tolerance. Side effects include headache, daytime somnolence, and GI upset. The starting dose is 5 mg PO every night at bedtime.
- Zaleplon has a half-life of approximately 1 hour and no active metabolites. Side effects include dizziness and impaired coordination. The starting dose is 10 mg PO at bedtime (5 mg for the elderly or patients with hepatic dysfunction).
- Eszopiclone offers a longer half-life compared to the previous agents. Side effects include headache and dizziness. Starting dose is 1 mg PO at bedtime.
- Ramelteon is a melatonin analog. The usual dose is 8 mg PO at bedtime.

Antihistamines

Over-the-counter antihistamines can be used for insomnia and anxiety, particularly in patients with a history of drug dependence. Anticholinergic side effects limit the utility, especially in the elderly.

PERIOPERATIVE MEDICINE

The role of the medical consultant is to estimate the level of risk associated with a given procedure, determine the need for further evaluation based on this risk estimate, and prescribe interventions to mitigate risk. Although preoperative consultations often focus on cardiac risk, it is essential to remember that poor outcomes can result from significant disease in other organ systems. Evaluation of the entire patient is necessary to provide optimal perioperative care.

Preoperative Cardiac Evaluation

GENERAL PRINCIPLES

Perioperative cardiac complications are generally defined as cardiac death, MIs (both ST and non-ST elevation), CHF, and clinically significant rhythm disturbances.

Epidemiology

- Overall, an estimated 50,000 perioperative infarctions and one million other cardiovascular complications occur annually.[14] Of those who have a perioperative MI, the risk of in-hospital mortality is estimated at 10%–15%.[15]
- Perioperative MI (PMI) is believed to occur via two distinct mechanisms. Type I PMI results from erosion or rupture of unstable atherosclerotic plaque, leading to coronary thrombosis and subsequent myocardial injury. Type II PMI occurs when myocardial oxygen demand exceeds supply in the absence of overt thrombosis.
- Although angiographic data suggest that existing stenoses may underpin some perioperative events, a significant number of PMIs are "stress" related (Type II) and not because of plaque rupture.[16,17]
- Autopsy data indicate that fatal PMIs occur predominantly in patients with multivessel and especially left main coronary artery disease, via the same mechanism as non-PMIs.[18]

DIAGNOSIS

Clinical Presentation

History

The aim is to identify patient factors and comorbid conditions that will affect perioperative risk. Current guidelines focus on identification of active cardiac disease and known risk factors for perioperative events, which include:

- Unstable coronary syndromes including severe angina
- Recent MI (defined as >7 but <30 days)
- Decompensated CHF (New York Heart Association class IV, worsening or new-onset heart failure [HF])
- Significant arrhythmia including nonsinus rhythm (rate controlled and stable)
- Severe valvular disease
- Clinical risk factors for coronary artery disease (CAD)
- Preexisting, stable CAD
- Compensated or prior CHF
- Diabetes mellitus
- Prior cerebrovascular accident (CVA) or transient ischemic attack (TIA)
- Chronic kidney disease
- Poorly controlled hypertension
- Abnormal ECG (e.g., left ventricular hypertrophy, left bundle branch block, ST-T wave abnormalities)
- Age >70 years identified in several studies as a significant risk factor but not uniformly accepted as independent.[19,20]

Physical Examination

Specific attention should be paid to the following:

- Vital signs, with particular evidence of hypertension. Systolic blood pressure (SBP) <180 and diastolic blood pressure (DBP) <110 are generally considered acceptable. The management of stage III hypertension (SBP >180 or DBP >110) is controversial. However, postponing elective surgery to allow adequate BP control in this setting seems reasonable; how long to wait after treatment is implemented remains unclear.
- Evidence of **decompensated CHF** (elevated jugular venous pressure, rales, S3, edema).
- **Murmurs suggestive of significant valvular lesions.** According to the 2014 American Heart Association (AHA)/American College of Cardiology (ACC) Guideline for the Management of Patients with Valvular Heart Disease, the risk of noncardiac surgery is increased in all patients with significant valvular heart disease, although symptomatic aortic stenosis (AS) is thought to carry the greatest risk. The estimated rate of cardiac complications in patients with undiagnosed severe AS undergoing noncardiac surgery is 10%–30%. However, aortic valve replacement is also associated with considerable risk. Risk–benefit analysis appears to favor proceeding to intermediate-risk elective noncardiac surgery (see below) with appropriate intra- and postoperative hemodynamic monitoring (including intraoperative right heart catheter or transesophageal echocardiogram) as opposed to prophylactic aortic valve replacement in the context of asymptomatic severe disease. The same recommendations (albeit with less supporting evidence) apply to asymptomatic severe mitral regurgitation, asymptomatic severe AR with normal ejection fraction, and asymptomatic severe mitral stenosis (assuming valve morphology is not amenable to percutaneous balloon mitral commissurotomy, which should otherwise be considered to optimize cardiac status prior to proceeding to surgery). Symptomatic severe valvular disease of any type should prompt preoperative cardiology consultation. See the section on Valvular Heart Disease in Chapter 6.

Diagnostic Criteria

The 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery offers a stepwise approach to preoperative evaluation and risk stratification (Figure 1-1).

- Step 1: Establish the urgency of surgery. Many surgeries are unlikely to allow for a time-consuming evaluation.
- Step 2: Assess for active cardiac conditions (see History, above).

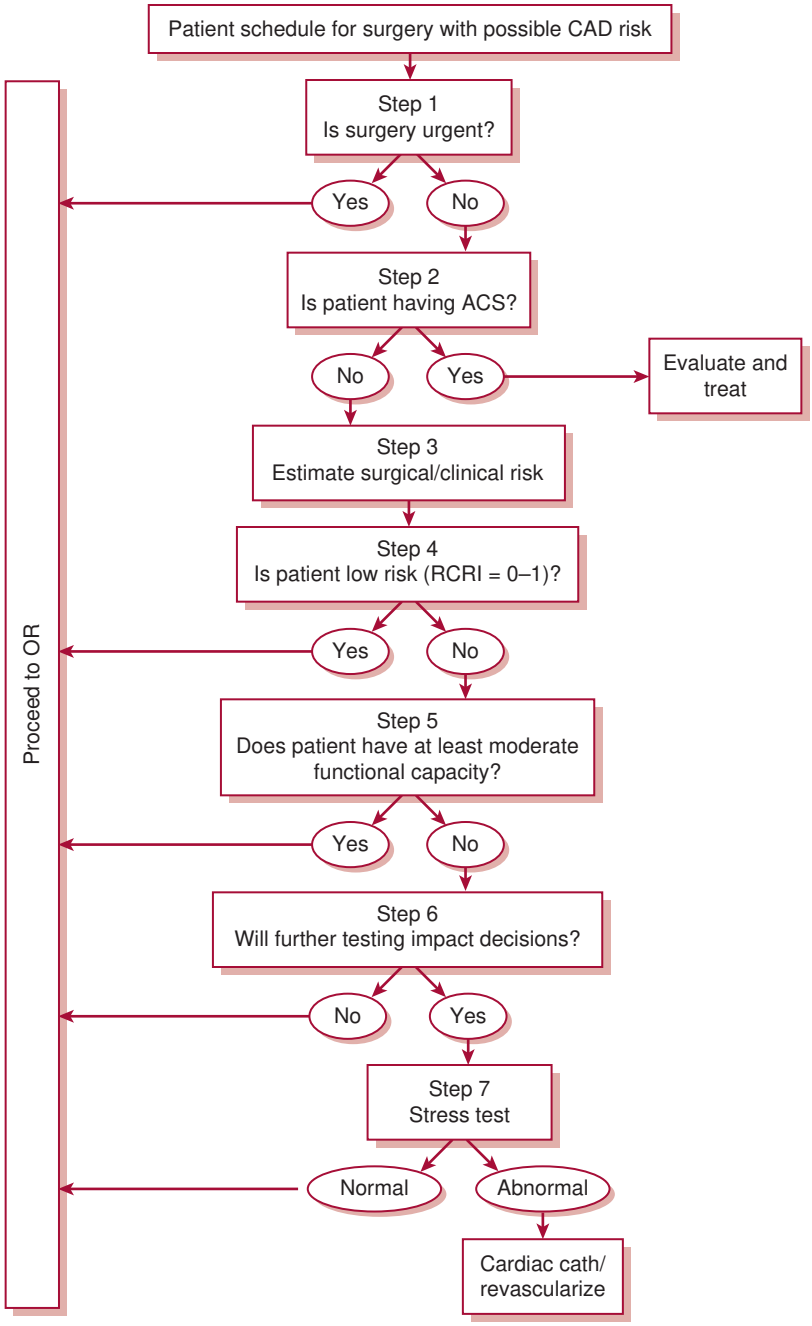

Figure 1-1. Cardiac evaluation algorithm for noncardiac surgery. (Modified from *Circulation*. 2014;130:e278-e333.)

- Step 3: Determine the surgery-specific risk as follows:
  - Low-risk surgeries (<1% expected risk of adverse cardiac events) include superficial procedures, cataract/breast surgery, endoscopic procedures, and most procedures that can be performed in an ambulatory setting.
  - Intermediate-risk surgeries (1%–5% risk of adverse cardiac events) include carotid endarterectomy, intraperitoneal/intrathoracic surgery, orthopedic surgery, head and neck surgery, and prostate surgery.
  - Vascular surgery involving extremity revascularization or aortic repair generally carries the highest risk (>5% risk of adverse cardiac events).
- Step 4: Assess the patient's functional capacity.

  Poor functional capacity (<4 metabolic equivalents [METs]) is associated with an increased risk of perioperative cardiac events.[21,22] Although exercise testing is the gold standard, functional capacity can be reliably estimated by patient self-report.[23] Examples of activities that suggest at least moderate functional capacity (>4 METs) include climbing one to two flights of stairs or walking a block at a brisk pace. Patients with a functional capacity of >4 METs without symptoms can proceed to surgery with relatively low risk.
- Step 5: Assess the patient's clinical risk factors.
  - The number of risk factors combined with the surgery-specific risk (intermediate vs. vascular) determines further management. The following risk factors are adapted from the Revised Cardiac Risk Index (RCRI)[24]
    - Ischemic heart disease
    - History of TIA or CVA
    - History of CHF
    - Preoperative serum creatinine ≥2 mg/dL
    - Diabetes mellitus requiring insulin
  - Patients with no clinical risk factors are at inherently low risk (<1% risk of cardiac events) and may proceed to surgery without further testing. Patients with one or two clinical risk factors are generally at intermediate risk and may proceed to surgery, although stress testing might help refine risk assessment in selected cases. Patients with three or more clinical risk factors are at high risk of adverse cardiac events, particularly when undergoing vascular surgery. In this population especially, stress testing may provide a better estimate of cardiovascular risk and may be considered if knowledge of this increased risk would change management.[25] A positive stress test in a high-risk patient portends a substantially increased risk of a perioperative cardiac event, whereas a negative study suggests a lower risk than that predicted by clinical factors alone.[19]

Diagnostic Testing

- **12-Lead ECG.** The value of a routine ECG is controversial. Per the 2014 ACC/AHA guidelines (level of evidence: B):
  - ECG is "reasonable" in patients with known CAD, significant arrhythmia, peripheral arterial disease, cerebrovascular disease, or other significant structural heart disease prior to intermediate-risk surgery and above (Class IIa);
  - "May be considered" for asymptomatic patients without known coronary heart disease prior to intermediate- and high-risk surgery (Class IIb);
  - Is "not useful" for asymptomatic patients undergoing low-risk surgical procedures (Class III).
- **Resting echocardiogram.** In general, the indications for preoperative echocardiographic evaluation are no different from those in the nonoperative setting. Murmurs found on physical exam suggestive of significant underlying valvular disease (see above) should be evaluated by echocardiogram. Assessment of left ventricular function should be considered when there is clinical concern for underlying undiagnosed CHF or if there is concern for deterioration since the last exam.

- **Noninvasive stress testing.** The decision to pursue a stress evaluation should be guided by an assessment of preoperative risk as detailed above. For further details on stress testing see Chapter 4, Ischemic Heart Disease.

Special Considerations

- Patients with drug-eluting coronary stents: see Perioperative Anticoagulation and Antithrombotic Management.
- Multiple studies have reported a correlation between delayed repair of hip fracture and increased morbidity and mortality.[26,27] For urgent surgical procedures (i.e., those that should be done within 48 hours of diagnosis), the value of additional testing is typically outweighed by the risk of worsened short- and long-term outcomes incurred with surgical delay. Unnecessary preoperative cardiac testing may be an independent risk factor for postoperative complications in hip fracture patients.[28] In such cases, it is advisable to optimize the patient's medical status and modifiable risk factors and then proceed to the operating room.

TREATMENT

Medications

- **β-Blockers**
  - Multiple studies have provided support for perioperative β-blockade in patients with or at risk for CAD undergoing noncardiac surgeries. The most pronounced benefit has been observed in high-risk patients undergoing vascular surgery where β-blocker dose was titrated to heart rate control.[25,29] However, a subsequent analysis has called into question the role of dose titration.[30] Although reduction in perioperative cardiac events has been observed consistently, it warrants mentioning that few data support the effectiveness of perioperative β-blockade in reducing mortality.
  - According to the 2014 ACC/AHA guidelines:
    - In patients with three or more RCRI risk factors (see above) or evidence of myocardial ischemia on preoperative stress testing, starting preoperative β-blockade is reasonable (level of evidence: B).
    - β-blockade should not be started on the day of surgery, as it is at minimum ineffective and may actually be harmful (level of evidence: B).
    - Patients already taking β-blockers should be continued on their medication (level of evidence: B).
- **Statins**
  - Statins are believed to improve cardiovascular outcomes by enhancing endothelial function, reducing vascular inflammation, and stabilizing atherosclerotic plaque in addition to their lipid-lowering effects. Multiple trials have shown a decrease in perioperative cardiac events and/or mortality with statin use in patients undergoing vascular surgery. Moreover, a recent cohort study of statin therapy in patients undergoing intermediate-risk noncardiac, nonvascular surgery revealed a fivefold reduced risk of 30-day all-cause mortality along with a statistically significant reduction in the composite end point of 30-day all-cause mortality, atrial fibrillation (AF), and nonfatal MI.[31]
  - Per the 2014 ACC/AHA guidelines:
    - Patients currently taking statins should be maintained on therapy (level of evidence: B).
    - Patients undergoing vascular surgery, and those with risk factors undergoing intermediate-risk surgery, may benefit from initiation of statin therapy perioperatively (level of evidence: B and C, respectively). Optimal dose, duration of therapy, and target low-density lipoprotein (LDL) levels for perioperative risk reduction are unclear.
- **Aspirin**

  For discussion, see Perioperative Anticoagulation and Antithrombotic Management.

Revascularization

- The best available data on preoperative revascularization come from the Coronary Artery Revascularization Prophylaxis (CARP) trial, a prospective study of patients scheduled to undergo vascular surgery.[32] Patients with angiographically proven significant CAD were randomized to revascularization versus no revascularization. There was no difference between the groups in the occurrence of MI or death at 30 days or in mortality with long-term follow-up. Patients with three or more clinical risk factors and extensive ischemia on stress testing were evaluated in a separate small study.[33] High event rates were seen in both study arms, and no benefit was seen with revascularization. Taken together, these studies suggest that the risk of adverse cardiac events is not altered by attempts at preoperative revascularization, even in high-risk populations. A notable possible exception are patients with left main disease, who appeared to have benefited from preoperative revascularization in a subset analysis of the CARP trial data.[34]
- Based on these cumulative results, a strategy of routinely pursuing coronary revascularization as a method of decreasing perioperative cardiac risk cannot be recommended. However, careful screening of patients is still essential to identify those high-risk subsets who may obtain a survival benefit from revascularization independent of their need for noncardiac surgery.

MONITORING/FOLLOW-UP

Postoperative Infarction and Surveillance

- Most events will occur within 48–72 hours of surgery, with the majority in the first 24 hours.[35]
- Most are not heralded by chest pain and may be **clinically asymptomatic**.[36] Although overall 30-day mortality has been linked to postoperative troponin elevation, the cause of death is not predictable, and no specific course of therapy may be offered.[37]
- The 2014 ACC/AHA guidelines offer the following[38]:
  - Routine postoperative ECGs and troponins are not recommended.
  - The benefit of troponin measurements and ECGs in high cardiac risk patients is uncertain.
  - Symptomatic infarctions should be addressed according to standard therapy of acute coronary syndromes (see Chapter 4, Ischemic Heart Disease). The major caveat is that bleeding risk with anticoagulants must be carefully considered.

Perioperative Anticoagulation and Antithrombotic Management

GENERAL PRINCIPLES

- Patients on chronic anticoagulation for AF, VTE, or mechanical heart valves often need to undergo procedures that pose risk of bleeding.
- The indication for anticoagulation and risk of interruption must be weighed against the risk of bleeding of the procedure (including possible neuraxial anesthesia).
- Until better research is available, decisions regarding perioperative anticoagulation will have to be made with the help of guidelines with relatively weak strength of evidence.[39]

TREATMENT

- Recommended management varies according to the indication for anticoagulation, medication used, and surgical bleeding risk.

- For patients being treated with oral anticoagulants/vitamin K antagonists (VKA):
  - **Low bleeding risk** procedures permit continuation of **oral anticoagulation** through the perioperative period (e.g., minor dental and dermatologic procedures, cataract extraction, endoscopy without biopsy, arthrocentesis). Pacemaker and implantable cardioverter defibrillator (ICD) placement lead to less hematoma if anticoagulation is not interrupted.[40]
  - **Significant bleeding risk procedures** require the anticoagulation to be discontinued.
    - Although the international normalized ratio (INR) at which surgery can be safely performed is subjective, an INR of <1.5 is typically a reasonable goal.
    - The VKA (e.g., warfarin) will typically need to be stopped 5 days preoperatively.
    - The INR should be checked the day before surgery. If a level <1.5 is not obtained, 1–2.5 mg oral vitamin K effectively achieves an INR <1.5 on the day of surgery.
    - The VKA can generally be resumed 12–24 hours postoperatively if postoperative bleeding has been controlled.[39]
  - **High bleeding risk procedures** (e.g., intracranial or spinal) with potential catastrophic outcomes because of bleeding will preclude any anticoagulation in the perioperative period. Other procedures with high bleeding risk (e.g., sessile polypectomy; bowel resection; kidney, liver, or spleen biopsy; extensive orthopedic or plastic surgery) should lead to a delay of at least 48 hours prior to resumption of anticoagulation.
- **Bridging therapy** refers to the administration of an alternative anticoagulation during the time the INR is anticipated to be below the therapeutic range. The potential decrease in thrombosis must be weighed against the increased risk of bleeding.[41]
- **High thrombotic risk patients** below should typically be treated with bridging therapy.
  - Mechanical mitral valve
  - Older-generation mechanical valve (e.g., Starr-Edwards ball-in-cage valve)
  - Any mechanical valve with a history of cardioembolism within the preceding 6 months
  - Nonvalvular AF with either a history of embolism in the last 3 months or $CHADS_2$ score ≥5 (see Chapter 7, Cardiac Arrhythmias)
  - Valvular AF
  - Recent VTE (<3 months)
  - Known thrombophilic state (e.g., protein C deficiency)
- For **moderate thrombotic risk patients** as below, bridging may be considered in patients with low bleeding risk. Deep venous thrombosis (DVT) prophylaxis dosing is acceptable.
  - Mechanical aortic valve (bileaflet) with one or more associated risk factors: AF, CHF, hypertension, age ≥75, DM, and prior CVA or TIA
  - History of VTE within preceding 3–12 months
  - Non–high-risk thrombophilia (e.g., heterozygous factor V Leiden mutation)
  - History of recurrent VTE
  - Active malignancy
- **Low thrombotic risk** patients are **not** believed to require bridging therapy. Treatment with DVT prophylaxis doses of LMWH or UFH is an alternative. This group includes patients with:
  - Mechanical aortic valve (bileaflet) without associated risk factors, as above
  - AF with a $CHADS_2$ score < 4, or history of prior embolism[42]
  - Prior VTE >12 months prior (without history of recurrent VTE or known hypercoagulable state)
- **Choices for bridging therapy** are generally the LMWHs and UFH, including patients with mechanical heart valves.[39] There is less experience in this setting with other agents (e.g., fondaparinux), and their use cannot be considered routine.
  - **LMWHs** have the advantages of relatively predictable pharmacokinetics and ability to be administered SC. Monitoring of anticoagulant effect is typically not required. Renal dosing is available for patients not on dialysis. Subcutaneous administration allows for outpatient therapy in appropriate patients. This decreases the length and cost of hospitalization. The last dose should be given 24 hours prior to surgery.

- **UFH** is the agent of choice for patients with end-stage renal disease (ESRD). It is typically administered IV and requires frequent monitoring of the activated partial thromboplastin time. UFH should be stopped at least 4 hours prior to the planned surgical procedure to allow the anticoagulant effect to wane. Fixed-dose subcutaneous UFH has been proven efficacious for treatment of VTE and may be considered as an option.[43]
- **Novel oral anticoagulants** have relatively short half-lives (dabigatran = 14 h, rivaroxaban = 9 h, apixaban = 12 h), obviating the need for bridging anticoagulation. Agents should be held for two or three half-lives for low bleed risk procedures and three or four half-lives for high bleed risk procedures, keeping in mind the effects of renal function on clearance.
- **Reversal agents** may be used if urgent surgery is required before this washout period.
  - **Idarucizumab** reverses dabigatran, **Andexanet alfa** reverses all Xa inhibitors.

- **Patients being treated with antiplatelet agents**
  - Continuing antiplatelet agents perioperatively carries a risk of bleeding, whereas discontinuation may increase cardiovascular events. Irreversible agents must be withheld for 5–7 days before effects fully abate. Clinicians are again left with little evidence and sometimes conflicting guidelines.
  - **Low bleeding risk procedures** (e.g., minor dermatologic or dental procedures) allow continuation of aspirin (acetylsalicylic acid [ASA]) being given for secondary prevention of cardiovascular disease.
  - **Noncardiac surgery patients** should generally have clopidogrel (or other thienopyridines) held 5 days preoperatively. Prompt reinitiation with a loading dose of 300 mg should take place postoperatively. Further stratification drives decisions regarding ASA:
    - **Moderate to high cardiac risk,** in which case ASA should be continued perioperatively
    - **Low cardiac risk,** in which case ASA should be held 7 days preoperatively
  - **Coronary artery bypass graft** candidates should generally continue ASA perioperatively and have clopidogrel held 5 days preoperatively.
  - **Coronary stents** pose a particular risk of in-stent thrombosis and infarction if dual antiplatelet therapy is prematurely withheld. Whenever possible, surgery should be deferred until the minimum period of dual antiplatelet therapy is completed (balloon angioplasty without stent, 14 days; drug-eluting stents, 6 months; bare metal stents, 30 days).
  - **Urgent surgeries** within the previous time frames should proceed with continued dual antiplatelet treatment, if possible. If the bleeding risk is felt to be high, ASA alone should be continued. Heparin bridging has not been shown to be of benefit. Bridging with IV glycoprotein IIb/IIIa antagonists or reversible oral agents (e.g., ticagrelor) is not routinely recommended.[44]

PERIOPERATIVE MANAGEMENT OF SPECIFIC CONDITIONS

Hypertension

GENERAL PRINCIPLES

- **Severe hypertension** (BP >180/110) preoperatively often results in wider fluctuations in intraoperative BP and has been associated with an increased rate of perioperative cardiac events (see the previous section, Preoperative Cardiac Evaluation).
- Antihypertensive agents that the patient has taken prior to admission for surgery may have an impact on the perioperative period.
  - When the patient is receiving β-blockers or clonidine chronically, withdrawal of these medications may result in tachycardia and rebound hypertension, respectively.

- Evidence suggests that holding angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on the day of surgery may reduce perioperative hypotension. These agents should not be held if given for CHF.

DIAGNOSIS

BP monitoring should be done as part of a patient's routine vital signs. A portable or wall blood pressure cuff should be used. In the setting of severe hypertension, BP should be checked in both arms and with suitably-sized BP cuffs to ensure accuracy.

TREATMENT

- Hypertension in the postoperative period is a common problem with multiple possible causes.
  - All **remediable causes of hypertension**, such as pain, agitation, hypercarbia, hypoxia, hypervolemia, and bladder distention, should be excluded or treated.
  - Poor control of essential hypertension secondary to discontinuation of medications the patient was previously taking in the immediate postoperative period is not uncommon; thus, reviewing the patient's home medication list is recommended.
  - A rare cause of perioperative hypertension is **pheochromocytoma**, particularly if its presence was unrecognized. Patients can develop an acute hypertensive crisis perioperatively which should be treated, with **phentolamine** or **nitroprusside** recommended in this situation. When the diagnosis of pheochromocytoma is suspected, preoperative treatment to minimize risk is recommended and can be classically accomplished by titration of **phenoxybenzamine** preoperatively.
- Many parenteral antihypertensive medications are available for patients who are unable to take medications orally. Transdermal clonidine also is an option, but the onset of action is delayed.

Pacemakers and ICDs

GENERAL PRINCIPLES

- The use of electrocautery intraoperatively can have adverse effects on the function of implanted cardiac devices.
- A variety of errors can occur, from resetting the device to inadvertent discharge of an ICD.
- Complications are rare but are more likely with abdominal and thoracic surgeries.
- The type of device (i.e., pacemaker or ICD) and manufacturer should be determined.
- The initial indication for placement and the patient's underlying rhythm should be determined. Ideally, this can be determined from the history and an ECG.
- The device should be interrogated within 3–6 months of a significant surgical procedure.

TREATMENT

- **If the patient is pacemaker dependent, the device should be reprogrammed to an asynchronous mode (e.g., VOO, DOO) for the surgery.**
- The application of a magnet will cause most pacemakers to revert to an asynchronous pacing mode; however, if this is the planned management, it should be tested preoperatively, especially in the pacemaker-dependent patient.
- It should be noted that the effect of a magnet on ICDs is typically different from the effect on pacemakers in that it affects the antitachycardia function but does not alter the

pacing function of most models. If the pacing function of an ICD needs to be altered perioperatively, the device will need to be reprogrammed.
- The antitachycardia function of an ICD will typically need to be programmed off for surgical procedures in which electrocautery may cause interference with device function, leading to the potential for unintentional discharge. The effect of a magnet on this function is variable, so programming is the preferred management. Continuous monitoring for arrhythmia is essential during the period when this function is suspended.
- Continuous ECG and pulse monitoring is recommended during surgery. Pulse monitoring should not be affected by electrocautery interference.
- Postoperative interrogation may be necessary, particularly if the device settings were changed perioperatively or if the patient is pacemaker dependent.
- **Consultation with an electrophysiologist** is strongly recommended if there is any uncertainty regarding the perioperative management of a device.

Pulmonary Disease and Preoperative Pulmonary Evaluation

GENERAL PRINCIPLES

Postoperative pulmonary complications are the second most common postoperative complication; their incidence ranges from 2% to 5.6% in the general surgical population.[45] Clinically significant pulmonary complications include atelectasis, pneumonia, bronchospasm, exacerbation of preexisting chronic lung disease, and respiratory failure.[46] Postoperative respiratory failure, defined as ventilator dependency for more than 48 hours or unplanned reintubation, carries a 30-day mortality rate as high as 26.5%.[47]

Risk Factors

Both patient-dependent and surgery-specific risk factors determine overall risk.[48]
- **Surgical site** is generally considered the greatest determinant of risk of pulmonary complications, with proximity to the diaphragm correlating with increasing risk.[49] Neurosurgery and surgeries involving the mouth and palate also impart increased risk.[47,50]
- **Duration of surgery** also correlates strongly with risk.[51-53]
- Regional anesthesia may reduce risk of pneumonia and respiratory failure as compared with **general anesthesia**, though it is difficult to draw firm conclusions.[54-57] Prolonged **neuromuscular blockade** is also strongly associated with postoperative pulmonary complications.[58]
- **COPD** is a well-known risk factor, with disease severity associated with risk of serious complications.[59] However, even patients with advanced lung disease can safely undergo surgery if deemed medically necessary; in contradistinction to hepatic disease (see "Liver Disease"), there is no identified threshold that precludes surgery.[60,61]
- **Interstitial lung disease** places patients at elevated risk for surgical lung biopsy and resection of malignancy but is not as well studied in patients undergoing general surgery.[62-64]
- **Pulmonary hypertension** is associated with significant morbidity in patients undergoing surgery.[65,66]
- Conversely, treated asthma and restrictive physiology associated with obesity do not appear to be significant risk factors.[48,67]
- **Congestive heart failure** may increase the risk of pulmonary complications to an even greater degree than that seen with COPD.[68]
- Multiple indices of general health status including **degree of functional dependence** and **American Society of Anesthesiologists class** have been linked to poor pulmonary outcomes.[68,69] Odds ratios for postoperative respiratory failure of 2.53 and 2.29 were observed for **hypoalbuminemia** (<3 g/dL) and **azotemia** (BUN > 30 mg/dL), respectively, in a large cohort.[50]

- **Age > 50 years** has been identified as an independent predictor of postoperative pulmonary complications. Risk increases linearly with age, in contrast to postsurgical cardiac risk (see "Preoperative Cardiac Evaluation"). Large observational studies informing currently used risk prediction models (see "Risk Stratification" below) have further validated these observations.
- **Smoking** is a well-established risk factor for both postoperative pulmonary and nonpulmonary complications.[70] As with malignancy, risk appears to be dose-dependent and associated with active use.[53,71]
- **Obstructive sleep apnea** (OSA) is increasingly being recognized as a risk factor for both cardiac and pulmonary complications.[72,73] OSA increases the odds of postoperative complications two- to fourfold.[74] Unrecognized OSA may pose an even greater risk; it is estimated that over 50% of patients with OSA presenting for surgery are undiagnosed.[75-77]

Risk Stratification

- Several validated risk indices have been developed for quantitating risk of postoperative pulmonary complications. Of these, the Arozullah respiratory failure index offers both practicality (in terms of a clearly defined outcome) and ease of use. It consists of six factors for which point scores are assigned based on multivariate analysis to stratify patients into five classes of postoperative respiratory failure risk (ranging from 0.5% to 26.6%).[50,78-80]

DIAGNOSIS

Clinical Presentation

History

Preoperative pulmonary evaluation should focus on the above-mentioned patient-dependent risk factors.

- Is there a history of lung disease? If so, what is the patient's baseline (e.g., level of exertional tolerance, degree of hypoxemia)? Is there evidence of recent deterioration (e.g., increased cough, sputum production)? Though not an absolute contraindication to surgery, it may be prudent to postpone an elective procedure until an exacerbation is treated or a superimposed upper respiratory tract infection has resolved.
- A full smoking history should be obtained.
- Screening for OSA should be undertaken. The STOP-Bang questionnaire (see "Obstructive Sleep Apnea-Hypopnea Syndrome", Chapter 10) can be implemented to determine risk of OSA.
- As nonpulmonary comorbidities impact the likelihood of pulmonary complications, (as delineated above), review of other organ systems is mandatory.

Physical Examination

- Vital signs can be helpful in determining pulmonary risk. Both **body mass index (BMI)** and **blood pressure** are components of the STOP-Bang questionnaire. Though hypoxemia itself does not appear to be a significant independent predictor of risk **oxygen saturation by pulse oximetry** may assist in risk stratification.[45,78]
- High **Mallampati class** (see "Obstructive Sleep Apnea-Hypopnea Syndrome", Chapter 10) may corroborate clinical suspicion for OSA. A study of 137 adults being evaluated for OSA found that every 1-point increase in Mallampati class increased the odds of OSA by 2.5.[81]
- **Stigmata of chronic lung disease** (e.g., increased anteroposterior dimension of the thorax, digital clubbing, adventitious lung sounds) should be actively sought along with **signs of decompensated heart failure** (jugular venous distention, rales, pretibial edema).

Diagnostic Testing

- Routine laboratory testing
  - As mentioned earlier, underlying chronic kidney disease and hypoalbuminemia portend increased risk of postoperative pulmonary complications. The addition of **serum bicarbonate 28 mmol/L or above** to a STOP-Bang score of three or above increases the specificity for detecting moderate to severe OSA from 30% to 82%, though sensitivity is accordingly reduced.[82]
- Chest radiography (CXR)
  - As many findings deemed abnormal on routine CXR are chronic and do not alter management, imaging is recommended only if signs or symptoms (e.g., unexplained dyspnea) warrant.[83,84]
- Arterial blood gas (ABG) analysis
  - No data exist that suggest that ABG results contribute to risk estimation beyond the variables delineated earlier. Nevertheless, ABG may be helpful in certain circumstances (e.g., to determine whether a patient's known chronic lung disease is compensated). See "Respiratory Failure", Chapter 8.
- Pulmonary function testing (PFTs)
  - The value of preoperative PFTs is at best debatable outside of lung resection surgery, where its role is relatively well defined (see Chapters 9, "Chronic Obstructive Pulmonary Disease", and 22, "Lung Cancer"). However, they may be considered in further evaluation of selected patients with unexplained dyspnea or exertional impairment or for those with known lung disease with unclear baseline.

TREATMENT

- Preoperative treatment should focus on those risk factors which are modifiable.
- The effect of preoperative smoking cessation on pulmonary complications has been largely described in cardiothoracic surgeries, where a **benefit to quitting smoking at least 2 months prior to surgery** has been shown.[85] Though the effect on a general surgical population is less clear, pooled data show a significant reduction in pulmonary complications.[86] Maximizing the preoperative smoking cessation period appears to minimize complications. Though it is unknown whether smoking cessation is beneficial within 2 weeks of surgery, previous concerns about a paradoxical increase in complications appear unfounded.[87,88]
- COPD and asthma therapy should be optimized (see Chapter 9, Obstructive Lung Disease), and respiratory tract infections should be treated. Indeed, risk of postoperative pulmonary complications is increased in the month following a respiratory tract infection.[89] Nonemergency surgery may need postponement to allow recovery of pulmonary function to baseline.
- OSA should be treated prior to elective high-risk surgery when feasible. Though evidence from randomized controlled trials remains limited, a recent cohort study revealed a significant reduction in cardiovascular complications (primarily cardiac arrest and shock) between undiagnosed and diagnosed OSA after prescription of CPAP.[90] A subsequent meta-analysis of 904 patients failed to show a significant difference in postoperative adverse events despite statistically significant reduction in apnea-hypopnea index with postoperative use of CPAP, a finding attributed to overall poor compliance.[91] Patients with known OSA should be continued on CPAP perioperatively.[92]
- Alternative procedures with reduced pulmonary risk should be considered for high-risk patients. Laparoscopic procedures may yield fewer pulmonary complications; regional