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Clinical Anesthesia Fundamentals

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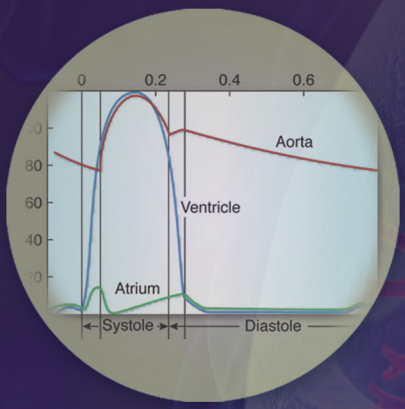
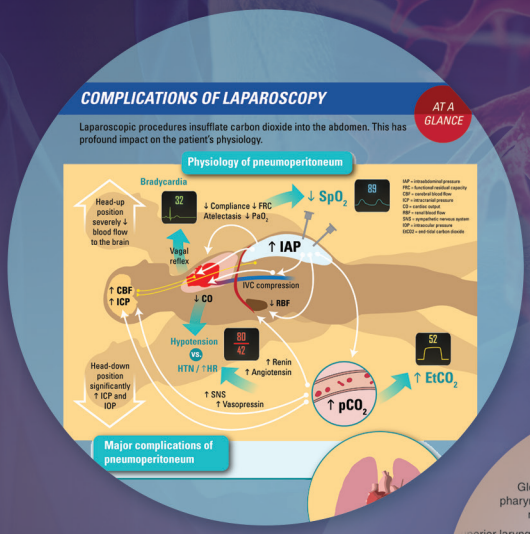
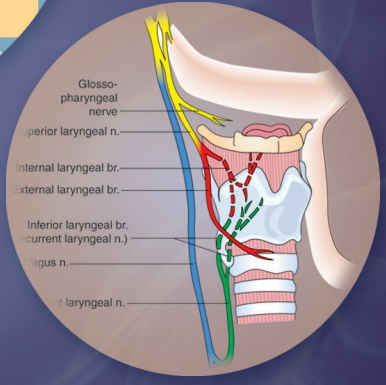


Did you Know

The pulse oximeter has a significant delay (15 to 30 seconds) in the detection of changes in arterial





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Preface

Published in 2015, the inaugural first edition of *Clinical Anesthesia Fundamentals* was the brainchild of Paul Barash—one of the founding editors (along with Bruce Cullen and Robert Stoelting) of the *Clinical Anesthesia* textbook series that has been in continuous publication since 1989—and was intended to be a complementary text to the larger and more comprehensive *Clinical Anesthesia* compendium (currently in its eighth edition). In contrast to this compendium that targets the seasoned trainee and veteran practitioner, *Clinical Anesthesia Fundamentals* was specifically designed to fill the void in anesthesia and perioperative care education exemplified by the early trainee's question "Where can I go to most efficiently learn the fundamentals of anesthesia care?". The book's primary goal was to provide a complete, yet succinct introduction to the essential clinical principles and practices for early learners of anesthesia, including medical students, junior anesthesiology residents, anesthesiology assistants, and student registered nurse anesthetists. The book's second goal was to incorporate novel formats that target the cognitive needs and learning tools demanded by "digital native" learners of the millennial generation, including a manageable print book size, liberal use of graphic and tabular presentations that facilitate trainees to thoughtfully apply their basic science knowledge to the clinical setting, and an extensive, "immediately at hand" companion eBook with digital teaching tools designed both to appeal to millennial learners and to reinforce content acquisition through complementary methods of content delivery.

Did the first edition of *Clinical Anesthesia Fundamentals* achieve its goal? You, the readers, are the final arbiters of that query—however, we are encouraged by reader reviews that not only support continued editions, but also offer specific suggestions for improvement. As a result, this second edition relies even more heavily on a fully interactive digital resource, including colorful and meticulously designed infographics in almost every chapter. These infographics serve as visual representations of the book's contents and provide an easy-to-understand overview of a variety of pertinent topics. The information is displayed succinctly and clearly to present learners with an alternative resource to study the material. Additionally, the electronic version of the book includes a collection of interactive questions based on each one of the infographics; all questions provide feedback expanding on the correct answer and explaining all incorrect choices. This learning innovation provides the opportunity to review the infographics and then engage in a challenging question and answer exercise intended for knowledge consolidation. All of the videos have been refreshed and the interactive lectures have been streamlined to facilitate broadcasting them swiftly over the internet.

As in the first edition, all components of the eBook are viewable through any web browser, and also as a download to one's smartphone or tablet, thus providing immediate and ubiquitous access for the reader. A new chapter on "Anesthesia for the Older Patient" brings the chapter total to 45. Finally, the

book concludes with a series of Appendices, carefully selected for their reference value and clinical relevance to early anesthesia trainees, including essential physiologic formulas/definitions, an electrocardiography atlas, pacemaker/defibrillator protocols, and key standards/algorithms from the American Society of Anesthesiologists, American Heart Association, and Anesthesia Patient Safety Foundation.

In a reflective and somber note, we are saddened to share that since publication of the first edition, two of our long-time editorial colleagues have passed away—Michael K. Cahalan in 2019 and Paul G. Barash in 2020. Both men were highly committed and tireless contributors to the *Clinical Anesthesia* series—Paul since its first edition in 1989 and Mike since its fifth edition in 2009—and are universally recognized in our field as consummate clinicians, dedicated educators, and invaluable mentors to both trainees and peers. Moreover, they were role models of professionalism and interpersonal relationships whose teachings, spirits, and senses of humor are legendary and will live on in each of us. We mourn their loss and keep them and their families in our hearts.

We wish to express our appreciation to both our new and returning contributors who not only provided fundamental content in a novel, yet highly concise format, but did so despite the unexpected and concurrent personal and professional demands of the COVID pandemic. Finally, we owe a debt of gratitude to Ashley Fischer, Senior Development Editor at Wolters Kluwer, whose day-to-day management of this endeavor resulted in a publication that exceeded the Editors' expectations.

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Contents

SECTION III: Clinical Practice of Anesthesia

Digital Contents

For access to digital contents and interactivities, please see eBook bundled with this text. Access instructions are located in the inside front cover.

17 Coexisting Diseases Impacting Anesthetic Management

Gerardo Rodriguez

Many conditions impact anesthetic management. Some are rare and are unlikely to be encountered during an anesthesiologist's career. It is essential to always investigate thoroughly how to properly manage a rare disorder. When encountering a patient with an uncommon condition, it is advisable to review sources detailing each topic.

I. Duchenne Muscular Dystrophy

Duchenne muscular dystrophy is an X-linked disorder leading to a loss of functional dystrophin, a protein integral to muscle membrane cytoskeleton stability. It presents in childhood and is characterized by proximal muscle weakness and painless muscle atrophy in boys. Serum creatine kinase levels are used for screening in newborns and assessment of muscle degeneration. Patients succumb to cardiopulmonary complications by middle age.

Cardiomyopathy and rhythm disorders are common. Surveillance with electrocardiography and echocardiography and treatment with angiotensin-converting enzyme inhibitors and beta-blockers are routine. Dysrhythmias should be periodically assessed with Holter monitoring.

Recurrent pneumonia occurs due to poor cough effort and inadequate secretion clearance. Derangements in gastric motility result in delayed gastric emptying.

? *Did You Know?*

In Duchenne muscular dystrophy, succinylcholine is contraindicated due to risk of hyperkalemia and rhabdomyolysis.

A. Management of Anesthesia

Gastric dysmotility increases the risk of aspiration. Succinylcholine is contraindicated due to risk of hyperkalemia and rhabdomyolysis. Prolonged muscle relaxation may occur with nondepolarizing agents. Potent volatile anesthetics should be used with caution, since exposure may trigger rhabdomyolysis and cardiac complications. Postoperative ventilatory support may be needed especially if there is poor preoperative pulmonary function.[1]

II. The Myotonias

Myotonic dystrophy is an autosomal dominant disorder caused by gene mutations that lead to RNA toxicity, ion channel dysfunction, and myotonias or impaired skeletal muscle relaxation. Progressive muscle wasting with weakness combined with multisystem involvement characterizes this disorder. Myotonic dystrophy is divided into two chief genetic entities. Myotonic dystrophy type 1 (DM1), the predominant major type, is subdivided into congenital, child, and

adult onset. Myotonic dystrophy type 2 is rare, with a highly variable, late adult-onset presentation.

Adult-onset DM1, the most common subtype, is characterized by muscle weakness, myotonias, and cataracts. Facial, neck, and distal limb weakness progress to muscle wasting, immobility, and bulbar palsies. Respiratory dysfunction is compounded by aspiration and respiratory muscle weakness.

Functional and anatomical brain dysfunction is manifested by cognitive dysfunction and diffuse white matter atrophy. Systolic and diastolic cardiac failure are complicated by conduction defects, such as atrioventricular conduction blocks and tachyarrhythmias. ***Sudden cardiac death*** due to dysrhythmias is common. Gastrointestinal signs include constipation and diarrhea. Impaired endocrine function results in hypothyroidism and insulin resistance. Treatment is primarily supportive.

A. Management of Anesthesia

Cardiopulmonary abnormalities, muscle weakness, and clinical myotonia are the primary causes of perioperative risk in adult-onset DM1, regardless of anesthetic technique. Sedatives should be used with caution due to potential exaggerated response to their respiratory depression side effects. Succinylcholine should be avoided due to its potential to trigger a severe myotonic muscle contraction. Both nondepolarizing and reversal agents may exacerbate muscle weakness and should be avoided. Respiratory insufficiency can occur. Transcutaneous pacing pads should be considered.

There is potential for prolonged labor, postpartum hemorrhage, and congenital myotonic dystrophy of the neonate.

III. Familial Periodic Paralysis

Channelopathies are a heterogenous group of defects in ion channel function that result in a spectrum of anomalies. Familial periodic paralysis is a subgroup of inherited defects comprising hyperkalemic and hypokalemic periodic paralysis.

A. Hyperkalemic Periodic Paralysis

Hyperkalemic periodic paralysis is an autosomal-dominant inherited disease characterized by episodes of hyperkalemia-related muscle weakness and myotonia. The episodes are triggered by transient hyperkalemia from exercise, fasting, or consumption of potassium-rich foods.

B. Hypokalemic Periodic Paralysis

Hypokalemic periodic paralysis, the most common periodic paralysis disease, is an autosomal dominant disease characterized by recurrent episodes of hypokalemia-related flaccid paralysis, lasting hours to days. Respiratory insufficiency and cardiac arrhythmias can occur during acute attacks. Chronic proximal myopathy is a common outcome in many cases.

C. Management of Anesthesia

Potassium homeostasis is the goal of perioperative management. Electrolyte levels should be monitored and corrected with an emphasis on avoiding metabolic states or medications that may alter serum potassium levels, either directly or indirectly. Nondepolarizing muscle relaxants are best avoided due to unpredictable patient sensitivities. Succinylcholine should be avoided, because it may cause transient hyperkalemia.[2]

? *Did You Know?*

Hypokalemic periodic paralysis is the most common periodic paralysis disease, characterized by recurrent episodes of hypokalemia-related flaccid paralysis, which can last hours to days.

IV. Myasthenia Gravis

Did You Know?

Myasthenia gravis is caused by a decrease in the number of functional postsynaptic, acetylcholine receptors in the neuromuscular junction available for acetylcholine binding.

Myasthenia gravis (MG) is a neuromuscular autoimmune disease characterized by skeletal muscle weakness worsened by exertion and improved with rest. Extraocular muscles are affected primarily, with less frequent impact on limb and respiratory muscles strength.

The etiology is a decrease in the number of functional postsynaptic, acetylcholine receptors (AChRs) in the neuromuscular junction available for acetylcholine binding. Direct antibody receptor blockade, increased antibody-mediated receptor turnover, and postsynaptic membrane complement–mediated injury can contribute to AChR decline. Abnormal thymus tissue is frequently involved.

Did You Know?

The newborn of a mother with myasthenia gravis can suffer from a condition known as transient neonatal myasthenia, which may present with feeding problems and respiratory distress at birth.

Signs include ptosis, blurred vision, diplopia, dysphagia, dysarthria, and generalized limb weakness. ***Myasthenic crisis*** is a progression to severe muscle weakness and respiratory failure, usually requiring ventilatory support. Cardiac abnormalities include bundle branch blocks, atrial fibrillation, and focal myocarditis.

Transient neonatal myasthenia is known to occur in newborns of women with active MG, with feeding problems and respiratory distress immediately postpartum. Edrophonium testing is used to diagnosis MG with high sensitivity. Serologic testing, tomographic imaging, and electrophysiological testing comprise a comprehensive MG workup. Treatment is aimed at both symptom management and immunomodulation.

Acetylcholinesterase inhibitors, such as pyridostigmine, minimize MG symptoms by increasing the acetylcholine available at neuromuscular junction sites. Excessive drug administration can result in severe cholinergic side effects, or ***cholinergic crisis***, characterized by hypersalivation, abdominal cramping, bradycardia, and weakness. Plasmapheresis and intravenous immunoglobulin can provide short-term relief. Chronic therapy includes steroids and nonsteroidal immunosuppressants. ***Thymectomy*** is recommended for MG patients with thymomas.[3]

A. Myasthenic Syndrome (Lambert-Eaton Syndrome)

Did You Know?

The Lambert-Eaton myasthenic syndrome is associated with small cell lung cancer, and in contrast to myasthenia gravis, exercise might improve the muscle weakness-related symptoms.

Lambert-Eaton myasthenic syndrome (LEMS) is an autoimmune, neuromuscular disorder of transmission mediated by antibodies to voltage-gated calcium channels at the presynaptic, motor nerve terminal, resulting in acetylcholine release reduction. It is characterized by proximal limb weakness, autonomic dysfunction such as dry mouth, and diminished deep tendon reflexes. In contrast to MG, exercise in LEMS might suddenly improve symptoms. LEMS is a paraneoplastic condition, often associated with small cell lung cancer. Increasing presynaptic, neurotransmitter release with 3,4-diaminopyridine is considered the mainstay of treatment.

V. Guillain-Barre Syndrome (Polyradiculoneuritis)

Guillain-Barre syndrome (GBS) is an autoimmune disorder characterized by the acute or subacute onset of ascending skeletal muscle weakness or paralysis of the legs occurring in the context of a viral or bacterial infection. This inflammatory, multifocal demyelinating disease usually produces varying degrees of autonomic dysfunction. Respiratory muscle weakness is common during severe cases of GBS. Treatment is primarily supportive.[4]

A. Management of Anesthesia

Multifocal demyelination and muscle disuse atrophy in GBS prohibit the use of succinylcholine due to the risk of life-threatening hyperkalemia. Expected muscle relaxation from nondepolarizing agents may be highly variable and unpredictable and should be avoided. Autonomic nervous system lability is common, which can result in hyperdynamic and hypodynamic responses to stimuli or transient preload changes, respectively; therefore, hemodynamic support should be judicious.

? *Did You Know?*

In addition to respiratory muscle weakness, GBS is accompanied by autonomic nervous system lability, which can result in hyperdynamic and hypodynamic responses.

VI. Central Nervous System Diseases

A. Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory multifocal demyelinating disorder caused by autoimmune neurodegenerative changes leading to progressively irreversible neurologic deficits. The clinical course is characterized by subacute, relapsing-remitting changes that correlate to activated T-cell blood-brain barrier penetration with subsequent multifocal gray and white matter demyelination and edema (**Figure 17.1**).

MS has a peak incidence at the age 20 to 40 years. Signs and symptoms can be vague or specific, usually determined by the neurologic site focally affected. Symptoms include headache, fatigue, and depression. Sensory symptoms such

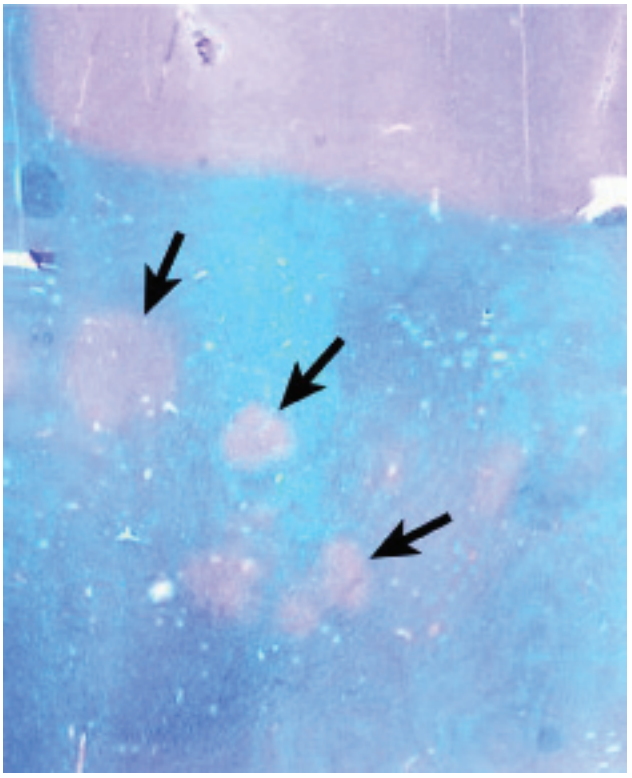

Figure 17.1 The subcortical white matter of a patient with multiple sclerosis showing multiple, small, irregular, partially confluent areas of demyelination (*arrows*). Normal intact myelin stains blue in this Luxol fast blue–stained section. (From Strayer DS, Saffitz JE, Rubin E. *Rubin's Pathology.* 8th ed. Philadelphia, PA: Wolters Kluwer; 2020. Figure 32.74.)

as numbness and paresthesias are common. Partial paralysis of the lower limbs is a common motor symptom that usually correlates to anterior column spinal cord lesions. Visual loss, diplopia, nystagmus, and papillary abnormalities reflect cranial nerve involvement. Diagnosis is based on history and clinical examination with reliance on magnetic resonance imaging to characterize demyelinating, often clinically silent, focal lesions. Cerebral spinal fluid may demonstrate intrathecal immunoglobulin production.

Management strategies are evolving to target acute relapse and symptomatic control. Corticosteroids can hasten acute clinical recovery. Plasma exchange removes harmful antibodies to treat relapses. Interferon-beta and glatiramer acetate block antigen presentation to minimize relapsing-remitting events. Mitoxantrone, an antineoplastic agent, reduces lymphocyte counts to delay progression to secondary degenerative phase. Symptomatic management is usually determined by the diffuse nature of MS. Severe fatigue is common and should be treated promptly with central nervous system stimulants, such as amantadine. Routine depression screening and early treatment are important given the propensity to affect quality of life in this disease. Spasticity treatment requires both physical therapy and antispasticity medications. Intrathecal baclofen pump implantation is reserved for severe cases. Pain is usually due to varied factors, such as neuropathic pain, indirect pain from MS, and treatment-related pain. As a result, pain management is multimodal, potentially involving antiepileptics, tricyclic antidepressants, nonsteroidal anti-inflammatory drugs (NSAIDs), and antispastic agents.

? *Did You Know?*

In multiple sclerosis, pain is caused by a variety of mechanisms; therefore, the best treatment is using multimodal analgesia.

B. Epilepsy

Epilepsy is a disorder characterized by sudden, unprovoked, and recurrent seizures. A seizure is a neurologic symptom characterized by a transient attack of rhythmic electroneuronal discharges, resulting in altered consciousness and disturbances in brain function. Seizures can be provoked by factors such as metabolic derangements, or unprovoked, by intrinsic brain disease.

Epilepsies and seizures are mostly clinical diagnoses with reliance on history, physical examination, laboratory testing, electroencephalography, and neuroimaging. Investigating the paroxysmal event, triggers, and recurrence potential helps exclude or confirm the diagnosis.

Epilepsies are broadly divided into ***focal*** and ***generalized***. In focal epilepsies, usually localized pathologic conditions, such as brain tumors, lead to focal cortical discharges that can generalize and recruit other cortical regions. In generalized epilepsies, diffuse cortical discharges develop, affecting the cortex and bilaterally. ***Grand mal seizure*** is the most recognized type of generalized epilepsy. It is characterized by a loss of consciousness followed by several minutes of a ***tonic phase*** of body stiffening, followed by a ***clonic phase*** of repetitive contractions, and ending in a prolonged ***postictal phase*** of lethargy and return of consciousness. During the tonic phase, breath-holding, incontinence, tongue biting, tremors, and sinus tachycardia may occur. Trauma, aspiration pneumonia, and arrhythmias may also occur during these seizures. Benzodiazepines or propofol can be used to terminate seizure activity. Ventilatory support may be needed. ***Status epilepticus*** is a potentially fatal convulsive disorder marked by serial tonic-clonic phases occurring without return of consciousness. Untreated, hyperpyrexia, hypoxia, and shock can develop acutely. Multiple precipitating risk factors exist, including brain tumor and drug intoxication. Treatment goals should be supportive care,

seizure termination, and prevention. Endotracheal intubation should be performed for airway protection. Intravenous phenytoin can be used for seizure recurrence prophylaxis. Refractory seizures may require benzodiazepine or propofol infusion; general anesthesia may even be necessary.[5]

C. Alzheimer Disease

Dementia is an irreversible, chronic, neurodegenerative disease marked by a constant decline in cognitive function, affecting memory, behavior, and executive function that, over time, degrades daily activities and social interaction. ***Alzheimer disease (AD)*** is the most common cause of dementia. Senile plaques and neurofibrillary tangles are the hallmarks of AD. Acetylcholinesterase inhibitors (AChEIs) are considered the first line of pharmacotherapy to treat the central cholinergic deficiency–related cognitive decline in AD. Side effects from cholinergic stimulation during AChEI therapy include hypotension, bradycardia, and bronchoconstriction. Drug interactions with AChEI and muscle relaxants may result in prolonged paralysis with succinylcholine and resistance to muscle relaxation with *N*-methyl-D-aspartates.[6]

D. Parkinson Disease

Parkinson disease (PD) is a neurodegenerative movement disorder marked by an acetylcholine-dopamine imbalance caused by loss of dopamine-producing cells within the substantia nigra. It is a clinical diagnosis confirmed by motor and nonmotor features in the absence of a pertinent drug history. Common motor features of PD are "pill-rolling" tremors at rest, rigidity, bradykinesia, postural instability, flexed posture, or incapacity to move. Nonmotor features include cognitive impairment, neuropsychiatric disorders, sensory disturbances, sleep disorders, and autonomic dysfunction.

VIDEO 17.1
Parkinson Disease

Medical management is determined by factors such as age of onset, symptom fluctuations, dopamine responsiveness, and end-stage disease. ***Levodopa*** remains the most effective form of oral therapy for motor symptoms. It is highly metabolized and can cause nausea and hypotension. Long-term levodopa use can result in confusion, dyskinesia, and poor symptom relief. Hepatic metabolism and peripheral side effects are commonly reduced by combining levodopa with carbidopa, a ***decarboxylase inhibitor***. Pramipexole, ropinirole, and bromocriptine are ***dopamine agonists*** used when levodopa response decreases. Side effects include hallucinations and confusion. Selegiline and rasagiline are ***monoamine oxidase-B inhibitors*** used to augment dopamine concentrations. ***Deep brain stimulation*** via implanted generator electrodes is a surgical treatment option.

VIDEO 17.2
Parkinson Disease and Deep Brain Stimulation

VII. Inherited Disorders

A. Malignant Hyperthermia

Malignant hyperthermia (MH) is an autosomal dominant, hypermetabolic disorder triggered by halogenated volatile anesthetics and succinylcholine. The principal diagnostic features of MH are unexplained hypercapnia, tachycardia, muscle rigidity, acidosis, hyperthermia, and hyperkalemia. The disorder is variable in its presentation. A ryanodine receptor (RYR) gene mutation is the etiology in the majority of cases. Precipitation of MH in genetically susceptible patients occurs when the RYR, a type of calcium channel located in the sarcoplasmic reticulum membrane, is activated during an exposure to a triggering agent, resulting in a tremendous release of intracellular calcium within skeletal muscle.

VIDEO 17.3
Malignant Hyperthermia

Detection and treatment are critical for survival. If MH is suspected, triggering agents should be discontinued immediately. Dantrolene should be administered intravenously, with an initial dose of 2.5 mg/kg, with repeat dosing as needed. MH can be lethal if untreated. Rhabdomyolysis and hyperkalemia should be managed with volume resuscitation and diuresis. Cooling should be instituted immediately with monitoring for coagulopathy. Ventilatory support should be maintained until the patient is stabilized. Once stabilized, the Malignant Hyperthermia Association of the United States hotline should be contacted. Recurrence of MH is possible, and patients should be monitored for up to 72 hours.

The in vitro contracture test is used to analyze the presence of muscle fiber contraction during halothane and caffeine exposure. It is the standard for diagnosis of MH susceptibility. Genetic testing may be pursued with appropriate counseling for patients about the implications of testing results. MH-susceptible patients planning to undergo surgery should have a thoroughly purged anesthesia machine available for use, whether or not the patient is to receive a general anesthetic. Triggering agents should be avoided. Total intravenous general anesthesia should be considered if regional anesthesia is not possible.[7]

B. Porphyria

Porphyrias are a group of enzyme deficiencies that result in heme and P450 cytochrome biosynthesis impairment and a concomitant accumulation of harmful metabolites. ***Acute intermittent porphyria (AIP)*** is among the most severe of the porphyrias. It is a deficiency in porphobilinogen deaminase that leads to nonspecific neuropsychiatric and abdominal complaints. Symptoms include severe abdominal pain, vomiting, seizures, tachycardia, and generalized weakness. Triggers include infection, fasting, ethanol, and medications, including barbiturates, etomidate, and phenytoin. Treatment of symptoms entails the discontinuation of triggers and infusion of hemin. Liver transplantation is reserved for AIP patients with severe, recurrent attacks (**Figure 17.2**).

C. Cholinesterase Disorders

Pseudocholinesterase (PChE) deficiency is an inherited or acquired disorder that results in an inability to efficiently metabolize specific ester substrates.

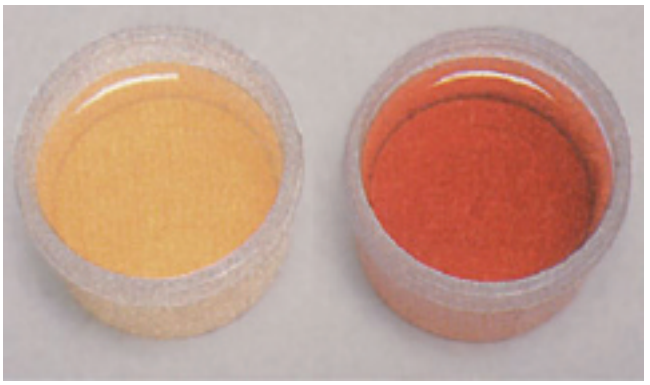

Figure 17.2 Urine from a patient with porphyria cutanea tarda (*right*) and from a patient with normal porphyrin excretion (*left*). (From Rich MW. *Porphyria cutanea tarda*. Postgrad Med. 1999;105:208–214.)

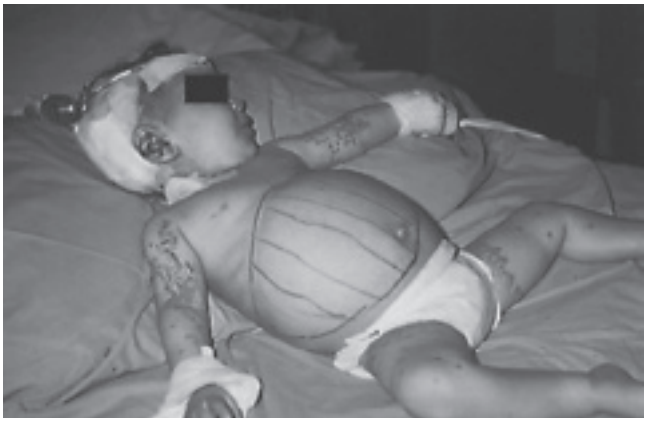

Figure 17.3 A 25-month-old child with von Gierke disease. Note the hepatomegaly and eruptive xanthomas on the arms and legs. The child is in the third percentile for height and weight, indicating a failure to thrive. (From Lieberman MA, Ricer R. *Lippincott's Illustrated Q&A Review of Biochemistry.* Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010, with permission.)

Prolonged paralysis after an anesthetic procedure using succinylcholine usually reveals this deficiency. Delayed metabolism is also seen with use of mivacurium, cocaine, chloroprocaine, procaine, and tetracaine. Deficiency of this hepatic esterase can be due to PChE gene mutations or systemic disease, such as severe liver disease, renal failure, carcinomas, and severe malnutrition. PChE activity and dibucaine inhibition testing can be used to identify individuals at high risk for prolonged paralysis following succinylcholine administration.

D. Glycogen Storage Diseases

Glycogen storage diseases (GSDs) are a rare group of inherited disorders of glycogen production and metabolism that result in excess glycogen storage. Hypoglycemia, metabolic ketoacidosis, and infiltrative organ dysfunction are common among most types of GSD. There are numerous types of GSD, each with a unique set of characteristics based on factors such as enzyme mutation and clinical features (**Figure 17.3**, **Table 17.1**).

E. Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is an inherited connective tissue disorder that produces a defect in type I collagen synthesis, which is critical to bone and tissue strength. Pediatric bone fractures from minimal trauma, blue sclera, and a family history of OI are usually adequate for diagnosis. Cardiovascular manifestations of OI include arterial dissections and aortic and mitral valve regurgitation. Several types of OI exist, classified by type, inheritance pattern, and clinical features.

VIII. Anemias

A. Nutritional Deficiency Anemias

Nutritional deficiency anemias are due to an insufficiency of any food component necessary for growth and development, with complex vitamin B and iron deficiencies being the most common. Megaloblastic anemia is a characteristic of folate and vitamin B12 (cobalamin) deficiencies. ***Folate deficiency*** is associated with malnutrition, chronic alcohol abuse, and medications that interfere

Table 17.1 Types of Glycogen Storage Diseases

Type	Enzyme Mutation	Clinical Features
Type I (von Gierke disease)	Glucose-6-phosphatase deficiency	Hypoglycemia, acidosis, and seizures
Type II (Pompe disease)	Lysosomal acid glucosidase deficiency	Infantile; cardiac infiltrative cardiomyopathy
Type III (Forbes or Cori disease)	Glycogen debranching enzyme deficiency	Hepatomegaly, muscle weakness, and cardiomyopathy
Type IV (Andersen disease)	Branching enzyme deficiency	Hepatosplenomegaly, cirrhosis, cardiomyopathy, hypotonia, and failure to thrive
Type V (McArdle disease)	Muscle glycogen phosphorylase deficiency	Rhabdomyolysis and myoglobinuria after exercise or succinylcholine
Type VI (Hers disease)	Hepatic phosphorylase deficiency	Benign; mild hypoglycemia, hepatomegaly
Type VII (Tarui disease)	Muscle phosphofructokinase deficiency	Muscle cramps, exercise intolerance, and episodic myoglobinuria
Type IX	Hepatic glycogen phosphorylase kinase deficiency	Hypotonia, short stature, and exertional myoglobinuria
Type XI (Fanconi-Bickel syndrome)	Glucose transporter enzyme deficiency	Hepatomegaly, fasting hypoglycemia, short stature, and proximal renal tubular acidosis
Type 0	Hepatic glycogen synthase deficiency	Severe fasting ketotic hypoglycemia, short stature, seizures, and severe developmental delay

with folate metabolism. Clinically evident ***cobalamin deficiency*** presents with signs of demyelinating disease. Features include peripheral neuropathy with lower extremity loss of proprioception and vibratory sensation. Clinically evident cobalamin deficiency is most often due to ***pernicious anemia***, an autoimmune loss of intrinsic factor from gastric parietal cells needed for cobalamin binding. Nitrous oxide exposure can interfere with cobalamin metabolism in susceptible patients. ***Iron deficiency*** leads to a microcytic, hypochromic anemia, associated with poor iron intake, impaired iron absorption, chronic blood loss, or systemic inflammation. Treatment for all three nutritional deficiency anemias entails supplementation and reversal of contributing causes.

B. Hemolytic Anemias

Hemolytic anemias are any inherited or acquired anemias caused by hemolysis of red blood cells (RBCs). The common presenting features of all hemolytic anemias are jaundice, splenomegaly, increased reticulocyte count, and hyperbilirubinemia. ***Hereditary spherocytosis*** is an inherited disorder characterized by fragile, spherical RBCs that are prone to rupture during transit and spleen sequestration. Another manifestation is cholelithiasis. Treatment recommendations include splenectomy, antipneumococcal vaccination presplenectomy, and prophylactic cholecystectomy.

Immune hemolytic anemias can be caused by autoimmunity, alloimmunity, and drug reactions. ***Autoimmune hemolytic anemias (AIHAs)*** can be caused primarily, usually idiopathic, or secondarily, which is divided into warm and

cold agglutinin diseases. Warm AIHA can be caused by leukemias, lymphomas, scleroderma, and rheumatoid arthritis. Cold AIHA can be triggered by infections and cold temperature exposure. ***Drug-induced immune hemolysis anemias*** can be subdivided into type II and type III hypersensitivity reactions. Penicillin and α-methyldopa can result in a type II reaction, where the drug binds to RBCs, triggering antibody-mediated destruction. Drugs known to potentially trigger a type III immune complex reaction include cephalosporins, hydrochlorothiazides, isoniazid, and tetracycline. Hemolytic disease of the newborn, or Rh incompatibility, is the most recognized example of an ***alloimmunity hemolytic disease***.

C. Glucose-6-Phosphate Dehydrogenase Deficiency

Glucose-6-phosphate dehydrogenase (G6PD) is an ubiquitous, X-linked maintenance enzyme present in RBCs and other cell types, which is essential to the pentose phosphate pathway that generates nicotinamide adenine dinucleotide phosphate for oxidative stress resistance. An acute, nonimmune hemolytic anemia reaction to ordinary infections, medications, or fava bean ingestion may be the presenting sign of G6PD deficiency. Aminoester local anesthetics and nitroprusside may trigger ***methemoglobinemia*** in patients with G6PD deficiency.

D. Hemoglobinopathies

Hemoglobinopathies are a group of predominantly genetic RBC diseases caused by aberrant hemoglobin production. Sickle cell disease and thalassemia are the most clinically relevant hemoglobinopathies. ***Sickle cell disease (SCD)*** is caused by an autosomal recessive β-globin gene defect that leads to structurally abnormal hemoglobin, called hemoglobin-S (HbS). RBCs affected with HbS have a propensity for "sickling" and for premature destruction. SCD produces acute and chronic multisystem complications. Acute, painful, and life-threatening attacks of SCD, called ***sickle cell crisis***, can occur spontaneously or be triggered by systemic stressors, such as dehydration, hypoxia, and infections.

Manifestations of sickle cell crisis include vaso-occlusive crisis, acute chest syndrome, splenic sequestration crisis, and aplastic crisis. Sickled RBCs clump together to obstruct capillaries and cause painful tissue ischemia and infarction, called a ***vaso-occlusive crisis***. This is the most common complication of SCD. Treatment consists of intravenous opioids, fluid replacement, and blood transfusion. Acute chest syndrome is a life-threatening manifestation of SCD, where pulmonary inflammation or infection triggers localized pulmonary infarctions that progress to death without appropriate supportive therapy. Clinical signs include acute dyspnea, chest pain, cough, and hypoxia. Aggressive fluid therapy, intravenous opioids, and exchange transfusion should be instituted promptly. Severe hypoxia may require ventilatory support. ***Splenic sequestration crisis*** is an acute splenic enlargement from sequestered abnormal RBCs, resulting in severe abdominal pain, anemia, and hypotension. Treatment is mainly supportive with fluid therapy and blood transfusion. Parvovirus B19 infection, a predominantly pediatric disease, can trigger an ***aplastic crisis*** in adults with SCD, characterized by profound depression of erythropoiesis resulting in life-threatening anemia.

Prophylactic treatment in SCD with oral penicillin, pneumococcal vaccination, and hydroxyurea is intended to reduce infections and recurrence of sickle cell crises.

Thalassemia is a diverse group of autosomal recessive disorders caused by insufficient α- or β-globin synthesis. The β-thalassemias in order of clinical severity include thalassemia major, thalassemia intermedia, and thalassemia minor. ***Thalassemia major*** usually presents by early childhood with anemia and failure to thrive. In time, young adult survivors go on to develop severe anemia, hypertrophic facial and long bone deformities, and secondary multiorgan dysfunction from severe transfusion-related hemochromatosis. Cardiac siderosis can lead to congestive heart failure and arrhythmias. Extensive endocrine dysfunction can present as hypopituitarism, hypothyroidism, hypoparathyroidism, diabetes, and adrenal insufficiency. Infections are common due to secondary immunodeficiency of hemochromatosis, blood-borne infections, and splenomegaly. Primary treatment includes periodic blood transfusions and iron chelating therapy.

IX. Collagen Vascular Diseases

A. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, autoimmune disease marked by systemic inflammation that primarily affects peripheral synovial joints, leading to symmetric painful arthritis. Eventual joint deformity, cartilage erosion, and ankylosing, or joint stiffening, develop in patients. ***Atlantoaxial subluxation*** is a common occult radiographic finding. Clinical signs of prolonged joint involvement, synovial fluid analysis, imaging, the presence of RA serology markers, such as rheumatoid factor, and nonspecific inflammatory markers, such as erythrocyte sedimentation rate and C-reactive protein, support the diagnosis. Extra-articular involvement is common and unpredictable. Chronic inflammation likely contributes to accelerated atherosclerotic disease, myocarditis, pericarditis, and valvulopathies. Ischemic heart disease is the most common cause of death. Rheumatoid lung disease can manifest as pleurisy, pulmonary nodules, interstitial lung disease, and pulmonary hypertension. Rheumatoid vasculitis can cause widespread organ injury, specifically renal failure and ischemic stroke.

Therapeutics for RA are broadly divided into NSAIDs, corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and biologic DMARDs. ***Prednisone*** is used during flare-ups or until DMARD therapy is optimized. Despite the risks of long-term corticosteroid use, many RA patients remain on chronic prednisone therapy. ***Methotrexate*** is the mainstay drug of DMARD therapy. Drug-induced interstitial lung disease is a known risk of methotrexate in RA therapy. Other DMARDs include leflunomide, hydroxychloroquine, and sulfasalazine. Biologic DMARDs are intended to target cell surface molecules and cytokines to block the inflammation cascade. Infection and hypersensitivity reactions are the most serious complications associated with DMARD therapy.[8]

B. Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disorder in which immune complexes formed by autoantibodies and soluble antigens, also known as ***type III hypersensitivity***, deposit in various organs, producing inflammation and tissue injury. Clinical features of SLE and detection of antinuclear antibody most often confirm diagnosis.

The presenting time course and symptoms are variable. Myalgias and fatigue are common symptoms. A photosensitive "butterfly rash" over the malar eminence is characteristic of SLE. Most patients experience mild to

severely debilitating polyarthritis. Lupus glomerulonephritis, if untreated, can lead to end-stage renal disease and death. Pericarditis and pleuritis are common manifestations of SLE. Vascular occlusive disease may present with Raynaud phenomenon, acute ischemic stroke, or myocardial infarction.

Current treatment options have reduced morbidity and mortality. Corticosteroids and hydroxychloroquine are first-line therapies for acute flare-ups. Inflammation, chronic pain, and arthralgias are usually controlled with NSAIDs. Potent immunosuppressive agents, such as cyclophosphamide or mycophenolate, are used to treat severe glomerulonephritis.

C. Systemic Sclerosis

Systemic sclerosis (SSc), or scleroderma, is a rare autoimmune disorder marked by destructive, multisystem microvasculopathy, and organ fibrosis. Skin thickening is the most obvious physical sign, whereas Raynaud phenomenon is usually the presenting sign associated with scleroderma. Traditionally, the presence of CREST syndrome (***C***alcinosis, ***R***aynaud phenomenon, ***E***sophageal dysmotility, ***S***clerodactyly, ***T***elangiectasia) has been used for diagnosis. Quality-of-life optimization, organ injury prevention, and delay of disease progression are the focuses of treatment. Painful ischemic digits are treated with calcium channel blockers, stress management, and cold temperature avoidance. Active skin disease can be treated with immunosuppressants, such as mycophenolate or cyclophosphamide. Corticosteroids for skin disease should be avoided, because they can lead to a scleroderma renal crisis, manifested by acute hypertension and oliguric renal failure. The most common problem in scleroderma is gastrointestinal dysfunction. Dysphagia, esophageal dysmotility, esophageal strictures, gastroesophageal reflux, and delayed gastric emptying are treated with proton-pump inhibitors and prokinetics. Myocarditis and conduction abnormalities are usually silent. Calcium channel blockers and other vasodilators may be used to preserve cardiac function. Lung disease is the primary cause of death in scleroderma.

D. Inflammatory Myopathies

Inflammatory myopathies are a rare group of muscle disorders typified by muscle inflammation and weakness. ***Dermatomyositis (DM)*** and ***polymyositis (PM)*** are the predominant subtypes of inflammatory myopathies. Both conditions are considered autoimmune disorders, with an acute to subacute presentation usually after a systemic infection. Presenting features of PM include muscle pain and weakness that typically affects muscles of the proximal limbs, posterior neck, pharynx, and larynx. Ocular muscles are spared. DM has a similar presentation, except that onset can be more severe with additional dermal features: heliotropic eyelid discoloration, periorbital edema, and erythematous scaly rash involving the face and the extensor surface of limbs. Muscle necrosis and inflammatory cells on muscle tissue biopsy confirms diagnosis. Complications of both PM and DM include cardiomyopathy, respiratory insufficiency, dysphagia, and aspiration pneumonia.

X. Skin Disorders

A. Epidermolysis Bullosa

Epidermolysis bullosa (EB) is a group of rare, acquired, and inherited skin disorders that result in epidermal fragility due to abnormalities in basement membrane integrity within skin and mucosa. Shear stress across skin can result

in epidermal layer detachment and painful bullae formation. Multiorgan dysfunction, such as cardiomyopathy, may develop depending on EB subtype. Esophageal strictures can be disabling, leading to malnutrition and dysphagia. Patients with EB are at risk for secondary bacterial infection and squamous cell carcinoma.[9]

B. Pemphigus Vulgaris

Pemphigus vulgaris (PV) is an autoimmune skin disorder that results in keratinocytes adhesion loss due to antibodies directed at desmoglein-1 and -3. The disorder is characterized by painful, epidermal blistering that develops immediately after minimal skin rubbing. This hypersensitivity reaction can be triggered by many medications, such as angiotensin-converting enzyme inhibitors, nifedipine, and penicillin. Painful, oral lesions are common. Corticosteroids are effective therapy for PV.

For further review and interactivities, please see the associated Interactive Video Lectures and "A Closer Look" infographic accessible in the complimentary eBook bundled with this text. Access instructions are located in the inside front cover.

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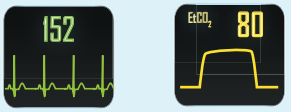
MALIGNANT HYPERTHERMIA

A CLOSER LOOK

Malignant hyperthermia (MH) is a genetic disorder in which the patient will develop a lethal hypermetabolic state when exposed to either volatile anesthetics or succinylcholine.

Signs and symptoms of MH



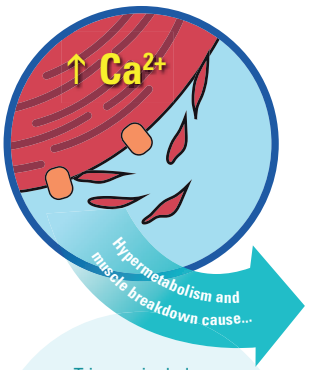
Unexplained tachycardia or arrhythmias

Severe hypercapnia

Hyperthermia

Muscle rigidity

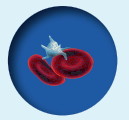
This syndrome is caused by an abnormal ryanodine receptor in skeletal muscle which, when activated by a triggering agent, results in massive intracellular Ca^{2+} release. This manifests as muscle rigidity and eventually muscle breakdown causing rhabdomyolysis.



Triggers include succinylcholine and halogenated agents

Hyperkalemia

Acidosis



Coagulopathy

Renal failure

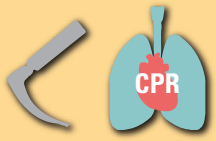
1-800-MH-HYPER (U.S. /Canada)
001-209-417-3722 (worldwide)

TREATMENT

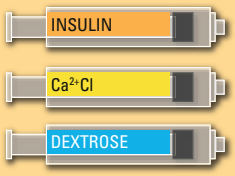
Call for help

2.5 mg/kg IV
May give at least 3 more doses

Discontinue any triggering agent immediately. Ventilate with 100% O_2 at high flows.



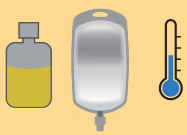
Manage airway and begin CPR and/or pacing depending on rhythm



Treat hyperkalemia induced arrhythmias:
Insulin 0.1 U/kg IV
Calcium 10 mg/kg IV
D50 1 mL/kg IV

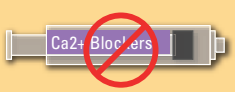
Bicarbonate to maintain pH > 7.25

Start total IV anesthesia



Start IV fluids, insert urinary catheter, start cooling measures

Obtain more IV access and draw blood samples for labs: K^+, DIC, Hb, Cr and CK levels



Avoid Ca^{2+} channel blockers

Call the MH hotline for 24-hour assistance

Infographic by: Naveen Nathan MD

Questions

1. **A 9-year-old boy with Duchenne muscular dystrophy is undergoing appendectomy. The patient receives vecuronium during general anesthesia. Which of the following conditions may occur in the immediate postoperative period?**

   A. Prolonged muscle relaxation
   B. Rapid gastric emptying
   C. Hypokalemia
   D. Bronchospasm

2. **Which of the following is a common finding in patients with Guillain-Barre syndrome?**

   A. Recent fungal infection
   B. Descending skeletal muscle weakness
   C. Autonomic dysfunction
   D. Predictable response to nondepolarizing agents

3. **A 33-year-old woman with multiple sclerosis presents for evaluation of relapsing and remitting, mild leg pain. Which of the following class of drugs is part of a first-line multimodal analgesic strategy?**

   A. Opioids
   B. Tricyclic antidepressants
   C. Dissociatives
   D. Topical local anesthetic

4. **Which of the following systemic diseases can induce an acquired pseudocholinesterase deficiency?**

   A. Community-acquired pneumonia
   B. Seizure
   C. Diabetic ketoacidosis
   D. Fulminant hepatic failure

5. **Which of the following is part of a routine, prophylactic treatment strategy for patients with sickle cell disease?**

   A. Oral cephalexin
   B. Hepatitis B vaccine
   C. Hydroxyurea
   D. Blood transfusion

6. **A 32-year-old woman with myasthenia gravis reports blurred vision and generalized limb weakness at the end of the day. Administration of which of the following medications is most appropriate?**

   A. Caffeine
   B. Pyridostigmine
   C. 3,4-diaminopyridine
   D. Mitoxantrone

Answers

1. A

Duchenne muscular dystrophy (DMD) is an X-linked disorder characterized by proximal muscle weakness and painless muscle atrophy due to abnormal dystrophin protein essential in muscle membrane cytoskeleton stability. Skeletal muscle in patients with DMD is susceptible to the effects of both depolarizing and nondepolarizing muscle relaxants. Hyperkalemia and rhabdomyolysis may be inadvertently induced with succinylcholine. Prolonged muscle relaxation may occur with nondepolarizing agents. Impaired gastrointestinal function is common, leading to delayed gastric emptying and increased risk of aspiration. Impaired pulmonary function, not bronchospasm, may increase the risk of postoperative ventilatory support.

2. C

Guillain-Barre syndrome (GBS) is an inflammatory, multifocal demyelinating disease characterized by acute or subacute onset of ascending skeletal muscle weakness or paralysis of the legs, occurring in the context of a viral or bacterial infection. In severe cases of GBS, hemodynamic instability may occur due to autonomic dysfunction. Response to nondepolarizing muscle relaxants may be unpredictable.

3. B

A multimodal analgesic strategy using medications with varying mechanisms of action is integral to pain management in multiple sclerosis (MS). Tricyclic antidepressants, antiepileptics, NSAIDs, and antispastic agents are the common class of drugs used in this analgesic strategy. Opioids are generally not recommended as first-line therapy for neuropathic pain syndromes, such as MS. Depression is common in patients with MS. Dissociatives, such as ketamine, have been used as alternative therapy for treatment resistant depression. Topical local anesthetics have a limited role in neuropathic syndromes.

4. D

Acquired pseudocholinesterase deficiency impairs ester substrates metabolism via a reduction in pseudocholinesterase activity. The liver is an important source of this hepatic esterase. Fulminant hepatic failure leads to significant reduction in hepatic function and, therefore, prolonged metabolism of administered esters. Neither pneumonia, seizure, nor diabetic ketoacidosis result in hepatic esterase reduction.

5. C

Sickle cell disease (SCD) is an inherited hemoglobinopathy that results in acute and chronic multisystem complications due to a structurally abnormal hemoglobin called hemoglobin-S or sickle-hemoglobin. Oral penicillin, pneumococcal vaccination, and hydroxyurea are preventative treatments in SCD to reduce infections and sickle crises recurrence. Blood transfusion is the mainstay of treatment for acute complications of SCD. Hepatitis B vaccine, though recommended for high-risk patients such as those with chronic liver disease, is not considered prophylactic therapy for SCD patients. Oral cephalexin is a cephalosporin used for active infection.

6. B

Myasthenia gravis (MG) is an autoimmune disease characterized by skeletal muscle weakness due to a reduction in functional postsynaptic, acetylcholine receptors in the neuromuscular junction. Pyridostigmine is an acetylcholinesterase inhibitor that reduces symptoms by increasing the concentration of acetylcholine available at neuromuscular junction sites. 3,4-diaminopyridine is used as a first-line treatment for patients with LEMS. Mitoxantrone is an antineoplastic agent used to delay progression to secondary degenerative phase of multiple sclerosis. Caffeine is a commonly consumed central nervous system stimulant that is not considered to be treatment for autoimmune diseases.

Anesthesiology

Clinical Anesthesia Fundamentals

SECOND EDITION

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