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## **EMERGENCY MEDICINE**

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EDUCATIONAL MATERIAL FOR INDEPENDENT STUDY  
FOR FOUR GRAD DENTAL FACULTY STUDENTS

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**Preface**

Beginning students of medicine and dentistry must acquire a set of skills that prepare them to become clinicians. This includes establishing rapport and a therapeutic relationship with the patient, basic interviewing, the specific conduct and content of medical data collection (the history and the physical examination), formulation of a problem list and diagnostic hypotheses, documentation and record-keeping, and communication with others involved in the patient's care. An introduction to these skills during the first years of medical school focuses on the basics of data collection and information synthesis rather than the specifics of disease, diagnosis, and treatment-that is, the emphasis is on process rather than specialized content.

There are many fine texts that provide detailed discussions of the medical history and physical examination. This instruction is not intended to replace these comprehensive approaches but rather to summarize methods and outline the basic principles essential to data collection.

The authors of this book have all been involved in teaching the Introduction to Clinical Medicine course at the Ukrainian Academy of Medicine and Dentistry. Their experience has informed the **problem based approach** used in this book. This book is structured to allow students to review a set of skills that will enable them to approach undifferentiated medical problems systematically and with confidence in preparation for clinical clerkships.

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## **LESSON 1.2. RADIATION EMERGENCY**

### **Lesson 1. Biologic effects of radiation.**

All organisms are continuously exposed to radiation from either natural or synthetic sources. In the United States, the average dose of radiation an individual receives per year is estimated to be 3.6 milliSieverts (mSv), 80% of which is from natural sources and 20% of which is from man-made sources. The full effects of low-dose natural radiation are not known, but high doses have been shown to be carcinogenic. At very high-dose exposures over a short period of time, immediate and lethal health effects can occur.

Generally, the toxicity caused by radiation is directly related to the quantity of energy deposited into the living organism and the subsequent disruption of metabolic and reproductive pathways. Low-level exposure from accidental contact with radioactive isotopes in laboratory research may lead to relatively minor toxicity. Alternatively, acute sickness and even death may occur after the inappropriate handling of high-level radioactive material such as cobalt-60 from radiographic or radiotherapy machinery. In a terrorism context, a radiation dispersal device (RDD), “dirty bomb,” could result in conventional blast and thermal injuries. If these devices are laced with significant amounts of radioactive material, the additional risk of radiation exposure would exist for both bomb victims and rescue workers. Detonation of nuclear weapons or improvised nuclear devices would lead to catastrophic blast and thermal injuries in addition to far-reaching lethal radiation consequences.

Over the past 50 years, most radiation incidents have had nonlethal consequences. According to the Radiation Accident Registry maintained by the Radiation Emergency Assistance Center/Training Site (REAC/TS) at the Oak Ridge Institute, from 1944-1999, 403 radiation accidents occurred worldwide, with 243 of those occurring in the United States. Of the total, 303 involved radiation devices from sealed sources or x-ray machinery, 81 involved radioisotopes, and 19 involved nuclear reactors. These incidents have led to 120 total deaths: 30 in the United States, 2 in Great Britain, and 32 in the former USSR

#### **Radioactivity**

Radioactive decay is the process in which unstable atomic nuclei assume a more stable configuration by emitting particles with kinetic energy (alpha or beta particles) or electromagnetic waves (gamma rays). If a person is exposed to these high-energy particles or electromagnetic waves, energy is deposited into the tissues and can cause injury.

#### **Ionizing versus nonionizing radiation**

Radiation can be broken down into 2 categories: ionizing radiation and nonionizing radiation. The term ionizing radiation refers to either high-energy particles or electromagnetic waves that have the ability to deposit enough energy to break chemical bonds and produce an ion pair. Ionization occurs when the process of energy transfer liberates an orbital electron from an atom or molecule producing this ion pair. If living cells receive this energy, cellular function becomes compromised by DNA damage and mutation.

Nonionizing radiation refers to radiation that lacks the energy to liberate orbital electrons. All radiation from the electromagnetic spectrum except x-rays and gamma rays are included in this

category. Examples of nonionizing radiation include microwaves, visible light, and infrared light. Because nonionizing radiation is lower energy radiation, injury is usually related to local heat production and is generally less severe. Ionizing radiation is consequently the focus of radiation-induced injury.

### **Ionizing radiation: electromagnetic radiation**

Energy can travel through space in the form of electromagnetic radiation. Electromagnetic radiation is composed of massless waves of oscillating electric and magnetic fields. In a vacuum, these waves move at a constant speed, the speed of light ( $3 \times 10^8$  m/s). All electromagnetic waves propagate with characteristic wavelength and frequency, with the wave's energy being directly proportional to frequency and inversely proportional to wavelength. Within the electromagnetic spectrum, only x-rays and gamma rays have enough energy to produce ion pairs. The remaining waves within the spectrum, such as microwaves and radiowaves, are nonionizing.

### **Ionizing radiation: particulate radiation**

Ionizing radiation can also be in the form of particulate radiation, which includes small charged or neutral particles traveling with high energy. These particles may be alpha particles, electrons (beta particles), neutrons, or protons.

Alpha particles are charged particles made up of 2 protons and 2 neutrons with zero electrons—essentially the nucleus of a helium atom. These particles are emitted from radioactive nuclei of uranium and radium. Because of their large mass and positive charge, alpha particles are highly effective in transferring energy to tissue but are also easily blocked by a piece of paper or clothing. These particles are only a concern when alpha-emitting isotopes are ingested or inhaled.

A well-recognized source of alpha radiation involves the decay of radium into radon gas. Radium is an alkaline earth metal and a decay product of uranium and is found in uranium-bearing rocks or ores. Radium decays into radon gas, which can accumulate in poorly ventilated areas such as basements. Inhalation of radon on dust particles can lead to substantial doses of alpha radiation to the bronchi or lungs. The US Environmental Protection Agency attributes 10,000-20,000 cases of lung cancer per year to radon exposure.

Beta particles are another type of particulate radiation. These particles are high-energy electrons emitted from decaying isotopes such as strontium-90. These high-energy electrons are also easily produced in linear accelerators and are commonly used to generate x-rays and in cancer radiotherapy. As in alpha radiation, the main hazard with beta particles lies with internal exposures. With significant skin exposure, however, beta particles have sufficient energy to cause cutaneous burns, “beta burns.”

A neutron is an electrically neutral particle found within the nucleus of an atom. Neutrons are slightly greater in mass than protons. High-energy neutrons rarely occur naturally but can be produced in a particle accelerator or in nuclear reactor as part of the fission process. Neutron exposure is most consequential in a nuclear reactor criticality accident or during nuclear weapons detonation.

A proton is a positively charged particle that is more than 1800 times the size of an electron. Protons make up a major component of cosmic radiation originating from the sun. All but a small amount of the sun's proton radiation is deflected by the earth's magnetic field.

## **Irradiation, contamination, and incorporation**

Irradiation occurs when a person is exposed to ionizing radiation. For example, patients who receive x-rays or CT scans become irradiated. Once the radiographic machinery is turned off, radiation is no longer produced. Because these individuals are only in the path of radiation energy as opposed to carrying a radioactive source on their bodies, they pose no radiation exposure risk to others.

Contamination refers to the presence of radioactive material where it is undesirable. If a person's skin or clothing is contaminated with radioactive material, irradiation continues to occur until the radioactive material is removed. Under some conditions of high contamination, these individuals may pose an exposure threat to others. Unless the contaminated patients are severely ill from the exposure, it is unlikely that they pose a significant risk to other patients or healthcare workers.

Incorporation of radioactive material occurs with cellular uptake of radioactive material via inhalation, via ingestion, or through open wounds. These radioactive atoms participate in the same physiologic pathways as nonradioactive atoms. Because removing radioactive material from the body is very difficult once incorporation occurs, the best treatment philosophy is to minimize exposure and decontaminate to prevent incorporation. As with contaminated individuals, only those who are severely ill truly pose a risk to others.

Ionizing radiation causes injury to cells via breakage of DNA strands (direct action) or from the production of hydroxyl or peroxide radicals that cause oxidative damage to DNA (indirect action). Both mechanisms ultimately lead to DNA strand breaks. Single-strand breaks can be mended rather easily utilizing the intact template on the remaining strand. However, double-strand DNA breaks have no intact template and repair is much more difficult. If the cell is unable to repair the damaged chromosome, it loses reproductive integrity and ultimately undergoes mitotic death.

Apoptosis, or programmed cell death, can also occur after exposure to ionizing radiation. Some human cells are particularly sensitive to low levels of radiation. Once exposed to radiation, these cells exhibit activation of a signaling cascade that leads to DNA fragmentation and rapid cell death. Human cells that undergo radiation-induced apoptosis include lymphocytes and acinar cells of the salivary glands.

## **Early versus late radiation effects**

Radiation toxicity can be divided into early and late effects. Early effects of radiation are seen after large doses of radiation are delivered over short periods of time. Early toxicity is generally seen in rapidly dividing, self-renewal organs including skin, bone marrow, and gut epithelium. Early radiation effects are responsible for clinical syndromes that may be encountered in the emergency department following a massive exposure.

Late toxicities are generally seen in organs with slowly dividing or quiescent, terminally differentiated cells. Organs in which late toxicities are common include the central nervous system, kidneys, and liver. Many late radiation effects are attributable to a combination of parenchymal cell death and microvascular disease.

The most well-known delayed complication of radiation exposure is malignancy. Exposures to the Chernobyl accident and atomic bomb testing in the Marshall Islands led to high incidences of thyroid malignancies. Atomic bomb survivors have been shown to have an increased risk of

leukemia, and young women with Hodgkin disease treated with radiation therapy have been shown to have an increased risk for breast cancer.

The absorbed dose of radiation is the amount of energy absorbed by biologic tissue. Radiation dose is measured in Gray (Gy) or radiation absorbed dose (rad). Gray is the SI unit for dose and is expressed as J/kg. One gray is equal to 100 rad. Since the biologic effects of different types of radiation (eg, gamma vs alpha vs neutron) vary significantly, expressing radiation exposure in terms of equivalent dose is sometimes useful. By assigning a weighting factor to each type of radiation (gamma = 1, alpha = 20), the equivalent dose can be calculated by multiplying the absorbed dose (Gy) by the radiation weighting factor. Equivalent dose is then expressed in sieverts (Sv).

### **Localized cutaneous injury**

Localized exposure to high doses of radiation may cause cutaneous injury similar to burns. Blistering, erythema, desquamation, and ulceration often present about 12-20 days after irradiation with the onset and severity related to the magnitude of exposure.

A local exposure of 3 Gy leads to epilation within 1-2 weeks. A local exposure of 6 Gy may cause immediate signs of burn. Greater exposures of 10-15 Gy lead to dry desquamation, and exposures of 20-50 Gy lead to wet desquamation (partial-thickness burn) within 2-3 weeks. For doses greater than 50 Gy, a cutaneous syndrome of necrosis and ulceration may occur from damage to endothelial cells and small blood vessels. Vascular complications may present months to years after exposure.

## **Lesson 2. Acute radiation syndrome**

The acute radiation syndrome (ARS) occurs after whole-body exposure to a large dose of ionizing radiation. This syndrome includes a number of characteristic signs and symptoms whose severity depends on magnitude of dose and duration of exposure. ARS, by definition, does not occur at doses less than 1 Gy and is uniformly fatal at doses greater than 10 Gy. The estimated LD<sub>50/60</sub> (the dose at which 50% of those exposed die within 60 days) is 3.5 Gy for humans without medical treatment and roughly 7.0 Gy with treatment.

Frequently, the exact details of an accidental exposure are not known, leaving uncertainty in dose assessments. Clinical presentation, symptomatology, and laboratory measures, especially in the early period, can be used to indirectly determine dosage of exposure and prognosis.

### **Stages of ARS**

ARS has been described according to progression of illness through 4 stages: (1) prodrome, (2) clinical latency, (3) manifest illness, and (4) recovery or death. The prodromal symptoms occur shortly after irradiation, with the dose of exposure determining severity, duration, and onset. Common prodromal symptoms include nausea, vomiting, anorexia, fatigue, diarrhea, abdominal cramping, and dehydration. At doses of greater than 10 Gy, those exposed show symptoms within 5-15 minutes; at lower doses such as 2-3 Gy, symptoms can take up to 12 hours to present. Immediate diarrhea, hypotension, and fever indicate a supralethal exposure. Severe and early onset of prodromal symptoms indicates higher dosage of exposure and a poor prognosis. Progression through the other phases depends on dosage of exposure.

### **Classic ARS syndromes**

ARS is further described by its 3 classic subsyndromes: the hematopoietic syndrome, the gastrointestinal syndrome, and the cerebrovascular syndrome. The hematopoietic syndrome

typically occurs after exposures of 2-5 Gy. At these doses, lymphocytes die from radiation-induced apoptosis, and precursor cells in the bone marrow are destroyed preventing new production of leukocytes and platelets. During the period of a few weeks (clinical latency), circulating cells die off with no replacements; it is at this nadir that the full syndrome becomes clinically apparent with development of infections and possible hemorrhage. Anemia from red cell depression usually does not occur alone in the absence of hemorrhage. Early supportive care, treatment and prevention of infections, and the consideration of cytokine therapy are all important aspects of care for this subsyndrome. However, even if the hematopoietic syndrome is treated, death commonly still occurs from multiorgan failure.

The gastrointestinal syndrome usually occurs after exposures of more than 5-12 Gy. Irradiation leads to death of intestinal mucosal stem cells in the crypts. After loss of mucosal cells at the villi through normal functioning, the stem cells are unable to produce new cells, leading to denudation of the GI tract. As the normal GI boundary is compromised, bacterial growth proliferates increasing the risk of sepsis. Common symptoms include anorexia, nausea, vomiting, prolonged bloody diarrhea, abdominal cramps, dehydration, and weight loss. Often the prodrome onset is rapid, followed by a latent period of roughly 1 week then return of symptoms. The mainstays of treatment are fluid and electrolyte balance and infection prevention, but death often follows in 3-10 days.

The cerebrovascular syndrome occurs after exposures of very high doses (>30 Gy) and is uniformly fatal. At doses of greater than 100 Gy, death occurs within hours. Although the exact mechanism of death is not fully understood, vascular damage is thought to lead to significant cerebral edema, producing neurologic and cardiovascular collapse. Immediate symptoms include nausea, vomiting, hypotension, ataxia, and convulsions, and death follows in a few days.

### **Time to emesis**

Past studies have suggested time to emesis (TE) as one clinical parameter that can be used to indirectly determine dosage exposure. TE postradiation exposure seems to decrease as dosage increases. For TE less than 1 hour, the whole-body dose is estimated to be greater than 4 Gy. For TE between 1 and 2 hours, whole-body dose is estimated to be greater than 3 Gy, and for TE greater than 4 hours, whole-body dose is estimated to be around 1 Gy.

The most useful laboratory test in the setting of acute radiation exposure is the serial complete blood count with differential obtained every 6-12 hours. Lymphocyte count serves as an indicator for prognosis and as an estimate for the dose of radiation received. Patients with a minimal lymphocyte count (MLC) of  $1000-1499/\text{mm}^3$  have an approximate absorbed dose of 0.5-1.9 Gy. Although these patients may have clinically significant effects, their prognosis is good because the absorbed dose is usually nonlethal.

Patients with MLC of  $500-999/\text{mm}^3$  have an approximate absorbed dose of 2.0-3.9 Gy with severe injuries and fair prognosis. An MLC of  $100-499/\text{mm}^3$  coincides with an approximate absorbed dose of 4.0-7.9 Gy predicting severe injury and a poor prognosis, and those with MLC less than  $100/\text{mm}^3$  have an estimated absorbed dose of greater than 8 Gy and have a high incidence of death despite bone marrow stimulation. Survival has not been documented for those exposed to greater than 10 Gy.

Blood can also be drawn for cytogenetic evaluation. If dicentrics (chromosomes with 2 centromeres) are found, they can be used to indicate extent of radiation exposure. Cytogenetic studies are time-consuming processes that are currently not being used for mass screening strategies. Realistically, these studies may be more useful from an inpatient standpoint.



## **Prehospital care**

In the instance of radiation accidents, prehospital personnel should wear appropriate protective gear prior to arrival at the scene and follow the guidance of the radiation safety officer or operations commander. If possible, field personnel should elicit type of radioactive material involved and extent of exposure. If a high radiation field is discovered, areas of operation should be determined. Clinical operations may be required in higher exposure areas, but exposure limits should be strictly regulated by supervisors.

Decontamination at or near the site of exposure is important, as simple clothing removal is believed to eliminate up to 90% of contamination. Unfortunately, proper decontamination is difficult to perform in the field, and personnel at receiving hospitals may find this step bypassed. If prehospital decontamination is possible, contaminated clothing and water should be collected as biohazardous material. If other injuries have occurred, BLS/ATLS protocols should be initiated and unstable patients should be rapidly transported to appropriately equipped hospitals.

## **Emergency department care**

In general, treatment of conventional injuries and illness takes precedence over radiation concerns. The quantity of radioactive material that a contaminated individual carries on his or her body is unlikely to present a significant radiation risk to hospital workers. No cases are known of healthcare personnel becoming acutely ill caring for contaminated or irradiated victims of radiation accidents. Critically ill and injured patients should be moved into critical care areas of the hospital and should be decontaminated during resuscitation. In a mass casualty event, most patients arrive without prehospital decontamination necessitating appropriate screening strategies in accordance with the Hospitals Incident Command Structure (HICS).

## **Specific treatments**

Patients with localized irradiation that present with cutaneous injury should be treated in the same manner as those with thermal burns. Pain control and infection prophylaxis are the mainstays of treatment. In the cases of severe burns, vasodilator therapy, grafts, or amputations may be necessary.

After whole-body radiation exposure, appropriate decontamination should occur. Patients who present with prodromal symptoms should be treated supportively with intravenous fluids, analgesics, and antiemetic medication. For exposures of around 5 Gy, most experts recommend supportive care, antibiotics for infection, consideration of cytokine therapy, and transfusions as needed. Blood products should be leukocyte-poor and irradiated to 25 Gy, but transfusions should not be given prophylactically because they may blunt the stimuli for cell regeneration. For exposures greater than 5 Gy, death from gastrointestinal syndrome is highly likely. Along with antibiotics and platelet transfusions as needed, physical trauma and avoidance of infection (isolation) should be stressed.

In cases of internal ingestion or contamination of unknown radioactive materials, some measures (eg, lavage, charcoal) to decrease absorption may be effective and can be used if not contraindicated. Similarly, specific therapies exist to remove some internally deposited radionuclide albeit with limited efficacy. These treatments are often in limited supply, complex in action, and associated with significant risks. Thoughtful and critical analysis should be taken place prior to administration.

Internal contamination by radioactive iodine can be treated with saturated solution of potassium iodide (SSKI), a blocking agent that reduces uptake of radionuclide in the thyroid. SSKI is most effective when taken within a few hours of exposure. In reactor accidents involving radioactive iodine, massive quantities are released into the environment. Both exposed victims and rescue personnel should take SSKI to reduce thyroid uptake of radioiodine to reduce risk of future malignancies. Specific dosages for SSKI administration can be viewed at [Guidance for Industry – KI in Radiation Emergencies—Questions and Answers](#).

Chelating agents, such as penicillamine, bind specific radioactive metals causing decreased tissue uptake and increased excretion. Exposure to isotopes of cesium can be treated with ferric hexacyanoferrate (Prussian blue) to decrease gastrointestinal absorption. Agents such as Ca-DTPA and Zn-DTPA can be administered after internal contamination with substances such as americium or plutonium. Administration of specific agents should be done in consultation with professionals familiar with these agents.

### **Further inpatient care**

During periods of infection, antibiotics should be tailored toward the source of infection. If absolute neutrophil count (ANC) is less than  $500 \text{ cells/mm}^3$ , most experts recommend prophylactic antibiotics including a fluoroquinolone, an antiviral agent (acyclovir in those with a history of herpes simplex virus), and an antifungal agent. Once fever and infection occur, broader antibiotics with additional antipseudomonal coverage should be initiated.

The use of bone marrow transplants remains controversial. Of the 13 Chernobyl victims who received bone marrow transplants, only 2 survived, one of whom had autologous marrow repopulation; thus only one survivor was thought to be saved by a bone marrow transplant. The dose window appropriate for bone marrow transplantation is thought to be between 8 and 10 Gy, as those who receive less than 8 Gy may survive with conservative treatment, antibiotics, and transfusions, whereas those who receive greater than 10 Gy uniformly die.

Administration of hematopoietic growth factors to stimulate bone marrow post irradiation also remains investigational. Past studies have shown a benefit in animal models increasing neutrophil counts in primates irradiated with Cobalt-60.

In a 2004 paper, Waselenko et al proposed recommendations for giving colony-stimulating factors (CSF) to victims of radiation exposure. His team recommended giving granulocyte-macrophage colony-stimulating factor (GM-CSF) to those who receive more than 3 Gy of radiation and in those with multiple injuries who are exposed to more than 2 Gy. Recommended doses include initiating therapy with filgrastim at  $5 \text{ } \mu\text{m/kg/day}$  or sargramostim at  $250 \text{ } \mu\text{m/m}^2\text{/day}$  subcutaneously immediately after exposure and continuing until absolute neutrophil count increases to greater than  $1,000 \text{ cells/mm}^3$ . Alternative treatment with subcutaneous pegfilgrastim.

## **LESSON 3. Chemical weapon agents**

Because of the ongoing risk of chemical attack, emergency physicians must be able to care for victims of chemical weapon agents (CWAs). This article reviews the physical properties and general clinical effects of CWAs. It also describes the medical management of victims of CWAs, including the use of personal protective equipment (PPE), victim decontamination, provision of supportive care, and provision of specific antidotal therapy. To illustrate these principles with specific agents, the properties, clinical effects, and medical management of nerve agents and vesicant agents are reviewed briefly.

For excellent patient education resources, visit eMedicine's [Bioterrorism and Warfare Center](#). Also, see eMedicine's patient education articles [Chemical Warfare](#) and [Personal Protective Equipment](#).

### **Risk of exposure to chemical warfare agents**

Injury from CWAs may result from industrial accident, military stockpiling, war, or terrorist attack.

Industrial accidents continue to be a significant potential source of exposure to the agents used in chemical weapons. Chemicals such as phosgene, cyanide, anhydrous ammonia, and chlorine are used widely and frequently are transported by industry. The accidental release of a methylisocyanate cloud (composed of phosgene and isocyanate) was implicated in the Bhopal disaster in 1984. These accidents continue today, with nearly 9000 occurring in the United States in 2001 alone.

CWAs first were used in 1915, when the German military released 168 tons of chlorine gas at Ypres, Belgium, killing an estimated 5000 Allied troops. Two years later, the same battlefields saw the first deployment of sulfur mustard. Sulfur mustard was the major cause of chemical casualties in World War I. CWAs have been used in at least 12 conflicts since, including the first Persian Gulf War (Iraq-Iran War). The Iraqi military also used chemical weapons against the Iraqi Kurds during the second Persian Gulf War.

Civilians have also been exposed inadvertently to chemical weapons many years after weapon deployment during war. Approximately 50,000 tons of mustard shells were disposed of in the Baltic Sea following World War I. Since then, numerous fishermen have been burned accidentally while hauling leaking shells aboard boats. Leaking mustard shells also have injured collectors of military memorabilia and children playing in old battlefields.

Although a number of international treaties have banned the development, production, and stockpiling of CWAs, these agents reportedly still are being produced or stockpiled in several countries.

Within the last decade, terrorists deployed chemical weapons against civilian populations for the first time in history. The release of sarin in Matsumoto, Japan, in June 1994 by the extremist Aum Shinrikyo cult left 7 dead and 280 injured. The following year, in March 1995, the Aum Shinrikyo cult released sarin vapor in the Tokyo subway system during morning rush hour, leaving 12 dead and sending more than 5000 casualties to local hospitals. A derivative of fentanyl was also used against terrorists holding hostages in a Moscow theater in 2002. Because of a lack of antidote available by the responders, more than 120 casualties among the hostages occurred from asphyxiation.

Several characteristics of CWAs lend themselves to terrorist use. Chemical substrates used in CWAs are widely available, and recipes for CWA production may be found on the Internet. CWAs are transported easily and may be delivered by a variety of routes. Chemical agents often are difficult to protect against and quickly incapacitate the intended targets. Most civilian medical communities are inadequately prepared to deal with a chemical terrorist attack

## **Types of chemical weapon agents**

CWAs comprise a diverse group of hazardous substances. Major categories of CWAs include the following:

- Nerve agents (eg, sarin, soman, cyclosarin, tabun, VX)
- Vesicating or blistering agents (eg, mustards, lewisite)
- Respiratory agents (eg, chlorine, phosgene, diphosgene)
- Cyanides
- Antimuscarinic agents (eg, anticholinergic compounds)
- Opioid agents (opioid derivatives)
- Riot control agents (eg, pepper gas, cyanide, CS)
- Vomiting agents (eg, adamsite)

## **Physical properties**

CWAs generally are stored and transported as liquids and deployed as either liquid aerosols or vapors. Victims usually are exposed to agents via one or more of 3 routes: skin (liquid and high vapor concentrations), eyes (liquid or vapor), and respiratory tract (vapor inhalation).

CWAs are characterized by 2 inversely related physical properties: volatility (ie, tendency of liquids to vaporize, which directly increases with temperature) and persistence (ie, tendency of liquids to remain in a liquid state).

In general, volatile liquids pose the dual risk of dermal and inhalation exposure, while persistent liquids are more likely to be absorbed across the skin. The effects of vapors largely are influenced by ambient wind conditions; even a slight breeze can blow nerve agent vapor away from its intended target. Effects of vapor are enhanced markedly when deployed within an enclosed space.

## **Clinical effects**

Depending on the agent and the type and amount (concentration) of exposure, CWA effects may be immediate or delayed. Large inhalation exposures to nerve agents or mustards are likely to be lethal immediately. Small dermal exposures to nerve agents and mustards are particularly insidious and generally require expectant observation for variable periods because of possible delayed effects. Specific clinical effects of CWAs are as varied as the agents.

## **Medical management**

To appropriately manage CWA exposures, emergency care personnel are required to protect themselves by performing the following:

- Using PPE
- Decontaminating patients immediately
- Providing supportive care
- Providing specific antidotes when indicated

## **Personal protective equipment**

The primary responsibility of those who treat victims of CWAs is to protect themselves by wearing adequate PPE. First responders are at serious risk from the chemically contaminated environment (hot zone), either from direct contact with persistent liquid or from inhaling vapor. First responders

and emergency care providers also are at risk from handling skin and clothing of victims contaminated with liquid CWAs (secondary skin and inhalation exposure). Conversely, providing care to those exposed only to vapor CWAs poses little risk to emergency care providers outside the hot zone. Regardless, until identification of the substance is made and it is deemed nontoxic, responders should wear their PPE.

Standard protective garments are inadequate for most CWAs. Double layers of latex gloves are useless against liquid nerve and blister agents, and surgical masks and air-purifying respirators are inadequate against nerve agent vapors.

### **Levels of personal protective equipment**

US regulatory agencies mandate the use of appropriate levels of PPE.

- Level A PPE is required for first responders and others working inside the hot zone, where vapor concentrations may be immediately dangerous to life and health. These suits are fully encapsulated, resistant to liquid and vapor chemical penetration, and include a self-contained breathing apparatus. Level A suits are also cumbersome, hot, and very difficult to wear for more than 30 minutes. There has been some move to mandate the use of level-A suits for hospital personnel. This is a hotly debated subject and as yet is unresolved. The use of level-A suits in hospital-based decontamination is probably not warranted.
- Level B PPE is required for hospital personnel involved in decontamination of unknown hazardous materials. These suits provide adequate protection against liquid and vapor chemicals when accompanied by a self-contained breathing apparatus or supplied air respirator.
- Level C PPE is used when chemical agents have been identified and are amenable to removal by an air-purifying respirator. This suit also provides some protection against penetration by chemical liquids and vapors.

### **Decontamination**

- Decontamination is the physical process of removing residual chemicals from persons, equipment, and the environment. Residual hazardous chemicals on those who have been exposed directly are a source of ongoing exposure to those persons and pose a risk of secondary exposure to first responders and emergency care personnel. Immediate decontamination is a major treatment priority for those with CWA exposure.
- Initial decontamination involves removal from the contaminated environment, removal of all contaminated clothes and jewelry, and copious irrigation with water.
- Rinse exposed persons with a 0.5% hypochlorite solution, which chemically neutralizes most CWAs (eg, nerve agents, mustards). A 0.5% hypochlorite solution conveniently is prepared by mixing 1 part 5% hypochlorite (household bleach) with 9 parts water.
- Avoid hot water and vigorous scrubbing, as they may increase chemical absorption.
- Vapor exposure alone does not require decontamination. Fully decontaminate patients with unclear exposure histories. As well, if a nerve agent is suspected, decontamination should be performed as the patient may off-gas significant levels of the agent with the potential of further exposure to both him or her and responders.
- Ideally, decontaminate as close as possible to the site of exposure to minimize duration of exposure and prevent further spread. Hospitals receiving contaminated persons should establish an area outside the emergency department in which to perform decontamination before people and equipment are allowed in. Portable decontamination equipment with showers and run-off water collection systems are commercially available. All hospitals should have the capacity to safely decontaminate at least one person.

## **Supportive and specific therapy**

Supportive therapy for victims of CWAs generally follows the universally accepted algorithm of first ensuring the adequacy of airway, breathing, and circulation, with one important exception. Severe nerve agent poisoning may require immediate administration of parenteral atropine. Many CWAs only can be treated supportively. Specific, well-established antidotes are available only for nerve agent and cyanide exposures. Since no laboratory tests are available to rapidly confirm exposure to CWAs, treatment is based on clinical

## **Mechanism of Action**

The 5 nerve agents, tabun (GA), sarin (GB), soman (GD), cyclosarin (GF), and VX, have chemical structures similar to the common organophosphate pesticide malathion. Like organophosphate insecticides, these agents phosphorylate and inactivate acetylcholinesterase (AChE). Acetylcholine accumulates at nerve terminals, initially stimulating and then paralyzing cholinergic neurotransmission throughout the body.

Inhibition of AChE may not account for all of the toxic effects of nerve agents. These agents also are known to bind directly to nicotinic receptors and cardiac muscarinic receptors. They also antagonize gamma-aminobutyric acid (GABA) neurotransmission and stimulate glutamate *N*-methyl-d-aspartate (NMDA) receptors. These latter actions may partly mediate nerve agent-induced seizures and CNS neuropathology.

## **Physical Properties**

Under temperate conditions, all nerve agents are volatile liquids. The most volatile agent, sarin, evaporates at approximately the same rate as water. The least volatile agent, VX, has the consistency of motor oil. This persistence and higher lipophilicity make VX 100-150 times more toxic than sarin when victims sustain dermal exposure. A 10-mg dose applied to the skin is lethal to 50% of unprotected individuals.

All nerve agents rapidly penetrate skin and clothing. Nerve agent vapors are heavier than air and tend to sink into low places (eg, trenches, basements).

## **Clinical Effects**

Nerve agents produce muscarinic, nicotinic, and direct CNS toxicity with a wide variety of effects on the respiratory tract, cardiovascular system, CNS, gastrointestinal (GI) tract, muscles, and eyes. Onset and severity of clinical effects vary widely, since numerous variables determine predominant effects. Agent identity, dose (determined by concentration and duration of exposure), and type of exposure primarily determine nerve agent toxicity. Toxic effects result from dermal exposure to liquid and ocular and inhalation exposure to vapor.

### **Liquid exposure**

Liquid agents easily penetrate skin and clothing. Onset of symptoms occurs from 30 minutes to 18 hours following dermal exposure.

Minimal liquid exposure (eg, a small droplet on the skin) may cause local sweating and muscle fasciculation, followed by nausea, vomiting, diarrhea, and generalized weakness. Even with decontamination, signs and symptoms may persist for hours.

In contrast, persons with severe liquid exposures may be briefly asymptomatic (1-30 min) but rapidly may suffer abrupt loss of consciousness, convulsions, generalized muscular fasciculation, flaccid paralysis, copious secretions (nose, mouth, lungs), bronchoconstriction, apnea, and death.

### **Vapor exposure**

Vapor inhalation produces clinical toxicity within seconds to several minutes. Effects may be local or systemic. Exposure to even a small amount of vapor usually results in at least one of the following categories of complaints: (1) ocular (miosis, blurred vision, eye pain, conjunctival injection), (2) nasal (rhinorrhea), or (3) pulmonary (bronchoconstriction, bronchorrhea, dyspnea).

Exposure to a vapor concentration of  $3.0 \text{ mg/m}^3$  for 1 minute causes miosis and rhinorrhea. Inhalation of a high concentration of vapor results in loss of consciousness after only one breath, convulsions, respiratory arrest, and death. For example, breathing  $10 \text{ mg/m}^3$  of sarin vapor for only 10 minutes ( $100 \text{ mg/m}^3$  for 1 min) causes death in approximately one half of exposed individuals. Severe vapor exposures also are characterized by generalized fasciculations, hypersecretions (mouth, lungs), and intense bronchoconstriction with respiratory compromise.

### **Respiratory tract**

Nerve agents act on the upper respiratory tract to produce profuse watery nasal discharge, hypersalivation, and weakness of the tongue and pharynx muscles. Laryngeal muscles are paralyzed, resulting in stridor. In the lower respiratory tract, nerve agents produce copious bronchial secretions and intense bronchoconstriction. If untreated, the combination of hypersecretion, bronchoconstriction, respiratory muscle paralysis, and CNS depression rapidly progresses to respiratory failure and death. Nerve agents depress the central respiratory drive directly. Thus, early death following large vapor exposure likely results from primary respiratory arrest, not from neuromuscular blockade, bronchorrhea, or bronchoconstriction.

### **Cardiovascular system**

The cardiovascular effects of nerve agents vary and depend on the balance between their nicotinic receptor–potentiating effects at autonomic ganglia and their muscarinic receptor–potentiating effects at parasympathetic postganglionic fibers that innervate the heart.

Sinus tachydysrhythmias with or without hypertension (sympathetic tone predomination) or bradydysrhythmias with or without variable atrioventricular blockade and hypotension (parasympathetic tone predomination) may occur.

Superimposed hypoxia may produce tachycardia or precipitate ventricular tachydysrhythmias.

Nerve agent–induced prolonged QT and torsades de pointes have been described in animals.

In victims of the Tokyo sarin gas attack, sinus tachycardia and hypertension were common cardiovascular abnormalities, while sinus bradycardia was uncommon.

### **Central nervous system**

Nerve agents produce a variety of neurologic signs and symptoms by acting on cholinergic receptors throughout the CNS. The most important clinical signs of neurotoxicity are a rapidly decreasing level of consciousness (sometimes within seconds of exposure) and generalized seizures.

Symptoms such as headache, vertigo, paresthesias, anxiety, insomnia, depression, and emotional lability also have been reported.

### **Musculoskeletal system**

Nerve agents initially stimulate and then paralyze neurotransmission at the neuromuscular junction. With minimal exposure, exposed persons may complain of vague weakness or difficulty walking. More significant exposures resemble the clinical effects that result from succinylcholine, with initial fasciculations followed by flaccid paralysis and apnea.

### **Ocular**

Nerve agent liquid or vapor readily penetrates the conjunctiva and exerts direct muscarinic parasympathetic effects. This results in constriction of the iris (miosis, blurred and dim vision, headache), constriction of the ciliary muscle (pain, nausea, vomiting), and stimulation of the lacrimal glands (tearing, redness). Although miosis is the most consistent clinical finding after vapor exposure to nerve agents (occurred in 99% of persons exposed in Tokyo sarin attack), it may be absent or delayed in dermal exposure. Duration of miosis varies according to the extent of ocular exposure (up to 45 d).

### **Laboratory Tests**

Routine toxicology testing does not identify nerve agents in serum or urine. Measurements of red blood cell (RBC) or plasma cholinesterase activity have been used as an index of the severity of nerve agent toxicity, but this approach is not always reliable. The reference range of RBC cholinesterase activity may vary widely, and mild exposures may be difficult to interpret without baseline measurement. In addition, RBC cholinesterase activity may not correlate with the severity of signs and symptoms following vapor exposure.

In the Tokyo subway sarin attack, 27% of patients with clinical manifestations of moderate poisoning had plasma cholinesterase activity in the normal range. Moreover, different organophosphates variably inhibit RBC and plasma cholinesterase. For example, in mild-to-moderate exposures to sarin or VX, RBC cholinesterase activity is decreased to a much greater extent than plasma cholinesterase activity.

Since plasma cholinesterase is produced by the liver, its activity also may be depressed in certain conditions (eg, liver disease, pregnancy, infections) or with certain drugs (eg, oral contraceptives). Conversely, a 20-25% reduction in RBC cholinesterase activity tends to correlate with severe clinical toxicity and, despite the exception noted above, activity of both enzymes approaches zero in most severely poisoned victims. Nevertheless, treatment decisions should be clinically based. Never withhold treatment from a symptomatic patient.

### **Personal Protective Equipment**

First responders are at serious risk of exposure within the contaminated environment (hot zone), either from direct contact with persistent liquid or from inhaling residual vapors. First responders and subsequent emergency care providers outside the hot zone are at risk from handling persons contaminated with liquid nerve agent (through both dermal and inhalation exposure).

Conversely, victims exposed to nerve agent vapor pose little risk to emergency care providers outside the hot zone; residual agent is not present and off-gassing may occur but rarely in



significant amounts. In the Tokyo sarin attack, approximately 90% of exposed persons reported to medical facilities by private or public transportation without notable contamination of others. Additionally, secondary injury to hospital staff was minimal and did not necessitate specific treatment.

Unless a clear history of vapor exposure only is obtained, emergency medical personnel should assume that liquid contamination is present and wear PPE. For most nerve agent exposures, first responders require level A PPE inside the hot zone, and hospital personnel involved in decontamination should wear level B PPE.

## **Decontamination**

Decontamination should proceed as described in General Considerations. Decontaminate with a triple wash, including initial irrigation with tepid water followed by 0.5% hypochlorite solution or soap and water (alkaline solutions also neutralize nerve agent) and repeated thorough water rinsing. In survivors, the amount of residual liquid contaminant is likely to be small, because victims with larger exposures probably will die before they reach the hospital. Other than removing clothing and jewelry, decontamination is unnecessary for victims of vapor nerve agent exposure.

## **Supportive Care**

Saving lives always depends on ensuring adequate airway, ventilation, and circulation. The larger the exposure, the more likely victims require early intubation and ventilation. Conversely, adequate ventilation may be impossible due to the intense muscarinic effects of nerve gas exposure (copious airway secretions, bronchoconstriction). In this situation, administer atropine before initiating other measures. The use of succinylcholine to assist intubation is not recommended, since nerve agents prolong the drug's paralytic effects.

Treat seizures with adequate oxygenation and liberal doses of benzodiazepines titrated to effect. Termination of seizure activity may reflect onset of flaccid paralysis from the nerve agent rather than adequacy of antiseizure therapy. A bedside electroencephalograph (EEG) may be required to assess ongoing seizure activity.

Animal data suggest that routine administration of diazepam reduces incidence of seizures and decreases severity of pathologic brain injury following nerve agent exposure.

## **Specific Therapy**

Treatment of victims with nerve gas toxicity is broadly similar to the treatment of those poisoned by organophosphate insecticides.

### **Atropine sulfate**

Symptomatic patients require immediate treatment with atropine. Atropine blocks muscarinic effects of nerve agents (eg, bronchorrhea, bronchoconstriction), improving ventilation by drying secretions and decreasing airway resistance. Atropine also blocks other muscarinic effects, such as nausea, vomiting, abdominal cramping, bradycardia, and diaphoresis. Atropine does not have nicotinic effects and thus does not reverse toxicity at autonomic ganglia and neuromuscular junctions. Atropine does not prevent or reverse paralysis.

Atropine therapy is guided by clinical signs and symptoms. Titrate dosing to the desired clinical effect. The goals of atropine therapy are to dry secretions and eliminate bronchoconstriction.

Administer more atropine if assisted ventilation remains difficult or secretions persist. Heart rate and pupil size are poor clinical indicators of adequate atropinization. Presence of tachycardia should not dissuade the clinician from initiating or continuing atropine therapy. Miosis may be absent or delayed in dermal exposures and is not reversed by systemic atropine.

- Adults with mild-to-moderate symptoms: 2 mg of atropine IV/IM/ET q2-5min
- Adults with severe symptoms: 5 mg IV/IM/ET
- Children: 0.02 mg/kg (0.1 mg minimum) IV/IM/ET
- Children with severe symptoms: 0.05 mg/kg IV/IM/ET

Up to 20 mg of atropine may be required the first day, unlike with organophosphate insecticide poisoning, where as much as 3000 mg of atropine may be required over 1 day. In the Tokyo sarin attack, only 19% of poisoned patients required more than 2 mg of atropine. Severely poisoned patients required 1.5-15 mg of atropine.

### **Oxime therapy**

Oximes are nucleophilic substances that bind to the phosphate moiety of the nerve agent more avidly than AChE to reactivate the nerve agent-inhibited enzyme. Reactivation is impossible once dealkylation or "aging" of phosphorylated AChE occurs. Once aging occurs, new AChE must be synthesized. The rate of aging varies among nerve agents. Aging occurs within 2 minutes after soman exposure, 5-8 hours after sarin exposure, and more than 40 hours after tabun and VX exposure.

Pralidoxime chloride (2-PAM) is the only conventional oxime available for clinical use in the US. Administer pralidoxime to symptomatic patients as early as possible, ideally concurrent with adequate doses of atropine. Pralidoxime has its greatest effect at the neuromuscular junction.

- Adult dose: 1-2 g IV
- Pediatric dose: 15-25 mg/kg IV over 30 min

Slowly administer pralidoxime IV to minimize adverse effects such as hypertension, headache, blurred vision, epigastric pain, nausea, and vomiting. When IV access cannot be established, 2-PAM also may be given IM (1 mg with 3 mL sterile saline).

With adequate decontamination and appropriate initial therapy, serious signs and symptoms of nerve agent toxicity rarely last more than a couple of hours. In the unusual event that toxicity persists or worsens clinically, administer repeat doses of 2-PAM at hourly intervals. In the Tokyo sarin attack, severely poisoned patients required 1-36 g. Since 2-PAM is excreted in the urine, lower repeat doses for patients with renal failure and maintain adequate hydration. If hypertension increases during pralidoxime administration, IV phentolamine may help (adults: 5 mg IV; children: 1 mg IV).

### **Mark I kit**

Mark I kit was designed for military self-administration in the field. It consists of two spring-loaded IM Autoinjectors containing 2 mg of atropine and 600 mg of pralidoxime, respectively. These antidote kits are not yet available for civilian use.

## Hemodialysis

Japanese physicians reported successful use of hemodialysis and hemoperfusion in one severely intoxicated victim of the Tokyo Subway sarin attack who remained unresponsive to pharmacotherapy.

## Disposition

Peak toxic effects occur within minutes to hours and resolve within 1 day. Observe asymptomatic patients exposed to nerve agent liquid for a minimum of 18 hours, since delayed onset of signs and symptoms have been reported (up to 18 h postexposure). Admit symptomatic patients with liquid exposure and monitor them for at least 1 day.

Cholinesterase levels alone should not guide disposition. Some sources recommend observation of asymptomatic patients exposed to nerve gas vapor for 1 hour. In reality, patients who present after inhaling nerve agent vapor have experienced peak effects long before arriving at the hospital, and no further absorption or worsening is expected. When patients experience no signs or symptoms other than eye findings, they may

## Mechanism of action

Sulfur mustard (2,2,-dichlorodiethyl sulfide) has been used as a chemical weapon since World War I. Nitrogen mustard, a derivative of sulfur mustard, was one of the first chemotherapy agents but never has been used in warfare. These vesicating agents cause blistering of exposed surfaces. Both mustard agents rapidly penetrate cells and generate a highly toxic intermediate episulfonium ion, which irreversibly alkylates DNA, RNA, and protein. This disrupts cell function and causes cell death. The chemical reaction is both temperature dependent and facilitated by the presence of water, which explains why warm, moist tissues are affected more severely. Actively reproducing cells, such as epithelial and hematopoietic cells, are most vulnerable to alkylation. Mustards also produce cytotoxicity by binding to and depleting cellular glutathione, a free radical scavenger. Glutathione depletion leads to the inactivation of sulfhydryl-containing enzymes, loss of calcium homeostasis, lipid peroxidation, cellular membrane breakdown, and cell death.

## Physical Properties

Mustards are oily liquids with odors of mustard, onion, garlic, or horseradish. Highly soluble in oils, fats, and organic solvents, mustards quickly penetrate skin and most materials, including rubber and most textiles. Sulfur mustard is considered a persistent agent with low volatility at cool temperatures but becomes a major vapor hazard at high ambient temperatures. Exposure to mustard vapor, not mustard liquid, is the primary medical concern. More than 80% of mustard casualties in World War I were caused by exposure to mustard vapor. Mustard vapor is 3 times more toxic than a similar concentration of cyanide gas; however, mustard liquid is also quite toxic. Skin exposure to as little as 1-1.5 tsp of liquid (7 g) is lethal to 50% of adults.

## Clinical Effects

Mustards injure the skin, eyes, respiratory tract, GI mucosa, and hematopoietic system. The pattern of toxicity depends partly on whether the person is exposed to liquid or vapor. Liquid exposure primarily damages the skin, producing an initial erythema followed by blistering similar to a partial-thickness burn. Vapor exposure preferentially damages the upper respiratory tract (skin usually is not affected). Mustards penetrate cells and alkylate intracellular components in less than 2 minutes,

yet signs and symptoms usually are delayed 4-6 hours (range, 1-24 h). The latent period is shorter with high-concentration exposures, such as those occurring at increased ambient temperature and humidity.

### **Skin**

Chemical burns secondary to mustard often appear deceptively superficial on initial presentation. Earliest symptoms are pruritus, burning, and stinging pain over exposed areas. Moist, thinner skin is affected more severely. Affected areas appear erythematous and edematous. If contamination is more extensive, superficial bullae occur within 24 hours of exposure. Most burns are partial thickness, but full-thickness burns with deep bullae and ulcers may result from exposure to higher concentrations. Severe exposures clinically and histologically may resemble scalded skin syndrome or toxic epidermal necrolysis. Blister fluid does not contain active mustard and is not toxic.

### **Eyes**

Eyes are especially sensitive to the effects of mustard. Ocular symptoms begin 4-8 hours postexposure. Earliest symptoms include burning pain, foreign body sensation, photophobia, tearing, and visual blurring. Clinical manifestations include eyelid edema, conjunctival injection and edema, chemosis, iritis, corneal abrasions, edema and ulceration, and decreased visual acuity. Permanent corneal scarring and blindness may occur with severe exposures.

### **Respiratory tract**

Mustards primarily damage upper airway mucosa. Inhalation of mustard vapor produces a direct inflammatory effect on the respiratory tract, with damage occurring in a progressive downward pattern. The lower respiratory tract and lung parenchyma rarely are affected. Following a variable latent period of 2-24 hours, injury is characterized by hemorrhagic inflammation and airway erosion.

Upper respiratory tract is affected first, evidenced by sinusitis, sinus congestion, sore throat, and hoarseness. Lower respiratory tract symptoms include cough, dyspnea, and respiratory distress. Direct necrotic effect of mustard on airway mucosa produces epithelial sloughing and pseudomembrane formation, causing small and large airway obstruction.

In severe cases, late pulmonary sequelae include bronchopneumonia and bronchial obstruction. Pulmonary edema rarely occurs, because mustard rarely affects the lung parenchyma and alveoli. Patients with extensive mucosal involvement may suffer fatal respiratory compromise as late as several days after exposure.

### **Gastrointestinal tract**

Mustard damages rapidly proliferating cells of the intestinal mucosa. GI involvement results in abdominal pain, nausea, vomiting, diarrhea, and weight loss.

### **Hematopoietic system**

Mustards cause unpredictable bone marrow suppression, as leukocyte precursors begin dying 3-5 days after exposure. A leukopenic nadir usually occurs in 3-14 days, depending on the severity of exposure. Anemia and thrombocytopenia are late findings. Complete bone marrow aplasia has been reported.

## **Laboratory Tests**

Diagnosis of mustard exposure is clinical. No laboratory tests identify or characterize acute exposure

## **Personal protective equipment**

Liquid mustard contamination poses a dermal contact risk for emergency care personnel. Specialized protective military garments containing a charcoal layer to absorb penetrating sulfur mustard provide protection for up to 6 hours. These protective garments (chemical protective overgarment, battle dress overgarment, mission-oriented protective posture) are not available outside the military. Level A PPE provides the best protection for civilian first responders, and hospital-based emergency care personnel involved in subsequent decontamination should wear level A PPE.

## **Decontamination**

Decontamination within 2 minutes of exposure is the most important intervention for patients with dermal exposure, since mustard rapidly becomes fixed to tissues, and its effects are irreversible. The classic description is an initial lack of signs and symptoms, which does not lessen the urgency to decontaminate patients as soon as possible.

Remove clothing immediately and wash the underlying skin with soap and water. Ocular exposure requires immediate copious irrigation with saline or water. Next, decontaminate the skin with 0.5% hypochlorite solution or with alkaline soap and water, which chemically inactivates sulfur mustard. Because mustard is relatively insoluble in water, water alone has limited value as a decontaminant. Decontamination after the first few minutes of exposure does not prevent subsequent damage but at least protects emergency care personnel from further contact exposure.

## **Supportive care**

Treatment of mustard exposure proceeds according to symptoms. Since the effects of mustards typically are delayed, persons with complaints immediately after exposure may have an additional injury. Patients with signs of upper airway obstruction require endotracheal intubation or the creation of a surgical airway. Also consider endotracheal intubation for persons with severe exposures. Use the largest endotracheal tube that can pass through, since sloughing epithelium may obstruct smaller tubes. Have patients inhale moist air. Mucolytics also are recommended for those with respiratory complaints.

Avoid overhydration, since fluid losses generally are less than with thermal burns. Monitor fluid and electrolyte status and replace losses accordingly. Mustard-induced burns are especially painful, warranting the liberal use of narcotic analgesia. Adequate burn care is essential, since skin lesions heal slowly and are prone to infection. Severe burns may require debridement, irrigation, and topical antibiotics, such as silver sulfadiazine. Address tetanus toxoid immunity.

Severe ocular burns require ophthalmologic consultation. Eye care typically includes daily irrigation, topical antibiotic solutions, topical corticosteroids, and mydriatics. Treat minor corneal injuries similarly to corneal abrasions. Apply petroleum jelly to prevent eyelid margins from sticking together. More severe corneal injuries may take as long as 2-3 months to heal. Permanent visual defects are rare.

## Specific therapy

Although no antidotes currently are available to treat mustard toxicity, several agents are under investigation, including antioxidants (vitamin E), anti-inflammatory drugs (corticosteroids), mustard scavengers (glutathione, *N*-acetylcysteine), and nitric oxide synthase inhibitors (*L*-nitroarginine methyl ester).

Administer granulocyte colony-stimulating factor to patients with bone marrow suppression following mustard exposure.

## Disposition

Patients with significant respiratory tract burns usually require ICU admission and aggressive pulmonary care. Admit patients with significant dermal burns to a burn unit for aggressive wound management, analgesia, and supportive care. Arrange to monitor blood cell counts for 2 weeks following significant exposures. For 12 hours prior to discharge, observe patients who are initially asymptomatic following mustard exposure.

Most patients recover completely. Only a small fraction have chronic ocular or pulmonary damage. Approximately 2% of those exposed to sulfur mustard in World War I died, mostly due to burns, respiratory tract damage, and bone

## Lesson 4. POISONING

The 3 most common alcohol poisonings result from ethanol, methanol, and isopropanol (isopropyl alcohol). The devastating and potentially life-threatening toxicity that results from ingestions of any of these alcohols makes recognition of alcohol poisoning an essential part of emergency medicine.

**History:** Humans have a long history of ingesting alcohols. Ethanol is the most common deliberate ingestion of this toxic substance. It is a component of a wide variety of beverages that are consumed nearly worldwide.

- Ethanol
  - Alcoholic beverages are the primary source of ingested ethanol. Other sources include colognes, perfumes, mouthwashes, medications, and aftershave lotions.
  - Ethanol may be ingested accidentally, as often occurs in children, or deliberately, as by the patient with alcoholism or for recreation.
  - Ethanol may be associated with other causes of altered mental status (eg, hypoglycemia, head trauma, mixed ingestions, post-ictal state, carbon dioxide narcosis, hypoxia, infection, hepatic encephalopathy). Consider these conditions when evaluating the patient with known alcohol ingestion.
- Methanol
  - Methanol ingestion may result in serious consequences, including blindness and death. A delay in treatment may lead to increased morbidity and mortality. Recognition and timely treatment are essential for a full recovery.

- Methanol commonly is found in numerous compounds, including solvents, photocopy inks and diluents, paints, varnishes, antifreeze, gasoline mixtures (eg, gasohol, "dry gas"), canned heat (eg, Sterno), and even wines (as a byproduct of the natural fermentation process). One study of 11 patients seen between 1995 and 1997 identified 8 patients who had ingested windshield wiper fluid, one who drank gasoline antifreeze, and 2 patients with the source unknown.
  - Toxicity most commonly ensues following accidental or intentional ingestion. Toxicity also may occur following inhalational exposure. Inhalation may be accidental (eg, industrial settings), or it may be deliberate (eg, volatile inhalant abuse, as in "bagging" or "huffing" solvents for their inebriant effects). Transdermal or respiratory tract absorption also may cause toxicity.
  - Following ingestion, methanol is rapidly absorbed from the GI tract. Peak levels occur within 30-90 minutes of ingestion.
  - Methanol is predominantly metabolized in the liver by hepatic alcohol dehydrogenase. At low serum concentrations (<20 mg/dL) and during hemodialysis, methanol elimination is quick and first-order, with an elimination half-life of about 3 hours. At higher serum concentrations, methanol elimination is slow and zero-order, at 8.5 mg/dL/h. Thus, following large doses, methanol is metabolized and eliminated very slowly. Duration of the latent period (time from ingestion until clinical toxicity is evident) is highly variable. Latent periods of 40 minutes to 72 hours have been reported; in most cases, onset of toxicity manifests in 12-24 hours. Co-ingestion of ethanol increases both the latent period (40-50 h) and elimination half-life.
  - Approximately 50% of patients report visual disturbances. These disturbances usually are described as blurry, indistinct, misty, or snowstormlike. Patients also have reported yellow spots, central scotomata, and photophobia.
  - CNS complaints include headache and vertigo. GI complaints may include nausea, vomiting, and abdominal pain due to direct irritation.
  - Complaints do not correlate with the amount or severity of the ingestion.
- Isopropanol
- Isopropanol is the second most commonly ingested alcohol. The most common source is rubbing alcohol (70% isopropyl alcohol). Other sources of isopropanol include window cleaners, antifreeze, detergents, jewelry cleaners, solvents, and disinfectants.
  - Ingestions typically occur in alcoholic patients, children, and those who attempt suicide. In children, exposure also may occur from inhalation or topical absorption (eg, sponge bath).
  - CNS complaints include headache, dizziness, poor coordination, and confusion. GI complaints include abdominal pain, nausea, vomiting, and gastritis with hematemesis.
  - Patients appear intoxicated but do not smell like ethanol; however, they may have the fruity odor of acetone.

- Obtaining a history of the substance and quantity ingested is important. The physician may need to acquire the history from emergency medical services (EMS), parents, relatives, or friends accompanying the patient. Consider other differential diagnoses for altered mental status, as more than a single cause may be present.

**Physical:** Alcohol ingestions may present in somewhat similar manners. An alteration in mental status is seen with all of the alcohols, given the ingestion of a sufficient quantity of the substance. This alteration may be present to varying degrees depending on the patient.

- Ethanol
  - Clinical presentation depends on BAC and tolerance to ethanol.
  - The patient may have a flushed face or diaphoresis and may be agitated or ebullient and loquacious due to early disinhibition. This condition may progress to ataxia, slurred speech, drowsiness, stupor, or coma. Nystagmus (horizontal) commonly is observed.
- Methanol
  - Ocular physical findings include sluggishly reactive or fixed and dilated pupils. Visual field constriction also may be present. Retinal edema or hyperemia of the optic disc may be seen. Optic atrophy may appear in late stages (permanent blindness). Visual symptomology can occur without visible fundoscopic changes. Visual acuity often is abnormal.
  - CNS signs include lethargy and confusion. Patients also may present in a comatose condition or with seizures. Cases have been reported of putaminal and cortical necrosis observed on MRI of patients surviving methanol ingestion. Neurologic sequelae (eg, parkinsonism, optic atrophy, focal cranial nerve deficits) have been described.
  - Respiratory signs include dyspnea (rare cases) or even Kussmaul respiration, despite acidosis. Cardiac signs (eg, hypotension, bradycardia) are late signs associated with a poor prognosis.
  - The patient may have severe abdominal tenderness.
  - Death usually is due to abrupt cessation of respiration. Until that endpoint, cardiovascular status is generally well maintained.
- Isopropanol
  - Nystagmus or miosis may be observed.
  - The patient usually appears intoxicated but smells of acetone instead of ethanol.
  - Sinus tachycardia may be present, but examination usually reveals no other cardiac dysrhythmias.
  - Isopropanol is a GI irritant that causes abdominal pain, nausea, vomiting, and gastritis with hematemesis.



- Severe ingestions may result in coma, respiratory depression, and hypotension secondary to vasodilatation and negative cardiac inotropy. Loss of deep tendon reflexes (DTRs) also may be observed.
- In rare cases, myoglobinuria, acute tubular necrosis, hepatic dysfunction, and hemolytic anemia may occur.

### Lab Studies:

- Finger stick for blood glucose level
  - With ethanol and methanol toxicity, the patient may be hypoglycemic.
  - With isopropanol toxicity, the patient is not hyperglycemic. This distinction helps differentiate alcohol toxicity from diabetic ketoacidosis (DKA).
- Serum electrolytes, blood urea nitrogen, creatinine, and glucose levels
  - For ethanol and methanol toxicity, look for increased serum osmolal gap accompanied by an increased serum anion gap and hypoglycemia.
  - Isopropanol toxicity also produces an elevated osmolal gap, but generally no abnormal anion gap, although this may be seen as a result of hypotension and lactic acidosis. A spurious increase in serum creatinine as a result of acetone may be seen.
  - Serum formic acid levels are a better indication of toxicity than are methanol levels. Formate concentrations are rarely available and are not accessible in time to guide therapy.
- Serum amylase or lipase level for detecting any associated pancreatitis
- Complete blood count
  - Ethanol: Leukocytosis, anemia, or thrombocytopenia may be present. Such findings are more common in the individual with chronic alcoholism.
  - Methanol: Anemia may be present.
  - Isopropanol: Hemolytic anemia may appear in rare instances.
- Serum osmolality
  - The osmolal gap is calculated by subtracting calculated serum osmolality from the measured serum osmolality (see Procedures for calculation).
  - Ethanol increases osmolal gap by 22 mOsm/L for each 100 mg/dL. Methanol increases the osmolal gap by 32 mOsm/L for every 100 mg/dL. Isopropanol increases the osmolal gap 17 mOsm/L for each 100 mg/dL of isopropanol and by 18 mOsm/L for each 100 mg/dL of blood acetone.
  - While usually helpful in guiding management, the osmolal gap is neither sensitive nor specific for the presence of a toxic alcohol or glycol. The absence of an osmolal gap does not rule out significant toxic alcohol ingestion.
- Arterial blood gas
  - Methanol: A severe anion gap metabolic acidosis is the hallmark. Severity of acidosis is the best predictor of prognosis when clinical status also is considered.

- Isopropanol: The patient is not acidotic.
- Urinalysis
  - Urine may possess an odor of formaldehyde.
  - Ethanol serum concentration: Used for confirmation of ethanol intoxication.
- Ethanol concentration also is important for methanol ingestions, since it predicts prolongation of toxic levels and of the latent period before onset of symptoms.
  - Ethanol effects at various BAC levels for nonhabituated drinkers are as follows:
    - § 20-50 mg/dL – Decreased fine motor function
    - § 50-100 mg/dL – Impaired judgment and coordination
    - § 100-150 mg/dL – Difficulty with walking and balance
    - § 150-250 mg/dL – Lethargy
    - § 300 mg/dL – Coma
    - § 400 mg/dL – Respiratory depression
    - § 500 mg/dL – Potential death
- Methanol concentration: This study confirms ingestion and helps guide treatment. Remember that low serum concentrations (ie, < 20 mg/dL) do not rule out significant toxicity; late presenters may have low methanol concentrations but elevated formic acid levels and severe clinical toxicity (eg, severe metabolic acidosis, blindness, coma). Methanol concentrations at various BAC levels are as follows:
  - 0-20 mg/dL – Usually asymptomatic
  - 20-50 mg/dL – Treatment required
  - 150+ mg/dL – Potentially fatal if untreated
  - Levels more than 20 mg/dL are considered toxic and are the action level (ie, when treatment should be initiated based on level alone.)
- Isopropanol concentration: This laboratory study confirms and quantitates alcohol concentration. Clinical presentation is a better indicator of prognosis.
  - Serum ketones may be increased within 30 minutes of ingestion of isopropanol because of acetone production.
  - Acetone is detected in urine 3 hours after ingestion.

### Procedures:

- Osmolal gap
  - To find the osmolal gap, subtract calculated serum osmolality from the measured serum osmolality.
  - The osmolal gap equals (measured serum osmolality) -  $[2(\text{Na}^+) + (\text{Glucose}/18) + (\text{BUN}/2.8) + (\text{serum ethanol}/4.6)]$ .
  - Serum osmolality is normally 285-300 mOsm/kg. Normal osmolal gap is 10-12 mOsm/kg. Elevation of the gap is due to presence of additional, unmeasured, low-molecular weight molecules that are osmotically active. The differential for an elevated osmolal gap may be recalled using the mnemonic "ME DIE" (Methanol;

Ethylene glycol; Diuretics, such as glycerol, mannitol, and sorbitol; Isopropanol; Ethanol).

- Anion gap
  - The anion gap is an indirect measure of phosphates, sulfates, and organic acids.
  - The anion gap equals  $[\text{Na}^+] - ([\text{HCO}_3^-] + [\text{Cl}^-])$ .
  - Normal anion gap is 12-16 mEq/L.
  - Increases in the anion gap are seen with excessive acid production or with addition of exogenous acids. The differential for an increased anion gap acidosis can be readily recalled using the mnemonic "CAT MUD PILES" (Carbon monoxide, Cyanide, Alcoholic ketoacidosis, Toluene, Methanol, Uremia, Diabetic ketoacidosis, Paraldehyde, Phenformin, Iron, Isoniazid, Lactic acidosis, Ethylene glycol, Salicylates).

**Prehospital Care:** Follow established protocols.

- Obtaining a detailed history of the ingestion or exposure from all available sources is important.
- Inspect bottles of ingested substances to help identify possible alcohols.
- Follow standard protocols for treating patients with airway obstruction, unconsciousness, or altered mental status.

**Emergency Department Care:** Provide airway, breathing, and circulation evaluation and support as necessary. Orogastric lavage with a large-bore (eg, Ewald) tube is not recommended. Standard-size nasogastric (NG) tube insertion, aspiration, and rapid lavage may be beneficial soon after ingestion and may be attempted up to 4 hours following ingestion (ie, food in the stomach may significantly delay alcohol absorption). Activated charcoal does not bind alcohols well but should be administered if a mixed ingestion is suspected. Administer naloxone if opiates are suspected. Administer thiamine (100 mg) and dextrose D50W (25-50 g) IV for the obtunded patient.

- Ethanol
  - Treatment of acute intoxication involves providing supportive measures (eg, fluid monitoring, oxygen, airway protection).
  - Remember that intoxicated patients are at an increased risk for other traumatic and medical pathologies, which must be ruled out or appropriately treated.
- Methanol
  - Supportive measures are indicated for patients with methanol ingestion. Monitor fluids and oxygen, and provide airway protection. Forced diuresis is recommended, since methanol is excreted renally; however, dialysis works better and has less danger of pulmonary edema, cerebral edema, or acute respiratory distress syndrome (ARDS).

- Attempted correction of acidosis using sodium bicarbonate is indicated if pH is less than 7.20; note that patients may require large quantities. An alkalemic pH makes it more likely that formic acid will exist as its anion (formate), which cannot access the CNS and optic nerve as readily.
- Administer folic acid (leucovorin) 50 mg IV every 4 hours for several days to potentiate the folate-dependent metabolism of formic acid to carbon dioxide and water.
- Ethanol infusion is recommended for patients with suspected methanol ingestion and/or levels greater than 20 mg/dL. Consider ethanol infusion in any patient with an unexplained osmolar gap and/or elevated anion-gap metabolic acidosis that is unaccounted for by ethanol, until a definitive diagnosis negating its administration is made.
  - § Ethanol is a competitive inhibitor of alcohol dehydrogenase and, thereby, impairs the metabolism of methanol and ethylene glycol. Ethanol has 10-20 times greater affinity for alcohol dehydrogenase than methanol does. This measure increases the half-life to approximately 40 hours.
  - § Maintain blood ethanol concentrations between 100-150 mg/dL. This level is intoxicating for nonalcoholics; the dosage may need to be increased for chronic drinkers. Ethanol levels must be followed frequently.
  - § Ethanol may be given PO or IV. PO administration requires an alert patient and may have variable rates of absorption and wide fluctuations in blood levels. Administration of ethanol also causes gastritis. IV administration provides more constant blood levels, but it may cause thrombophlebitis. Parenteral alcohol is indicated if the patient has evidence of pancreatitis.
  - § Begin treatment with a loading dose of 0.6-0.8 g/kg IV or PO. Maintenance levels typically range from 0.8-1.4 g/kg/h. For infusion with 10% ethanol in D5W, loading dose is 10 mL/kg, and maintenance is 1.6 mL/kg/h. Administration of an oral loading dose is possible using commercially available beverages. Dosage may be calculated using the following equation: Ethanol in grams = (mL beverage) X 0.8 X (proof/2).
  - § The goal of ethanol administration is to maintain a serum ethanol concentration more than or equal to 100 mg/dL. Maintain this ethanol level until the methanol level is less than 20 mg/dL. Some physicians advocate continuing ethanol infusion until the methanol level reaches zero.
- Dialysis may be needed to remove methanol and its principal toxic metabolite, formate. Dialysis is 40-50 times faster than renal clearance. Hemodialysis is recommended for intractable/severe acidosis (ie, pH <7.20), renal failure, visual symptoms, or methanol serum concentrations more than 50 mg/dL.
- Studies have shown that prognosis is not dependent on the blood concentration of methanol but on the degree of metabolic acidosis present. This observation is logical when considering toxins as the cause of the acidosis; worsening acidosis means more toxic metabolites are present. Prognosis probably correlates closely with the plasma formate concentration on presentation (a test not readily available).

#### · Isopropanol

- Treat hypotension with fluids and pressors, if needed. NG suctioning is ineffective, since minimal resecretion to the stomach occurs.

- Initiate emergent hemodialysis for patients with refractory hypotension or blood levels more than 400 mg/dL.

## CARBON MONOOXYDE

Carbon monoxide (CO) is a colorless, odorless gas produced by incomplete combustion of carbonaceous material. Commonly overlooked or misdiagnosed, CO intoxication often presents a significant challenge, as treatment protocols, especially for hyperbaric oxygen therapy, remain controversial because of a paucity of definitive clinical studies.

CO is formed as a by-product of burning organic compounds. Although most fatalities result from fires, stoves, portable heaters, and automobile exhaust cause approximately one third of deaths. These often are associated with malfunctioning or obstructed exhaust systems and suicide attempts. Cigarette smoke is a significant source of CO. Natural gas contains no CO, but improperly vented gas water heaters, kerosene space heaters, charcoal grills, hibachis, and Sterno stoves all emit CO. Other sources of CO exposure include propane-fueled forklifts, gas-powered concrete saws, inhaling spray paint, indoor tractor pulls, and swimming behind a motorboat.

CO intoxication also occurs by inhalation of methylene chloride vapors, a volatile liquid found in degreasers, solvents, and paint removers. Dermal methylene chloride exposure may not result in significant systemic effects but can cause significant dermal burns. Liver metabolizes as much as one third of inhaled methylene chloride to CO. A significant percentage of methylene chloride is stored in the tissues, and continued release results in elevated CO levels for at least twice as long as with direct CO inhalation.

Children riding in the back of enclosed pickup trucks seem to be at particularly high risk. Industrial workers at pulp mills, steel foundries, and plants producing formaldehyde or coke are at risk for exposure, as are personnel at fire scenes and individuals working indoors with combustion engines or combustible gases.

**Pathophysiology:** CO toxicity causes impaired oxygen delivery and utilization at the cellular level. CO affects several different sites within the body but has its most profound impact on the organs (eg, brain, heart) with the highest oxygen requirement.

Toxicity primarily results from cellular hypoxia caused by impedance of oxygen delivery. CO reversibly binds hemoglobin, resulting in relative anemia. Because it binds hemoglobin 230-270 times more avidly than oxygen, even small concentrations can result in significant levels of carboxyhemoglobin (HbCO).

An ambient CO level of 100 ppm produces an HbCO of 16% at equilibration, which is enough to produce clinical symptoms. Binding of CO to hemoglobin causes an increased binding of oxygen molecules at the 3 other oxygen-binding sites, resulting in a leftward shift in the oxyhemoglobin dissociation curve and decreasing the availability of oxygen to the already hypoxic tissues.

CO binds to cardiac myoglobin with an even greater affinity than to hemoglobin; the resulting myocardial depression and hypotension exacerbates the tissue hypoxia. Decrease in oxygen delivery is insufficient, however, to explain the extent of the toxicity. Clinical status often does not correlate well with HbCO level, leading some to postulate an additional impairment of cellular respiration.

CO binds to cytochromes *c* and P450 but with a much lower affinity than that of oxygen; very low levels of in vitro binding result. Additionally, the patient groups exhibiting neuropsychiatric deficits often are not acutely acidotic.

Studies have indicated that CO may cause brain lipid peroxidation and leukocyte-mediated inflammatory changes in the brain, a process that may be inhibited by hyperbaric oxygen therapy. Following severe intoxication, patients display central nervous system (CNS) pathology, including white matter demyelination. This leads to edema and focal areas of necrosis, typically of the bilateral globus pallidus. Interestingly, the pallidus lesions, as well as the other lesions, are watershed area tissues with relatively low oxygen demand, suggesting elements of hypoperfusion and hypoxia.

Recent studies have demonstrated release of nitric oxide free radical (implicated in the pathophysiology of atherosclerosis) from platelet and vascular endothelium, following exposure to CO concentrations of 100 ppm.

HbCO levels often do not reflect the clinical picture, yet symptoms typically begin with headaches at levels around 10%. Levels of 50-70% may result in seizure, coma, and fatality.

CO is eliminated through the lungs. Half-life of CO at room air temperature is 3-4 hours. One hundred percent oxygen reduces the half-life to 30-90 minutes; hyperbaric oxygen at 2.5 atm with 100% oxygen reduces it to 15-23 minutes.

**History:** Misdiagnosis commonly occurs because of the vagueness and broad spectrum of complaints; symptoms often are attributed to a viral illness. Specifically inquiring about possible exposures when considering the diagnosis is important. Any of the following should alert suspicion in the winter months, especially in relation to the previously named sources and when more than one patient in a group or household presents with similar complaints. Symptoms may not correlate well with HbCO levels.

- Acute poisoning
  - Malaise, flulike symptoms, fatigue
  - Dyspnea on exertion
  - Chest pain, palpitations
  - Lethargy
  - Confusion
  - Depression
  - Impulsiveness
  - Distractibility
  - Hallucination, confabulation
  - Agitation
  - Nausea, vomiting, diarrhea
  - Abdominal pain

- Headache, drowsiness
- Dizziness, weakness, confusion
- Visual disturbance, syncope, seizure
- Fecal and urinary incontinence
- Memory and gait disturbances
- Bizarre neurologic symptoms, coma
- Chronic exposures also present with the above symptoms; however, they may present with loss of dentation, gradual-onset neuropsychiatric symptoms, or, simply, recent impairment of cognitive ability.

**Physical:** Physical examination is of limited value. Inhalation injury or burns should always alert the clinician to the possibility of CO exposure.

- Vital signs
  - Tachycardia
  - Hypertension or hypotension
  - Hyperthermia
  - Marked tachypnea (rare; severe intoxication often associated with mild or no tachypnea)
- Skin: Classic cherry red skin is rare (ie, "When you're cherry red, you're dead"); pallor is present more often.
- Ophthalmologic
  - Flame-shaped retinal hemorrhages
  - Bright red retinal veins (a sensitive early sign)
  - Papilledema
  - Homonymous hemianopsia
- Noncardiogenic pulmonary edema
- Neurologic and/or neuropsychiatric
  - Patients display memory disturbance (most common), including retrograde and anterograde amnesia with amnestic confabulatory states.

- Patients may experience emotional lability, impaired judgment, and decreased cognitive ability.
- Other signs include stupor, coma, gait disturbance, movement disorders, and rigidity.
- Patients display brisk reflexes, apraxia, agnosia, tic disorders, hearing and vestibular dysfunction, blindness, and psychosis.
- Long-term exposures or severe acute exposures frequently result in long-term neuropsychiatric sequelae. Additionally, some individuals develop delayed neuropsychiatric symptoms, often after severe intoxications associated with coma.
- After recovery from the initial incident, patients present several days to weeks later with neuropsychiatric symptoms such as those just described. Two thirds of patients eventually recover completely.
- MRI changes may remain long after clinical recovery. Predicting and preventing long-term complications and delayed encephalopathy have been the object of recent studies, many of which focus on the role of hyperbaric oxygen therapy.

### **Causes:**

- Most unintentional fatalities occur in stationary vehicles from preventable causes such as malfunctioning exhaust systems, inadequately ventilated passenger compartments, operation in an enclosed space, and utilization of auxiliary fuel-burning heaters inside a car or camper.
- Most unintentional automobile-related CO deaths in garages have occurred despite open garage doors or windows, demonstrating the inadequacy of passive ventilation in such situations.
- Colorado state data revealed that sources of 1149 poisonings were residential furnaces (40%), automobile exhaust (24%), and fires (12%).
- Furnaces were determined to be the source in 46% of nonfatal CO poisonings but in only 10% of fatal poisonings. This suggests that the role of home heating appliances is prominent in the large group of underreported nonfatal exposures.
- Most developing countries utilize unvented cookstoves, burning wood, charcoal, animal dung, or agricultural waste. Studies have shown a concurrent rise in HbCO with these types of exposure in developing countries.

### **Lab Studies:**

- HbCO analysis requires direct spectrophotometric measurement in specific blood gas analyzers. CO can be measured with a handheld analyzer, although less accurately.
  - Elevated levels are significant; however, low levels do not rule out exposure, especially if the patient already has received 100% oxygen or if significant time has elapsed since exposure.



- Individuals who chronically smoke may have mildly elevated CO levels as high as 10%. Presence of fetal hemoglobin, as high as 30% at 3 months, may be read as an elevation of HbCO level to 7%.
- Arterial blood gas
  - PaO<sub>2</sub> levels should remain normal. Oxygen saturation is accurate only if directly measured but not if calculated from PaO<sub>2</sub>, which is common in many blood gas analyzers.
  - As with pulse oximetry, estimate PCO<sub>2</sub> levels by subtracting the carboxyhemoglobin (HbCO) level from the calculated saturation. PCO<sub>2</sub> level may be normal or slightly decreased. Metabolic acidosis occurs secondary to lactic acidosis from ischemia.
- Troponin, creatinine kinase-MB fraction, myoglobin
  - Myocardial ischemia frequently is associated with CO exposure.
  - Patients with preexisting disease can experience increased exertional angina with HbCO levels of just 5-10%. At high HbCO levels, even young healthy patients develop myocardial depression.
- Creatinine kinase, urine myoglobin: Nontraumatic rhabdomyolysis can result from severe CO toxicity and can lead to acute renal failure.
- Complete blood count
  - Look for mild leukocytosis.
  - Disseminated intravascular coagulation (DIC) and thrombotic thrombocytopenic purpura (TTP) require further hematologic studies.
- Electrolytes and glucose level - Lactic acidosis, hypokalemia, and hyperglycemia with severe intoxication
- BUN and creatinine levels - Acute renal failure secondary to myoglobinuria
- Liver function tests - Mild elevation in fulminant hepatic failure
- Urinalysis - Positive for albumin and glucose in chronic intoxication
- Methemoglobin level - Included in the differential diagnosis of cyanosis with low oxygen saturation but normal PaO<sub>2</sub>
- Toxicology screen - For instances of suicide attempt
- Ethanol level - A confounding factor of intentional and unintentional poisonings
- Cyanide level - If cyanide toxicity also is suspected (eg, industrial fire); cyanide exposure suggested by an unexplained metabolic acidosis; rapid determinations rarely are available. Smoke inhalation is the most common cause of acute cyanide poisoning.

### **Imaging Studies:**

- Chest radiography
  - Obtain a chest radiograph with significant intoxications, pulmonary symptoms, or if hyperbaric oxygen is to be used.
  - Findings usually are normal.
  - Changes such as ground-glass appearance, perihilar haze, peribronchial cuffing, and intra-alveolar edema imply a worse prognosis than normal findings.
- CT scan
  - Obtain a CT scan of the head with severe intoxication or change in mental status that does not resolve rapidly.
  - Assess cerebral edema and focal lesions; most are typically low-density lesions of the basal ganglia.
  - Positive CT scan findings generally predict neurologic complications.
  - In one study, 53% of patients hospitalized for acute CO intoxication had abnormal CT scan findings; all of these patients had neurologic sequelae. Of those patients with negative scan results, only 11% had neurologic sequelae.
  - MRI is more accurate than CT scans for focal lesions and white matter demyelination and is often used for follow-up care.
  - Serial CT scans may be necessary, especially with mental status deterioration.
  - A recent report describes the evolution of acute hydrocephalus in a child poisoned with CO, documented by serial CT scans.

### **Other Tests:**

- Electrocardiogram
  - Sinus tachycardia is the most common abnormality.
  - Arrhythmias may be secondary to hypoxia, ischemia, or infarction.
  - Even low HbCO levels can have severe impact on patients with cardiovascular disease.
- Neuropsychologic testing
  - Formal neuropsychologic testing of concentration, fine motor function, and problem solving consistently reveal subtle deficits in even mildly poisoned patients.
  - Abridged versions of these tests, more applicable to the emergency department (ED) setting, have been developed as possible means to assess the risk of delayed

neurologic sequelae, to assess the need for hyperbaric oxygen therapy, and to determine the success of hyperbaric therapy in preventing delayed sequelae.

- These tests are used in some institutions, but studies prospectively confirming the conclusions are lacking.
- Abridged tests can be performed in about 30 minutes by a well-trained examiner.
- Recent research indicates a specific link to deficits in context-aided memory; such specific testing has been proposed as a tool for measuring the severity of neurologic involvement in the ED.

### **Prehospital Care:**

- Promptly remove from continued exposure and immediately institute oxygen therapy with a nonrebreather mask.
- Perform intubation for the comatose patient or, if necessary, for airway protection.
- Institute cardiac monitoring. Pulse oximetry, although not useful in detecting HbCO, is still important because a low saturation causes an even greater apprehension in this setting.
- Give notification for comatose or unstable patients because rapid or direct transfer to a hyperbaric center may be indicated.
- If possible, obtain ambient CO measurements from fire department or utility company personnel, when present.
- Early blood samples may provide much more accurate correlation between HbCO and clinical status; however, do not delay oxygen administration to acquire them.
- Obtain an estimate of exposure time, if possible.
- Avoid exertion to limit tissue oxygen demand.

### **Emergency Department Care:**

- Cardiac monitor: Sudden death has occurred in patients with severe arteriosclerotic disease at HbCO levels of only 20%.
- Pulse oximetry: HbCO absorbs light almost identically to that of oxyhemoglobin. Although a linear drop in oxyhemoglobin occurs as HbCO level rises, pulse oximetry will not reflect it. Pulse oximetry gap, the difference between the saturation as measured by pulse oximetry and one measured directly, is equal to the HbCO level.
- Continue 100% oxygen therapy until the patient is asymptomatic and HbCO levels are below 10%. In patients with cardiovascular or pulmonary compromise, lower thresholds of 2% have been suggested.
- Calculate a gross estimate of the necessary duration of therapy using the initial level and half-life of 30-90 minutes at 100% oxygen. Complicated issues of treatment of fetomaternal poisoning are discussed in Special Concerns.

- In uncomplicated intoxications, venous HbCO levels and oxygen therapy are likely sufficient. Evaluate patients with significant cardiovascular disease and initial HbCO levels above 15% for myocardial ischemia and infarction.
- Consider immediate transfer of patients with levels above 40% or cardiovascular or neurologic impairment to a hyperbaric facility, if feasible. Persistent impairment after 4 hours of normobaric oxygen therapy necessitates transfer to a hyperbaric center.
- Serial neurologic examinations, including funduscopy, CT scans, and, possibly, MRI, are important in detecting the development of cerebral edema. Cerebral edema requires intracranial pressure (ICP) and invasive blood pressure monitoring to further guide therapy. Head elevation, mannitol, and moderate hyperventilation to 28-30 mm Hg PCO<sub>2</sub> are indicated in the initial absence of ICP monitoring. Glucocorticoids have not been proven efficacious, yet the negative aspects of their use in severe cases are limited.
  - Do not aggressively treat acidosis with a pH above 7.15 because it results in a rightward shift in the oxyhemoglobin dissociation curve, increasing tissue oxygen availability. Acidosis generally improves with oxygen therapy.
  - In patients who fail to improve clinically, consider other toxic inhalants or thermal inhalation injury. Be aware that the nitrites used in cyanide kits cause methemoglobinemia, shifting the dissociation curve leftward and further inhibiting oxygen delivery at the tissue level. Combined intoxications of cyanide and CO may be treated with sodium thiosulfate 12.5 g intravenously to prevent the leftward shift.
  - Admit patients to a monitored setting and evaluate acid-base status if HbCO levels are 30-40% or above 25% with associated symptoms.

### **Consultations:**

- Hyperbaric oxygen therapy
  - Locate the nearest hyperbaric oxygen center by contacting the Divers Alert Network (DAN) at Duke University at (919) 684-2948.
  - Hyperbaric oxygen therapy (HBO) currently rests at the center of controversy surrounding management of CO poisoning. Increased elimination of HbCO clearly occurs. Certain studies proclaim major reductions in delayed neurologic sequelae, cerebral edema, pathologic central nervous system (CNS) changes, and reduced cytochrome oxidase impairment.

## **Mushroom toxicity**

Mushroom toxicity is a worldwide concern. The increased use of mushrooms as components of organic diets, for alternative therapies, and by unsupervised children accounts, in part, for the renewed interest in mycetism. While most mushroom ingestions do not cause a clinically significant toxidrome, the lethal potential of a select few make mushroom toxicity an important subject. The incidence of mushroom poisoning in the US peaks in accordance with regional mushroom growing seasons, and case frequency has increased on the West Coast. Ingestion is the most common route of entry, but intravenous injection of mushroom toxins and inhalation of mushroom spores have been reported.

Mushroom toxidromes may be classified according to toxin and clinical presentation. Mushroom toxins have been divided into the following 7 main categories:

- Amatoxins (cyclopeptides)
- Orellanus (*Cortinarius* species)
- Gyromitrin (monomethylhydrazine)
- Muscarine
- Ibotenic acid
- Psilocybin
- Coprine (disulfiramlike)

Some authors have created an eighth category comprising a vast range of species that only cause gastrointestinal symptoms.

Amanitin phalloides syndrome or *Mycetismus choleriformis* accounts for 90-95% of all fatalities from mushroom poisoning in North America. This discussion follows a clinical format because the offending mushroom is frequently unavailable for identification and poisoning may occur from a single species or a combination of different species. Trestrail's data indicate that the mushroom was available for identification in only 3.4% of exposures.

Query patients presenting to the emergency department with compatible clinical scenarios about mushroom ingestion. Even a small piece of a toxic mushroom may cause death. Cooking, salting, or drying does not inactivate all mushroom toxins, and cooking fumes from certain species can cause poisoning.

**Pathophysiology:** Each mushroom group exerts its toxic effect by a different mechanism, and certain toxins have a predilection for individual organ systems. The amatoxins (cyclic octapeptides), which include amanitin, verotoxin, and phalloides, cause severe hepatocellular damage by inhibiting RNA polymerase II, thereby inhibiting protein synthesis at the cellular level, causing cell death. Other organ systems with high turnover rates (eg, gastrointestinal tract, kidneys) also are affected severely. Ibotenic acid and muscimol bind to glutamic acid and GABA receptors, respectively, and thereby interfere with CNS receptors. Monomethylhydrazine (MMH) from gyromitrin-containing mushrooms affects the GI tract, liver, and kidneys by inhibiting pyridoxine-dependent pathways in the synthesis of GABA. Muscarine affects the autonomic nervous system. It acts through depolarization of muscarinic acetylcholine receptors and exerts a peripheral cholinergic effect through stimulation of the postganglionic parasympathetic receptors. Coprine inhibits aldehyde dehydrogenase, producing a disulfiramlike reaction in those consuming ethyl alcohol. Psilocybin indole exerts its effect on the central nervous system by stimulation of serotonin receptors. Orellanine and orelline, the bipyridyl toxins isolated from *Cortinarius orellanus*, exhibit their nephrotoxic effects by inhibiting alkaline phosphatase of the proximal tubule cells. Genetic factors may contribute to the clinical manifestations of this toxin, which has toxicity that is not reduced by cooking or drying.

### History:

- Try to ascertain the species or varieties of the wild mushrooms ingested, the type of preparation, volume ingested, and symptoms of others sharing the mushroom meal. Comorbidity, concomitant medications, allergies to medications, and drug and alcohol use may influence the clinical picture and should be elicited. Symptoms and signs are discussed relative to onset postingestion, with gastrointestinal dysfunction being a nearly universal component. Early symptoms may be observed with mixed ingestions, and they do not exclude a potentially fatal poisoning.

- A short latency period (30-180 min) may be observed with GI mushroom (eg, *Chlorophyllum molybdites*, *Entoloma lividum*, *Boletus* species, *Paxillus* species) syndromes, muscarine-containing mushrooms (*Inocybe* species, *Clitocybe* species), psilocybin-containing mushrooms (*Paneolus* species, *Psilocybe* species, *Gymnopilus* species), and coprine-containing mushrooms.
  - GI mushroom syndromes present exclusively with abdominal discomfort, cramping, nausea, vomiting, and/or diarrhea. Dehydration is the most common complication. Most symptoms resolve by 24 hours and the prognosis is generally good.
  - Anticholinergic symptoms can occur with ibotenic and muscimol ingestions. Dizziness, incoordination, ataxia, GABAergic effects, seizures, hallucinations, muscle spasms, flushing, and dilated pupils may be observed.
  - Cholinergic effects may result from muscarine ingestion. Perspiration, salivation, lacrimation, blurred vision, miosis, hypotension, bradycardia, and bronchoconstriction have been described. Although muscarine was first isolated from the *Amanita muscaria* mushroom in 1868, the signs and symptoms of poisoning from *A muscaria* are not related to muscarine.
  - Neuropsychiatric symptoms, including hallucinations or delirium, have been associated with mycetism caused by ibotenic acid, muscimol, and psilocybin. Muscle weakness, drowsiness, hallucinations, hyperkinesia, and mydriasis have been described. Patients may have hallucinations while awake and then have a prolonged sleep that lasts hours; in each case, the prognosis is generally good and symptoms resolve within 24 hours with supportive care. Rare residual effects have been reported.
  - Muscarine and coprine intoxications have also been associated with neurovegetative symptoms.
  - The Coprinus syndrome is characterized by a rapid onset of nausea, vomiting, tachycardia, palpitations, paresthesias, diaphoresis, and flushing. Hypotension also can occur. This syndrome has been referred to as a disulfiramlike reaction; it is associated with ethanol use from 30 minutes to 5 days following a mushroom meal, and symptoms generally last 2-4 hours. Interestingly, if alcohol is consumed at the time of the mushroom meal, symptoms may not occur.
  - Intravenous injection of mushroom toxins from *Psilocybe* species has been reported. The clinical course includes vomiting, fever, muscle cramps, and hypoxia.
- A long latency period (>6 h) can be observed with amatoxins, orellanus, and gyromitrin syndromes. This generally signifies a serious ingestion and should be considered potentially life threatening.
  - Amatoxin toxicity presents in the following 3 stages.
    - § Stage one presents with abdominal cramping, nausea, vomiting, and profuse watery diarrhea after a latent period of 6-12 hours.
    - § The second stage begins with clinical recovery of gastrointestinal dysfunction after 24 hours and lasts 2-3 days, during which liver damage is ongoing.
    - § In the third stage, hepatic and renal damage becomes clinically evident.

- Orellanine toxicity initially may present with gastrointestinal dysfunction 24-48 hours postingestion of mushrooms from the genus *Cortinarius*. Acute renal failure may follow from 36 hours to 2 weeks postingestion and present with flank pain, polydipsia, polyuria, oliguria, and malaise.
- Gyromitrin toxicity typically presents 6-10 hours postingestion (but may be delayed up to 48 h) with gastrointestinal dysfunction. Patients may display symptoms and signs of volume depletion, hepatic injury, methemoglobinemia, intravascular hemolysis, and CNS effects (eg, malaise, tremor, myoclonus, delirium, seizures, encephalopathy).

### Lab Studies:

- Consider the following tests for an initial laboratory evaluation of a symptomatic patient in the emergency department:
  - As with all suspected toxic ingestions, blood, urine and gastric contents should be saved.
  - Consider CBC, urinalysis, coagulation studies, glucose, BUN, creatinine, electrolytes, fibrinogen, and arterial blood gas as possible the initial tests.
  - If the patient has evidence of hemolysis, haptoglobin and Coombs tests may be helpful.
- Perform clotting studies and conduct hepatic and renal profiles if phalloides syndrome is suspected.
- In *Gyromitra* species intoxications, a methemoglobin level may be indicated.
- Identify the mushroom whenever possible. This may be done with the help of a regional Poison Control Center, the consulting mycologist, or by referring to the *Poisindex* or a mycology handbook.
- If the mushroom is available, the following information may be helpful for determining the mushroom's identity:
  - Provide the mycologist with all available information, including the size, shape, and color of the mushroom. Be able to describe the surface and the underside of the cap, the stem, gills, veil, ring, spores and the color and texture of the flesh. If the specimen is not available for the mycologist to examine personally, cut the specimen to see if the gills are attached to the stalk. It also is helpful to know the location and conditions in which the mushroom grew (eg, wood, soil).
  - Wrap the mushroom in foil or wax paper and store in a paper bag in a cool dry place, pending transport to your mycologist. Do not store in a plastic bag or container because the moisture may alter the mushroom's features. Do not freeze.
  - Consider making a spore print using a piece of black and white paper. To make a spore print, remove the stem and place the mushroom cap, gill side down, on the paper. Cover with a bowl to prevent disturbance. Wait at least 4 hours and evaluate the print, noting the pattern and color. Fix the print with artist's fixative or hair spray. *Amanita* varieties have white spores. Immature mushrooms may not shed spores.

- The Meixner test (a qualitative bedside assay) is used to detect amatoxins (eg, alpha-amanitin, beta-amanitin) in the mushroom. It is not recommended for use with stomach contents nor to determine edibility of a mushroom because false-positive and false-negative results have been described.
- If the mushroom is unavailable, the following information may be helpful for determining the mushroom's identity:
  - Save emesis or gastric lavage fluid for microscopic examination for spores. If mushroom fragments are available, they can be stored in a 70% solution of ethyl alcohol, methanol, or formaldehyde and placed in the refrigerator. Otherwise, emesis can be centrifuged and the heavier layer on the bottom can be examined under a microscope for the presence of spores.
  - Consider high performance liquid chromatography for quantification of alpha or beta amanitin in urine, plasma, or gastric contents.
  - Consider the amanitin radioimmunosorbent assay kit to detect alpha-amanitin in blood if used within 24 hours postingestion. False-positive results have been reported.

**Prehospital Care:** If it is known that mushroom ingestion has occurred, make every attempt to supply the hospital personnel with any remaining sample of the mushrooms involved. This may involve saving the patient's emesis. Otherwise, care is supportive (eg, intravenous hydration for volume depletion, pharmacologic sedation for agitation).

### **Emergency Department Care:**

- Asymptomatic patients
  - Obtain specimen, if possible, of mushroom or emesis.
  - Contact a regional poison control center.
  - Give 1 g/kg of activated charcoal orally.
  - Encourage fluids and administer a balanced diet.
  - Monitor patients in the emergency department for at least 4 hours. Discharge patients home if they continue to be asymptomatic and can be contacted and reliably monitored at home. Advise patients to contact the hospital immediately if they become symptomatic. If the mushroom is identified as potentially toxic or the patient becomes symptomatic, admission to the hospital is recommended.
- Symptomatic patients
  - The basic elements of supportive care are critical in the evaluation and management of the poisoned patient. Attention to airway maintenance, breathing, and adequacy of circulation should be ongoing.
  - Provide intravenous glucose to obtunded patients as a priority. Dextrostix evaluation can help guide therapy initially.



- Obtain the mushroom specimen, if possible, and facilitate expeditious transport to mycologist.
- Consider gastric lavage followed by activated charcoal administration every 2-6 hours. Airway protection is critical in these patients because of the risk of aspiration.
- Cardiopulmonary monitoring should be continuous.
- Monitor fluid, electrolyte, and glucose status; correct accordingly. Rehydrate with isotonic fluids. Forced diuresis is not recommended.
- If amanitin ingestion is suspected or proven, careful attention to clotting studies and renal and hepatic profiles is important. Early consultation with a medical toxicologist is recommended.
- If symptoms or laboratory parameters become critical, admit the patient to a critical care unit and consider specific treatment options.
- Additional treatment options may be considered under the following circumstances:
  - § For anticholinergic symptoms consistent with ibotenic acid or muscimol, consider physostigmine administration. This option should be used only for life-threatening anticholinergic signs and symptoms. It may cause bradycardia, asystole, or seizures. Atropine and emergency resuscitation equipment should be available immediately at the bedside.
  - § Consider atropine administration for cholinergic effects consistent with muscarine.
  - § Disulfiram effect consistent with coprine may require cardiac dysrhythmic medications (eg, beta-blockers) or fluids and catecholamine infusions (eg, norepinephrine, dopamine) for severe hypotension.
  - § Hallucinations or delirium consistent with muscimol, ibotenic acid, or psilocybin usually responds to reassurance and a quiet environment; however, benzodiazepines may be necessary. Atropine may exacerbate these symptoms.
  - § Amatoxin syndrome merits special attention because it is responsible for the most serious morbidity and mortality in mycetism. Although specific antidotes and controlled clinical trials do not exist, anecdotal and animal studies suggest a potential benefit of high dose penicillin, silibinin (a constituent of the extract silymarin derived from the milk thistle, *Silybum marianum*), cimetidine, aucubin (an iridoid glycoside of *Aucuba japonica*), and kutkin.
  - § Intravenous pyridoxine may be considered for MMH induced coma or seizures refractory to standard treatment.

## Lesson 5. CARDIOLOGY EMERGENCY

### HYPERTENSIVE EMERGENCY

Approximately 10 million people in the Ukraine are affected by hypertension (HTN).

New data show an increased lifetime risk of developing HTN and an increased risk of cardiovascular complications associated with blood pressures (BPs) previously considered to be normal. Given this information, the Joint National Committee (JNC-7) has introduced a new classification system for HTN.<sup>2</sup>

- Prehypertension - Systolic blood pressure (SBP) 120-139 mm Hg or diastolic blood pressure (DBP) 80-89 mm Hg

- Stage I HTN - SBP 140-159 mm Hg or DBP 90-99 mm Hg
- Stage II HTN - SBP >160 mm Hg or DBP >100 mm Hg

**Hypertensive crises encompass a spectrum of clinical presentations where uncontrolled BPs lead to progressive or impending target organ dysfunction (TOD). The clinical distinction between hypertensive emergencies and hypertensive urgencies depends on the presence of acute TOD and not on the absolute level of the BP.**

### **Hypertensive emergency**

Hypertensive emergencies represent severe HTN with acute impairment of an organ system (eg, central nervous system [CNS], cardiovascular, renal). In these conditions, the BP should be lowered aggressively over minutes to hours.

### **Hypertensive urgency**

Hypertensive urgency is defined as a severe elevation of BP, without evidence of progressive TOD. These patients require BP control over several days to weeks.

### **Emergency department considerations**

Optimal control of hypertensive situations balances the benefits of immediate decreases in BP against the risk of a significant decrease in target organ perfusion. The emergency physician must be capable of the following:

- Appropriately evaluating patients with an elevated BP
- Correctly classifying the HTN
- Determining the aggressiveness and timing of therapeutic interventions
- Making disposition decisions

An important point to remember in the management of the patient with any degree of BP elevation is to "treat the patient and not the number."

The most common clinical presentations of hypertensive emergencies are cerebral infarction (24.5%), pulmonary edema (22.5%), hypertensive encephalopathy (16.3%), and congestive heart failure (12.0%). Less common presentations include intracranial hemorrhage, aortic dissection, and eclampsia.

### **Central nervous system**

Cerebral autoregulation is the inherent ability of the cerebral vasculature to maintain a constant cerebral blood flow (CBF) despite changes in blood pressure. As mean arterial pressure (MAP) increases, the cerebral endothelium is disrupted and the blood-brain barrier can become interrupted. Fibrinoid material deposits in the cerebral vasculature and causes narrowing of the vascular lumen. The cerebral vasculature then attempts to vasodilate around the narrowed lumen. This leads to cerebral edema and microhemorrhages. Patients with chronic HTN can tolerate higher MAPs before

they have disruption of their autoregulation system. However, such patients also have increased cerebrovascular resistance and are more prone to cerebral ischemia when flow decreases.

Hypertensive encephalopathy is one of the clinical manifestations of cerebral edema and microhemorrhages seen with dysfunction of cerebral autoregulation. Without treatment, hypertensive encephalopathy can lead to cerebral hemorrhage, coma, and death.

### **Cardiovascular system**

HTN affects the structure and function of the coronary vasculature and left ventricle. HTN also activates the renin-angiotensin-aldosterone system, causing systemic vasculature constriction. This results in increasing myocardial oxygen demand by increasing the left ventricular wall tension and leads to left ventricular hypertrophy and coronary compression. During hypertensive emergencies, the left ventricle cannot overcome systemic vascular resistance. This leads to left ventricular failure and pulmonary edema or myocardial ischemia.

### **Renal system**

Chronic HTN causes pathologic changes to the small arteries of the kidney. The arteries develop endothelial dysfunction and impaired vasodilation, which alter renal autoregulation. When the renal autoregulatory system is disrupted, the intraglomerular pressure starts to vary directly with the systemic arterial pressure, thus offering no protection to the kidney during BP fluctuations. During a hypertensive crisis, this can lead to acute renal ischemia.

## **CLINICAL**

### **History**

The history should focus on the presence of TOD, the circumstances surrounding the HTN, and any identifiable etiology. The history and physical examination determine the nature, severity, and management of the hypertensive event. Details of antihypertensive drug therapy and compliance

Assess whether specific symptoms suggesting TOD are present.

- Chest pain - Myocardial ischemia or infarction
- Back pain - Aortic dissection
- Dyspnea - Pulmonary edema, congestive heart failure
- Neurologic symptoms - Seizures, visual disturbances, altered level of consciousness (hypertensive encephalopathy)

### **Physical**

The physical examination should assess whether TOD is present.

- Vitals
  - - BP should be measured in both the supine position and the standing position (assess volume depletion).

- BP should also be measured in both arms (a significant difference suggests an aortic dissection).
- ENT: The presence of new retinal hemorrhages, exudates, or papilledema suggests a hypertensive emergency.
- Cardiovascular - Evaluate for the presence of heart failure.
  - - Jugular venous distension
    - Crackles
    - Peripheral edema
- Abdomen - Abdominal masses or bruits
- CNS
  - Level of consciousness
  - Visual fields
  - Focal neurologic signs

## Causes

The most common hypertensive emergency is a rapid unexplained rise in BP in a patient with chronic essential HTN. Most patients who develop hypertensive emergencies have a history of inadequate hypertensive treatment or an abrupt discontinuation of their medications.

## Lab Studies

- Electrolytes, BUN, and creatinine levels to evaluate for renal impairment
- CBC and smear to exclude microangiopathic anemia
- Urinalysis
- ECG

## Imaging Studies

- Chest radiography is indicated in patients with chest pain or shortness of breath.
  - - Cardiac enlargement
    - Pulmonary edema
    - Widened mediastinum
- Head CT and/or brain MRI are indicated in patients with abnormal neurologic examinations or clinical concern for the following.
  - - Intracranial bleeding
    - Cerebral edema
    - Cerebral infarction
- Chest CT scan, transesophageal echocardiography, or aortic angiography is indicated in cases where aortic dissection is suspected.

## Prehospital Care

- Address the manifestations of a hypertensive emergency, such as chest pain or heart failure. Reduction of BP may not be indicated in the prehospital setting.
- Under most circumstances, attempting to treat HTN directly in the prehospital setting is unwise. In particular, rapid lowering of BP can critically decrease target organ perfusion.

## Emergency Department Care

The fundamental principle in determining the necessary ED care of the hypertensive patient is the presence or absence of TOD.

- Initial considerations (if the patient is not in distress)
  - 
  - Place the patient who is not in distress in a quiet room and reevaluate after an initial interview. In one study, 27% of patients with an initial DBP higher than 130 mm Hg had their DBP fall below critical levels after relaxation without specific treatment.
  - Consider the context of the elevated BP (eg, severe pain often causes increase in BP).
- Screen for TOD: The patient's history, physical examination, laboratory studies, and diagnostic tests, as outlined in Workup, should be used to determine if TOD exists.
- Patients without evidence of TOD may be discharged with follow-up.
- The misconception remains that a patient never should be discharged from the ED with an elevated BP. As a result of this belief, patients are given oral medicines, such as nifedipine, in an effort to lower BP rapidly before discharge. This is not indicated and may be dangerous.
- Attempts to temporarily lower BP by using these medicines may result in a precipitous and difficult-to-correct drop in BP. Should this occur, target organ hypoperfusion may result. Furthermore, patients who present with high BP may have had this elevation for some time and may need chronic BP control but may not tolerate rapid return of BP to a "normal" level.
- Acute lowering of BP in the narrow window of the ED visit does not improve long-term morbidity and mortality rates. The follow-up recommended for these situations by the Joint National Committee on High Blood Pressure is outlined in Follow-up.
- Patients with TOD usually require admission and rapid lowering of BP using intravenous medications. Suggested medication depends on the affected organ system.
- Even in cases of hypertensive emergencies, the BP should not be lowered to normal levels.
- Rapid reduction in BP below the cerebral, renal, and/or coronary autoregulatory range results in marked reduction in organ blood flow, possibly leading to ischemia and infarction.
- In general, the MAP should be lowered by no more than 20% in the first hour of treatment. If the patient remains stable, the BP should then be lowered to 160/100-110 mm Hg in the next 2-6 hours. Please note the exceptions to this general rule listed below.
- These BP goals are best achieved by a continuous infusion of a short-acting, titratable, parenteral antihypertensive agent along with constant, intensive patient monitoring.
- Rapid BP reduction is indicated in the following circumstances:
- Acute myocardial ischemia
  - Intravenous nitroglycerin
  - Intravenous beta-blockers
- CHF with pulmonary edema
  - Intravenous nitroglycerin
  - Intravenous furosemide (Lasix)
  - Intravenous nitroprusside
  - Intravenous angiotensin-converting enzyme inhibitors
- Acute aortic dissection: In cases of acute aortic dissection, the SBP should be decreased as rapidly as possible to a goal of 100-110 mm Hg or lower.
  - Intravenous labetalol
  - Alternative – Intravenous nitroprusside with intravenous beta-blocker (eg, esmolol)

- Cerebral vascular accident: Evidence exists that patients who have acute strokes have better outcomes with higher BPs. Antihypertensive therapy is not routinely recommended for patients with acute stroke and HTN.
  - BP control affects the use of thrombolytic agents in ischemic stroke. SBP higher than 185 mm Hg or diastolic pressures higher than 110 mm Hg are contraindications to the use of tissue plasminogen activator (tPA) within the first 3 hours of an ischemic stroke.
  - The current recommendation by the American Stroke Association states that a patient with a recent ischemic stroke and a SBP higher than 220 mm Hg or a DBP higher than 120-140 mm Hg can undergo cautious reduction of BP by about 10-15% (with IV nitroprusside or IV labetalol), if the patient is carefully monitored for neurologic deterioration related to the lower pressure.
- Intracranial hemorrhage (ICH): No evidence exists to suggest that HTN provokes further bleeding in patients with ICH.
  - A precipitous fall in SBP may compromise cerebral perfusion and increase mortality. Do not exceed a 20% reduction in BP.
  - The controlled lowering of BP with intravenous nitroprusside or intravenous labetalol (in the absence of bradycardia) is currently recommended only when the SBP is higher than 200 mm Hg or the DBP is higher than 110.
- Monoamine oxidase (MAO)-tyramine interactions with acute hypertension - Intravenous phentolamine
- Pheochromocytoma
  - Intravenous phentolamine
  - Intravenous labetalol
- Hypertensive encephalopathy: Do not exceed a 20% reduction in BP.
  - Intravenous nitroprusside
  - Intravenous labetalol
  - Intravenous fenoldopam
- Acute renal failure
  - Intravenous fenoldopam
  - Intravenous nicardipine
  - Intravenous beta-blockers
- Eclampsia
  - Intravenous hydralazine
  - Intravenous labetalol
  - Intravenous magnesium
- Sympathomimetic intoxication: Avoid unopposed beta-blockade.
  - Benzodiazepine
  - Intravenous labetalol
  - Intravenous nitroglycerin
- Acutely lowering of BP in the ED for clinical situations other than those listed here is controversial and generally should be avoided.

## Consultations

- Consultations may be indicated for comorbid conditions and their definitive treatment.
- Because HTN is usually a chronic problem, access to a primary care physician and long-term follow-up are essential for all patients.

## ACUTE CORONARY SYNDROME

The initial diagnosis of acute coronary syndrome (ACS) is based on history, risk factors, and, to a lesser extent, ECG findings. The symptoms are due to myocardial ischemia, the underlying cause of which is an imbalance between supply and demand of myocardial oxygen.

Patients with ACS include those whose clinical presentations cover the following range of diagnoses: unstable angina, non–ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI). This ACS spectrum concept is a useful framework for developing therapeutic strategies.

### History

- Typically, angina is a symptom of myocardial ischemia that appears in circumstances of increased oxygen demand. It is usually described as a sensation of chest pressure or heaviness, which is reproduced by activities or conditions that increase myocardial oxygen demand.
- Not all patients experience chest pain. Some present with only neck, jaw, ear, arm, or epigastric discomfort.
- Other symptoms, such as shortness of breath or severe weakness, may represent anginal equivalents.
- A patient may present to the ED because of a change in pattern or severity of symptoms. A new case of angina is more difficult to diagnose because symptoms are often vague and similar to those caused by other conditions (eg, indigestion, anxiety).
- Patients may have no pain and may only complain of episodic shortness of breath, weakness, lightheadedness, diaphoresis, or nausea and vomiting.
- Patients may complain of the following:
  - 
  - Palpitations
  - Pain, which is usually described as pressure, squeezing, or a burning sensation across the precordium and may radiate to the neck, shoulder, jaw, back, upper abdomen, or either arm
  - Exertional dyspnea that resolves with pain or rest
  - Diaphoresis from sympathetic discharge
  - Nausea from vagal stimulation
  - Decreased exercise tolerance
  - Patients with diabetes and elderly patients are more likely to have atypical presentations and offer only vague complaints, such as weakness, dyspnea, lightheadedness, and nausea.
- Stable angina
  - Involves episodic pain lasting 5-15 minutes
  - Provoked by exertion
  - Relieved by rest or nitroglycerin
- Unstable angina: Patients have increased risk for adverse cardiac events, such as MI or death. Three clinically distinct forms exist, as follows:
  - New-onset exertional angina
  - Angina of increasing frequency or duration or refractory to nitroglycerin

- Angina at rest
- Variant angina (Prinzmetal angina)
  - Occurs primarily at rest
  - Triggered by smoking
  - Thought to be due to coronary vasospasm
- Elderly persons and those with diabetes may have particularly subtle presentations and may complain of fatigue, syncope, or weakness. Elderly persons may also present with only altered mental status. Those with preexisting altered mental status or dementia may have no recollection of recent symptoms and may have no complaints whatsoever.
- As many as half of cases of ACS are clinically silent in that they do not cause the classic symptoms described above and consequently go unrecognized by the patient. Maintain a high index of suspicion for ACS especially when evaluating women, patients with diabetes, older patients, patients with dementia, and those with a history of heart failure.

## Physical

- Physical examination results are frequently normal. If chest pain is ongoing, the patient will usually lie quietly in bed and may appear anxious, diaphoretic, and pale.
- Hypertension may precipitate angina or reflect elevated catecholamine levels due to either anxiety or exogenous sympathomimetic stimulation.
- Hypotension indicates ventricular dysfunction due to myocardial ischemia, infarction, or acute valvular dysfunction.
- Congestive heart failure (CHF)
- Jugular venous distention
  - Third heart sound ( $S_3$ ) may be present.
  - A new murmur may reflect papillary muscle dysfunction.
  - Rales on pulmonary examination may suggest left ventricular (LV) dysfunction or mitral regurgitation.
  - Presence of a fourth heart sound ( $S_4$ ) is a common finding in patients with poor ventricular compliance due to preexisting ischemic heart disease or hypertension.

## Causes

- Atherosclerotic plaque is the predominant cause. Coronary artery vasospasm is less common.
- Alternative causes of angina include the following:
  - Ventricular hypertrophy due to hypertension, valvular disease, or cardiomyopathy
  - Embolic occlusion of the coronary arteries
  - Hypoxia, as in carbon monoxide poisoning or acute pulmonary disorders
  - Cocaine and amphetamines, which increase myocardial oxygen demand and may cause coronary vasospasm
  - Underlying coronary artery disease, which may be unmasked by severe anemia
  - Inflammation of epicardial arteries
  - Coronary artery dissection
- Risk factors for ACS should be documented and include the following:
  - Male gender
  - Diabetes mellitus (DM)
  - Smoking history
  - Hypertension
  - Increased age
  - Hypercholesterolemia



- Hyperlipidemia
- Prior cerebrovascular accident (CVA) - These patients constitute 7.5% of patients with ACS and have high-risk features.
- Inherited metabolic disorders
- Methamphetamine use
- Occupational stress
- Connective tissue disease

## Lab Studies

- Troponin I is considered the preferred biomarker for diagnosing myocardial necrosis. Troponins have the greatest sensitivity and specificity in detecting MI, and elevated serum levels are considered diagnostic of MI. They also have prognostic value.
  - For early detection of myocardial necrosis, sensitivity of troponin is superior to that of the creatine kinase-MB (CK-MB). Troponin I is detectable in serum 3-6 hours after an MI, and its level remains elevated for 14 days.
  - Troponin is a contractile protein that normally is not found in serum. It is released only when myocardial necrosis occurs.
  - Troponin should be used as the optimum biomarkers for the evaluation of patients with ACS who have coexistent skeletal muscle injury.
- Troponin T has similar release kinetics to troponin I, and levels remains elevated for 14 days. False-positive results may occur in patients with renal failure. Minor elevations in troponin T level also identify patients at risk for subsequent cardiac events.
- Elevated troponin levels may also point to minor myocardial injury due to other causes. Zellweger et al described 4 patients with elevated troponin levels after supraventricular tachycardia without evidence of coronary artery disease and very low risk scores for ACS.<sup>1</sup> Similarly, Koller found that endurance athletes may show elevated serum troponin levels in the absence of ACS.<sup>2</sup>
- CK-MB levels begin to rise within 4 hours after MI, peak at 18-24 hours, and subside over 3-4 days. A level within the reference range does not exclude myocardial necrosis.
  - The upper limit of normal for CK-MB is 3-6% of total CK. A normal level in the ED does not exclude the possibility of MI. A single assay in the ED has a 34% sensitivity for MI. Serial sampling over periods of 6-9 hours increases sensitivity to approximately 90%. Serial CK-MB over 24 hours detects myocardial necrosis with a sensitivity near 100% and a specificity of 98%.
  - Occasionally, a very small infarct is missed by CK-MB; therefore, troponin levels should be measured for patients suspected to have MI who have negative results from serial CK-MB tests.
  - One study looked at using the 2-hour delta (increase or decrease) of cardiac markers as 1 of 6 criteria in making the diagnosis of ACS and MI. According to one of the Erlanger criteria, an increase in the CK-MB level of 1.5 ng/mL or greater or an increase of the cardiac troponin I level of 0.2 ng/mL or greater over 2 hours in itself would allow one to make the provisional diagnosis of ACS with a high degree of sensitivity and specificity, even if the total levels were within the normal range. Patients with recent MI were also identified by a decreasing curve of CK-MB. Using this 2-hour delta of cardiac markers greatly reduces the number of cases of MI and ACS that are overlooked in patients who are then inappropriately discharged home.
- Myoglobin, a low-molecular-weight heme protein found in cardiac and skeletal muscle, is released more rapidly from infarcted myocardium than troponin and CK-MB and may be detected as early as 2 hours after MI. Myoglobin levels, although highly sensitive, are not

cardiac specific. They may be useful for early detection of MI when performed with other studies.

- Cardiac markers should be used liberally to evaluate patients with prolonged episodes of ischemic pain, with new changes on ECG, or with nondiagnostic or normal ECGs in whom the diagnosis of ACS or MI is being considered.
- Complete blood count is indicated to determine if anemia is a precipitant. Transfusion with packed red blood cells may be indicated.
- A chemistry profile is indicated. Obtain a basic metabolic profile, including a check of blood glucose level, renal function, and electrolytes levels, for patients with new-onset angina. Potassium and magnesium levels should be monitored and corrected. Creatinine levels must be considered before using an angiotensin-converting enzyme (ACE) inhibitor.
- Other biochemical markers
  - C-reactive protein (CRP) is a marker of acute inflammation. Patients without biochemical evidence of myocardial necrosis but elevated CRP level are at increased risk of an adverse event.
  - Interleukin 6 is the major determinant of acute-phase reactant proteins in the liver, and serum amyloid A is another acute-phase reactant. Elevations of either of these can be predictive in determining increased risk of adverse outcomes in patients with unstable angina.
- In one study, patients presenting to the ED with suspected myocardial ischemia showing higher levels of inflammatory cytokines were associated with an increased risk of a serious cardiac event during the subsequent 3 months. However, the cytokines have limited ability to predict a serious adverse cardiac event.
- Erythrocyte sedimentation rate rises above reference range values within 3 days and may remain elevated for weeks.
- Serum lactate dehydrogenase level rises above the reference range within 24 hours of MI, reaches a peak within 3-6 days, and returns to the baseline within 8-12 days.

## Imaging Studies

- Chest radiograph may demonstrate complications of ischemia, such as pulmonary edema, or it may provide clues to alternative causes of symptoms, such as thoracic aneurysm or pneumonia.
- Echocardiogram often demonstrates wall motion abnormalities due to ischemia. It is of limited value in patients whose symptoms have resolved or in those with preexisting wall motion abnormalities. However, echocardiogram may be useful in identifying precipitants for ischemia, such as ventricular hypertrophy and valvular disease.
- Radionuclide myocardial perfusion imaging has been shown to have favorable diagnostic and prognostic value in this setting, with an excellent early sensitivity to detect acute myocardial infarction (MI) not achieved by other testing modalities.
  - A normal resting perfusion imaging study has been shown to have a negative predictive value of more than 99% in excluding MI. Observational and randomized trials of both rest and stress imaging in the ED evaluation of patients with chest pain have demonstrated reductions in unnecessary hospitalizations and cost savings compared with routine care.
  - Perfusion imaging has also been used in risk stratification after MI and for measurement of infarct size to evaluate reperfusion therapies. Novel "hot spot" imaging radiopharmaceuticals that visualize infarction or ischemia are currently undergoing evaluation and hold promise for future imaging of ACS. (See Myocardial Ischemia - Nuclear Medicine and Risk Stratification.)
- Recent advances include dual-source 64-slice CT scanners that can do a full scan in 10 seconds and produce high-resolution images that allow fine details of the patient's coronary

arteries to be seen. This technology allows for noninvasive and early diagnosis of coronary artery disease and thus earlier treatment before the coronary arteries become more or completely occluded. It allows direct visualization of not only the lumen of the coronary arteries but also plaque within the artery. Dual-source 64-slice CT scanning is being used with intravenous contrast to determine if a stent or graft is open or closed.

- Technetium-99m (99mTc) tetrofosmin single-photon emission computed tomography (SPECT) is a useful method to exclude high-risk patients among patients with chest pain in the emergency department.
- Resting cardiac magnetic resonance imaging (MRI) has exhibited diagnostic operating characteristics suitable for triage of patients with chest pain in the ED. Performed urgently to evaluate chest pain, MRI accurately detected a high fraction of patients with ACS, including patients with enzyme-negative unstable angina. MRI can identify wall thinning, scar, delayed enhancement (infarction), and wall motion abnormalities (ischemia). Coronary artery assessment may be coupled with magnetic resonance (MR) angiography in the future.

## Other Tests

- ECG is the most important ED diagnostic test for angina. It may show changes during symptoms and in response to treatment, which would confirm a cardiac basis for symptoms. It also may demonstrate preexisting structural or ischemic heart disease (left ventricular hypertrophy, Q waves). A normal ECG or one that remains unchanged from the baseline does not exclude the possibility that chest pain is ischemic in origin. Changes that may be seen during anginal episodes include the following:
  - Transient ST-segment elevations (fixed changes suggest acute MI) may be observed. In patients with elevated ST segments, consider LV aneurysm, pericarditis, Prinzmetal angina, early repolarization, and Wolff-Parkinson-White syndrome as possible diagnoses.
  - Dynamic T-wave changes (inversions, normalizations, or hyperacute changes) may be observed. In patients with deep T-wave inversions, consider CNS events or drug therapy with tricyclic antidepressants or phenothiazines.
  - ST depressions may be junctional, downsloping, or horizontal.
  - Diagnostic sensitivity may be increased by performing right-sided leads (V<sub>4R</sub>), posterior leads (V<sub>8</sub>, V<sub>9</sub>), and serial recordings.

## Prehospital Care

Generally, patients transported with chest pain should initially be managed under the assumption that the pain is ischemic in origin. Prehospital interventions should be guided by the nature of the presenting complaint, individual risk factors, and associated symptoms (eg, breathing difficulty, hemodynamic instability, appearance of ectopy). Airway, breathing, and circulation should be rapidly assessed with institution of CPR, ACLS-guided interventions, or other measures as indicated for the unstable patient.

- Obtain intravenous access.
- Administer supplemental oxygen.
- Aspirin (162-325 mg) should be given in the field, chewed and swallowed.
- Telemetry and prehospital ECG, if available, may be helpful in selected circumstances. Certain EMS systems have investigated protocols for prehospital administration of thrombolytic therapy. This has not become a trend due to unproven benefit and due to the

increase in availability of percutaneous coronary intervention (PCI) in many medical centers as an alternative to thrombolysis for STEMI.

- Perform pulse oximetry.
- Administer sublingual or aerosolized nitroglycerin if chest pain is ongoing and is believed to be cardiac in origin.

## Emergency Department Care

The ACS spectrum concept is a useful framework for developing therapeutic strategies. Antithrombin therapy and antiplatelet therapy should be administered to all patients with an ACS regardless of the presence or the absence of ST-segment elevation. Patients presenting with persistent ST-segment elevation are candidates for reperfusion therapy (either pharmacological or catheter based) to restore flow promptly in the occluded epicardial infarct-related artery. Patients presenting without ST-segment elevation are not candidates for immediate pharmacological reperfusion but should receive anti-ischemic therapy and PCI when appropriate. "Time is myocardium" is a dictum to be remembered as survival has been shown to correlate with time to reperfusion in patients with acute MI. Many centers set goals for, and routinely record, door-to-ECG, door-to-needle (thrombolytic therapy), or door-to-vascular access (for patients receiving PCI) times as measures of quality of care provided.

- Goals of ED care are rapid identification of patients with STEMI, exclusion of alternative causes of nonischemic chest pain, and stratification of patients with acute coronary ischemia into low- and high-risk groups.
- Obtain intravenous access, administer supplemental oxygen, and provide telemetry monitoring if these procedures have not already been accomplished in the prehospital phase. In addition, obtain a 12-lead ECG as soon as possible after arrival.
- Complete a history and physical examination, with focus on risk factors for coronary ischemia; onset, duration, and pattern of symptoms; and early identification of complications of myocardial ischemia (eg, new murmurs, CHF).
- Perform frequent reassessment of vital signs and symptoms in response to administered therapies.
- Serial ECGs and continuous ST-segment monitoring may be useful.
- Many EDs have an observation unit that may be an appropriate disposition for patients who meet admission criteria.
- Medical therapy, as discussed in Medication, is indicated.

## Consultations

Cardiology or interventional cardiology consultation may be indicated for patients with any of the following:

- STEMI - Depending on the center, the patient may be a candidate for PCI, and immediate interventional cardiology consultation is indicated.
  - Ongoing symptoms highly suggestive of acute coronary ischemia and nondiagnostic ECG (eg, left bundle-branch block [LBBB])
  - Ongoing symptoms refractory to aggressive medical therapy
  - Hemodynamic instability
  - Evidence of acute valvular dysfunction
  - Shock
  - Known severe aortic stenosis and ongoing symptoms
  - Uncertainty of the diagnosis

## MYOCARDIAL INFARCTION

Myocardial infarction (MI) is the rapid development of myocardial necrosis caused by a critical imbalance between oxygen supply and demand of the myocardium. This usually results from plaque rupture with thrombus formation in a coronary vessel, resulting in an acute reduction of blood supply to a portion of the myocardium.

Although the clinical presentation of a patient is a key component in the overall evaluation of the patient with MI, many events are either "silent" or are clinically unrecognized, evidencing that patients and physicians often do not recognize symptoms of a MI. The appearance of cardiac markers in the circulation generally indicates myocardial necrosis and is a useful adjunct to diagnosis.

Cardiac markers help to categorize MI, which is considered part of a spectrum referred to as acute coronary syndrome that includes ST-elevation MI (STEMI), non-ST-elevation MI (NSTEMI), and unstable angina. This categorization is valuable because patients with ischemic discomfort may or may not have ST-segment elevations on their electrocardiogram. Those without ST elevations may ultimately be diagnosed with NSTEMI or with unstable angina based on the presence or absence of cardiac enzymes. Additionally, therapeutic decisions, such as administering an intravenous thrombolytic or performing percutaneous coronary intervention (PCI), are often made based on this categorization.

### Pathophysiology

The most common cause of MI is narrowing of the epicardial blood vessels due to atheromatous plaques. Plaque rupture with subsequent exposure of the basement membrane results in platelet aggregation, thrombus formation, fibrin accumulation, hemorrhage into the plaque, and varying degrees of vasospasm. This can result in partial or complete occlusion of the vessel and subsequent myocardial ischemia. Total occlusion of the vessel for more than 4-6 hours results in irreversible myocardial necrosis, but reperfusion within this period can salvage the myocardium and reduce morbidity and mortality.

Nonatherosclerotic causes of MI include coronary vasospasm as seen in variant (Prinzmetal) angina and in patients using cocaine and amphetamines; coronary emboli from sources such as an infected heart valve; occlusion of the coronaries due to vasculitis; or other causes leading to mismatch of oxygen supply and demand, such as acute anemia from GI bleeding. MI induced by chest trauma has also been reported, usually following severe chest trauma such as motor vehicle accidents and sports injuries.

### Lab Studies

- Troponin is the preferred biomarker for diagnosis.
- - Troponins have the greatest sensitivity and specificity in detecting MI. The test result is both diagnostic as well as prognostic of outcome.
  - Troponin is a contractile protein that normally is not found in serum. It is released only when myocardial necrosis occurs.

- For early detection of myocardial necrosis, sensitivity of this laboratory test is superior to that of the creatine kinase-MB (CK-MB). Troponin I is detectable in serum 3-6 hours after an AMI and its level remains elevated for 14 days.
- Troponin is also the optimum biomarker for the evaluation of patients with MI who have coexistent skeletal muscle injury.
- Creatine kinase–MB level
  - 
  - CK-MB levels begin to rise within 4 hours after injury, peak at 18-24 hours, and subside over 3-4 days. A level within the reference range does not exclude myocardial necrosis.
  - Occasionally, very small infarcts can be missed by CK-MB; therefore, a troponin level should be measured for patients suspected of having had MI who have negative serial CK-MBs.
- Myoglobin levels
  - 
  - Myoglobin, a low-molecular-weight heme protein found in cardiac and skeletal muscle, is released more rapidly from infarcted myocardium than troponin and CK-MB and may be detected as early as 2 hours after MI. Myoglobin levels rise early in the course of MI.
  - The marker has high sensitivity but poor specificity. When performed in conjunction with other studies, it may be useful for the early detection of MI.
- Complete blood count
  - 
  - CBC is indicated if anemia is suspected as a precipitant. Transfusion with packed red blood cells may be indicated.
  - Leukocytosis may be observed within several hours after an AMI. It peaks in 2-4 days and returns to levels within the reference range within 1 week.
- Chemistry profile
  - 
  - Potassium and magnesium levels should be monitored and corrected.
  - Creatinine levels must be considered before using an angiotensin-converting enzyme (ACE) inhibitor.
- C-reactive protein (CRP) is a marker of acute inflammation. Patients without biochemical evidence of myocardial necrosis but with elevated CRP level are at increased risk of a subsequent ischemic event.
- Erythrocyte sedimentation rate (ESR) rises above reference range values within 3 days and may remain elevated for weeks.
- Serum lactate dehydrogenase (LDH) level rises above the reference range within 24 hours of MI, reaches a peak within 3-6 days, and returns to the baseline within 8-12 days.

## Imaging Studies

- Chest radiography
  - 
  - Chest radiography may provide clues to an alternative or complicating diagnosis (eg, aortic dissection, pneumothorax). Other imaging studies such as a contrast chest CT scan or transesophageal echocardiography should be used to differentiate MI from aortic dissection in patients in whom the diagnosis is in doubt. Stanford type A aortic dissections may dissect in a retrograde fashion causing coronary blockage and dissection, which may result in MI. In one study, 8% of patients with Stanford type A dissections had ST elevation on ECG.

- Chest radiography also reveals complications of MI such as pulmonary edema secondary to heart failure.
- Echocardiography
  - 
  - Use 2-dimensional and M-mode echocardiography when evaluating wall motion abnormalities and overall ventricular function.
  - Echocardiography can identify complications of MI (eg, valvular insufficiency, ventricular dysfunction, pericardial effusion).
- Technetium-99m sestamibi scan
  - 
  - Technetium-99m is a radioisotope that is taken up by the myocardium in proportion to the blood flow and is only minimally redistributed after initial uptake. This allows for time delay between injection of the isotope and imaging.
  - It has potential use in identifying infarct in patients with atypical presentations or in patients with ECGs that are not interpretable.
  - Normal scan findings are associated with an extremely low risk of subsequent cardiac events.
- Thallium scanning: Thallium accumulates in the viable myocardium.
- Perfusion imaging has been used in risk stratification after MI and for measurement of infarct size to evaluate reperfusion therapies. Novel "hot spot" imaging radiopharmaceuticals that visualize infarction or ischemia are currently undergoing evaluation and hold promise for the future. (See Myocardial Ischemia - Nuclear Medicine and Risk Stratification.)
- Recent advances include dual-source 64-slice CT scanning that can do a full scan in 10 seconds and produce high-resolution images that allow fine details of the patient's coronary arteries to be seen. This technology allows for noninvasive and early diagnosis of coronary artery disease and thus earlier treatment before the coronary arteries become more or completely occluded. It allows direct visualization of not only the lumen of the coronary arteries but also plaque within the artery. Dual-source 64-slice CT scanning is being used with intravenous contrast to determine if a stent or graft is open or closed.
- MRI can identify wall thinning, scar, delayed enhancement (infarction), and wall motion abnormalities (ischemia). Currently, this is not a primary diagnostic modality for MI, but coronary artery assessment may be enhanced by magnetic resonance angiography (MRA) in the future.

## Other Tests

- Electrocardiography
  - 
  - An ECG should be obtained as soon as possible after presentation to the ED.
  - Approximately one half of patients have diagnostic changes on their initial ECG.
  - Because the symptoms of AMI can be subtle or protean, an ECG should be performed on any patient who is older than 45 years and is experiencing any form of thoracoabdominal discomfort, including new epigastric pain or nausea.
  - In younger patients, an ECG should be considered when suggestive symptoms are present or in patients with risk factors for early coronary artery disease. Younger patients are disproportionately represented in missed cases. An ECG is a rapid, low-risk, relatively low-cost measure.
  - Results that indicate high probability of MI are ST-segment elevation greater than 1 mm in 2 anatomically contiguous leads or the presence of new Q waves.
  - Results that indicate intermediate probability of MI are ST-segment depression, T-wave inversion, and other nonspecific ST-T wave abnormalities.

- Results that indicate low probability of MI are normal findings on ECG; however, normal or nonspecific findings on ECG do not exclude the possibility of MI.
- Localization of MI based on distribution of ECG abnormalities is as follows:
  - § Inferior wall - II, III, aVF
  - § Lateral wall - I, aVL, V<sub>4</sub> through V<sub>6</sub>
  - § Anteroseptal - V<sub>1</sub> through V<sub>3</sub>
  - § Anterolateral - V<sub>1</sub> through V<sub>6</sub>
  - § Right ventricular - RV<sub>4</sub>, RV<sub>5</sub>
  - § Posterior wall - R/S ratio >1 in V<sub>1</sub> and V<sub>2</sub>; T-wave changes (ie, upright) in V<sub>1</sub>, V<sub>8</sub>, and V<sub>9</sub>

## Procedures

- Percutaneous coronary interventions (PCIs) are a group of catheter-based technologies used to establish coronary reperfusion. Angiography provides essential knowledge of the extent of coronary disease and is performed prior to PCI. PCI may then be performed as a primary intervention or as an intervention after thrombolysis failure. Evidence suggests that primary PCI is more effective than thrombolysis and should be performed for confirmed STEMI, new or presumably new left bundle-branch block (LBBB), severe congestive heart failure, or pulmonary edema if it can be performed within 12 hours of symptom onset. Door-to-balloon time should be 90 minutes or less.
  - Percutaneous transluminal coronary angioplasty (PTCA) (balloon angioplasty) is the primary therapeutic modality used at centers where it can provide reperfusion as quickly as fibrinolytic therapy. In other centers, it is used selectively for patients failing to respond to thrombolytics.
  - PCI has fewer bleeding complications and recurrent ischemia when compared with thrombolysis. PCI restores coronary artery patency in more than 90% of patients.
  - A drawback of PCI is the need for 24-hour availability of an angioplasty suite with the required staff and the availability of backup cardiothoracic capabilities. Primary PCI for STEMI should be performed at hospitals with readily available cardiothoracic surgery. Readily available may be defined as the ability to transport patients quickly to a hospital with cardiothoracic capabilities.
- Coronary artery bypass graft may be indicated based on angiographic findings.
- Morbidity and mortality from MI are significantly reduced if patients and bystanders recognize symptoms early, activate the EMS system, and thereby shorten the time to definitive treatment. Trained prehospital personnel can provide life-saving interventions if the patient develops cardiac arrest. The key to improved survival is the availability of early defibrillation. Approximately 1 in every 300 patients with chest pain transported to the ED by private vehicle goes into cardiac arrest en route. Several studies have confirmed that patients with STEMI usually do not call 911; in one study, only 23% of patients with a confirmed coronary event used EMS.

## TREATMENT

### Prehospital Care

- All patients being transported for chest pain should be managed as if the pain were ischemic in origin unless clear evidence to the contrary is established.
- If available, an ALS unit should transport patients with hemodynamic instability or respiratory difficulty.



- Prehospital notification by Emergency Medical Services (EMS) personnel should alert ED staff to the possibility of a patient with MI. EMS personnel should receive online medical advice for a patient with high-risk presentation.
- The American Heart Association (AHA) protocol can be adopted for use by prehospital emergency personnel. This protocol recommends empirical treatment of patients with suspected STEMI with morphine, oxygen, nitroglycerin, and aspirin.
- Specific prehospital care includes the following:
  - Intravenous access, supplemental oxygen, pulse oximetry
  - Immediate administration of aspirin en route
  - Nitroglycerin for active chest pain, given sublingually or by spray
  - Telemetry and prehospital ECG, if available
- EMS protocol should be formulated to strongly consider taking patients with suspected MI/ACS, and certainly patients with STEMI, to facilities capable of PCI if geographically possible.
- Prehospital thrombolysis allows eligible patients to receive thrombolysis 30-60 minutes sooner than if treatment were given in the ED; however, prehospital thrombolysis is still under investigation.

## Emergency Department Care

For purposes of determining appropriate treatment, viewing MI as part of a spectrum of coronary syndromes is helpful; this spectrum includes (1) STEMI, (2) NSTEMI, and (3) unstable angina. Patients with persistent ST elevation should be considered for reperfusion therapy (thrombolysis or primary PCI.) Those without ST elevation will be diagnosed with either NSTEMI if cardiac marker levels are elevated or with unstable angina if serum cardiac marker levels provide no evidence of myocardial injury. Patients presenting with no ST-segment elevation are not candidates for immediate thrombolytics but should receive anti-ischemic therapy and may be candidates for PCI urgently or during admission. Confirmation of the diagnosis of NSTEMI requires waiting for the results of cardiac markers. In the case of unstable angina, diagnosis may await further diagnostic studies such as coronary angiography or imaging studies to confirm the diagnosis and to distinguish it from noncoronary causes of chest pain.

The initial focus should be on identifying patients with STEMI. An ECG should be performed and shown to an experienced emergency medicine physician within 10 minutes of ED arrival. If STEMI is present, the decision as to whether the patient will be treated with thrombolysis or primary PCI should be made within the next 10 minutes. The goal for patients with STEMI should be to achieve a door-to-drug time of within 30 minutes and a door-to-balloon time of within 90 minutes. If STEMI is not present, then the workup should proceed looking for unstable angina or NSTEMI and for alternative diagnoses.

Treatment is aimed at (1) restoration of the balance between the oxygen supply and demand to prevent further ischemia, (2) pain relief, and (3) prevention and treatment of complications.

- Delays in administration of thrombolysis often occur because of delay in obtaining an ECG, interpretation, lack of immediate availability of thrombolytic agents, and outdated protocols requiring cardiology consultation before thrombolytic treatment.
- An ECG should be performed as soon as possible after the patient presents to the ED. The ECG should be hand-delivered to an experienced physician for timely review.
- All patients should be placed on telemetry.
- Two large-bore IVs should be inserted if the EMS has not already completed this.
- Pulse oximetry should be performed, and appropriate supplemental oxygen should be given (maintain oxygen saturation >90%).

- A chest radiograph should be obtained soon after arrival to screen for alternative causes of chest pain and identify possible contraindications to thrombolysis (eg, aortic dissection).
- Pharmacologic intervention is likely to include the following:
  - Aspirin should be administered immediately if not already taken by the patient at home or administered by EMS before arrival. Aspirin has been shown to decrease mortality and reinfarction rates after MI. Use clopidogrel (Plavix) in case of aspirin allergy.
  - Beta-blocker therapy for heart rate control and resultant decrease of myocardial oxygen demand if not contraindicated. Metoprolol (Lopressor) is the standard and is a selective beta<sub>1</sub>-adrenergic receptor blocker that decreases automaticity of contractions. Beta-blockers reduce the rates of reinfarction and recurrent ischemia and may also reduce mortality.
  - Morphine sulphate may be administered for relief of pain and anxiety.
- Nitrates are useful for preload reduction and symptomatic relief but have no apparent impact on mortality rate in MI. Systolic BP <90, HR <60 or >100, and RV infarction are a contraindications to nitrate use. Intravenous nitroglycerin is indicated for relief of ongoing ischemic discomfort, control of hypertension, or management of pulmonary congestion. Nitrates should not be administered to patients who have taken any phosphodiesterase inhibitor for erectile dysfunction within the last 24 hours (extend timeframe to 48 h for tadalafil).
- Thrombolytic therapy has been shown to improve survival rates in MI.
  - Door-to-drug time should be no more than 30 minutes. Thrombolytic therapy administered within the first 2 hours can occasionally abort MI and dramatically reduce the mortality rate.
  - The optimal approach is to administer thrombolytics as soon as possible after onset of symptoms (up to 12 h from symptom onset according to some authors) in patients with ST-segment elevation greater than 1 mm in 2 or more anatomically contiguous ECG leads, new or presumed new left bundle-branch block, or anterior ST depression where posterior infarction is suspected. With ST-segment elevation, the diagnosis is relatively secured; therefore, initiation of reperfusion therapy should not be delayed for the results of cardiac markers.
  - Thrombolysis is generally preferred to PCI in cases where the time from symptom onset is less than 3 hours and if there would be a delay to PCI, greater than 1-2 additional hours to door-to-balloon time. A detailed list of contraindications and cautions for the use of fibrinolytic therapy is shown in Table 12 of the ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction—Executive Summary, at the American College of Cardiology.
- Administer a platelet glycoprotein (GP) IIb/IIIa-receptor antagonist (eptifibatide, tirofiban, or abciximab), in addition to aspirin and unfractionated heparin, to patients with continuing ischemia or with other high-risk features and to patients in whom PCI is planned. Studies suggest that the addition of intravenous platelet glycoprotein (GP) IIb/IIIa-receptor antagonists to aspirin and heparin improves both early and late outcomes, including mortality, Q-wave MI, need for revascularization procedures, and length of hospital stay.
- Despite the traditional use of unfractionated heparin in ST elevation MI for decades, controversy regarding its role continues.
  - patients treated with fibrinolytic therapy, recommendations for heparin therapy depend on the fibrinolytic agent. Heparin has an established role as an adjunctive agent in patients receiving alteplase, reteplase, or tenecteplase but should not be used with nonselective fibrinolytic agents such as streptokinase and anistreplase.
  - Heparin is also indicated in patients undergoing primary PCI. Data are scant with regard to heparin efficacy in patients not receiving thrombolytic therapy in the

setting of MI; however, considerable rationale exists for ancillary heparin therapy to inhibit the coagulation cascade.

- Low-molecular-weight heparins (LMWH) are commonly used because of convenient dosing and reliable therapeutic levels, but there have been no definitive trials of LMWH in patients with STEMI to provide a firm basis for recommendations. Low-molecular-weight heparin should not be used as an alternative to unfractionated heparin as ancillary therapy to fibrinolytics in patients aged older than 75 years or in patients with significant renal dysfunction (serum creatinine level >2.5 mg/dL in men or >2 mg/dL in women).
- An ACE inhibitor (Captopril) should be given orally within the first 24 hours of STEMI to patients with anterior infarction, pulmonary congestion, or left ventricular ejection fraction (LVEF) less than 40% in the absence of hypotension.
- An angiotensin receptor blocker (valsartan or candesartan) should be administered to patients with STEMI who are intolerant of ACE inhibitors and who have either clinical or radiological signs of heart failure or LVEF less than 40%.
- Note that routine use of lidocaine as prophylaxis for ventricular arrhythmias in patients who have experienced an MI has been shown to increase mortality rates and its use is class indeterminate.
- Use of calcium channel blockers in the acute setting has come into question, with some randomized controlled trials and retrospective studies showing increased adverse effects. Diltiazem and verapamil should be avoided in patients with pulmonary edema or severe left ventricular (LV) dysfunction.

The main goals of ED medical therapy are rapid intravenous thrombolysis and/or rapid referral for PCI, optimizing oxygenation, decreasing cardiac workload, and controlling pain.

### **Further Inpatient Care**

- All patients with known or suspected MI should be admitted to an ICU.
- Patients should continue to receive beta-blockers, nitrates, and heparin, as indicated.
- ACE inhibitors have been shown to improve survival rates in patients who have experienced an MI. In the acute setting, afterload reduction from ACE inhibitors may reduce the risk of CHF and sudden death.
- Lidocaine may be indicated for patients with ventricular ectopy that is complex or for patients with hemodynamically significant, nonsustained, or sustained ventricular tachycardia. Recall that the routine use of lidocaine as prophylaxis for ventricular arrhythmias is contraindicated.

### **Transfer**

- A recent study showed that the transfer of patients to an invasive-treatment center for primary PCI is superior to on-site fibrinolysis provided that the transfer can be accomplished within 2 hours. Transfer should be considered for those patients who are likely to benefit from PCI or cardiac surgery but who are in an institution where access to such interventions is not immediate. The benefits of transferring such a patient must outweigh the risks. Patients for whom transfer might be considered include the following:

- Patients with new or worsening hemodynamically significant mitral regurgitant murmurs
- Patients with known or suspected critical aortic stenosis and either ongoing ischemia or hemodynamic instability
- Patients who have received thrombolysis and fail to reperfuse
- Patients with significant LV dysfunction or cardiogenic shock

## **Deterrence/Prevention**

- Patients should avoid risk factors when possible and act upon treatable risk factors.
- Seeking medical attention or calling 911 with the first symptoms or signs of angina may initiate the cascade of interventions that will ultimately prevent or limit damage to the myocardium. All patients should be educated as to these symptoms and signs and when to call 911.
- Daily low-dose aspirin may be helpful, but the decision to prescribe aspirin as a preventative measure for MI must be made by the patient's physician(s) considering his or her overall condition and risk-benefit ratio.

## **Complications**

- Monitoring and treatment of arrhythmias and conduction disturbances are an important part of the treatment of a post-MI patient within the first 48 hours. Conduction disturbances are most commonly observed in inferior MI but are more ominous when they occur with anterior MI.
- Tachyarrhythmia
  - Sinus tachycardia is a poor prognostic sign that is indicative of ventricular dysfunction or failure.
  - PVCs - Simple (ie, <10/h), no need to treat
  - PVCs - Complex, NSVT/VT, lidocaine DOC
  - Accelerated idioventricular rhythm (AIVR) is the most common reperfusion arrhythmia, but it usually is well tolerated and does not require treatment.
- Bradyarrhythmia
  - Type I second-degree heart block (ie, Wenckebach) is associated with inferior wall MI. Treat using temporary pacing or atropine only if it is hemodynamically significant.
  - Type II second-degree heart block is associated with anterior wall MI and may require a permanent pacemaker. Bundle branch blocks (BBB) that are new or preexisting with new second-degree heart block may also mandate consideration for a permanent pacemaker.
- Cardiogenic shock
  - In the setting of an MI, cardiogenic shock is associated with an 80% in-hospital mortality rate.
  - Patients should undergo thrombolysis or PCI, placement of an intra-aortic balloon pump, or CABG.
- Valvular insufficiency
  - This may occur acutely when ischemia or an infarct of the papillary muscle occurs resulting in mitral regurgitation. It usually presents as flash pulmonary edema and hypotension. Papillary muscle rupture may require valve repair.
  - Ischemia often responds to medical therapy and thrombolysis.

- Congestive heart failure can be due to systolic or diastolic dysfunction in MI. The severity of the heart failure and systolic dysfunction depends on the extent of the infarct and the presence of any other complications, such as acute mitral regurgitation. Treatment may include nitrates, morphine, diuretics, and ACE inhibitors. Digoxin has no role in acute CHF due to ischemia.
- Right ventricular infarct occurs in the setting of an inferior wall infarction. Because patients with an RV infarct are preload-dependent, they often are identified by profound hypotension with normal pulmonary auscultation, particularly after nitroglycerin therapy. They respond to volume loading. This can be diagnosed by ST-segment elevation in right-sided chest leads (ie, V<sub>4</sub>R, V<sub>5</sub>R).
- Ventricular rupture occurs in the interventricular septum or the left ventricle free wall. Rupture represents a catastrophic event with mortality rates greater than 90%. Prompt recognition, stabilization, and surgical repair are crucial to any hope of survival. An echocardiogram usually defines the abnormality, and a right heart catheterization may show an oxygenation increase with septal rupture. It is more common in women, patients with hypertension, and those receiving NSAIDs or steroids.
- Other complications include pericarditis, ventricular aneurysm, and mural thrombus.

## Prognosis

- MI may be associated with a mortality rate as high as 30%, with more than half of deaths occurring in the prehospital setting. Prognosis is highly variable and depends on a number of factors related to the timing and nature of intervention, success of the intervention (ie, infarct size), and post-MI management.
- Better prognosis is associated with factors including the following:
  - 
  - Successful early reperfusion
  - Preserved LV function
  - Short-term and long-term treatment with beta-blockers, aspirin, and ACE inhibitors
- Poorer prognosis is associated with the following:
  - 
  - Delayed or unsuccessful reperfusion
  - LV function is the strongest predictor of outcome in the post-MI patient.
- Ventricular dysrhythmias
  - 
  - Recent experience with amiodarone suggests that it may improve long-term mortality in survivors of MI with ectopy and ventricular tachycardia.

## CARDIOGENIC SHOCK

Cardiogenic shock is characterized by a decreased pumping ability of the heart that causes a shocklike state (ie, global hypoperfusion). It most commonly occurs in association with, and as a direct result of, acute myocardial infarction (AMI).

Similar to other shock states, cardiogenic shock is considered to be a clinical diagnosis characterized by decreased urine output, altered mentation, and hypotension. Other clinical characteristics include jugular venous distension, cardiac gallop, and pulmonary edema. The most recent prospective study of cardiogenic shock defines cardiogenic shock as sustained hypotension (systolic blood pressure [BP] less than 90 mm Hg lasting more than 30 min) with evidence of tissue hypoperfusion with adequate left ventricular (LV) filling pressure (Hochman, 1999). Tissue

hypoperfusion was defined as cold peripheries (extremities colder than core), oliguria (<30 mL/h), or both.

**Physical:** The physical examination findings are consistent with shock. Patients are in frank distress, are profoundly diaphoretic with mottled extremities, and are usually visibly dyspneic. Clinical assessment begins with attention to the ABCs and vital signs.

- Although the patient may eventually require endotracheal intubation, the airway usually is patent initially.
- Breathing may be labored, with audible coarse crackles or wheezing.
- As in any shocklike state, circulation is markedly impaired. Tachycardia, delayed capillary refill, hypotension, diaphoresis, and poor peripheral pulses are frequent findings.
- Other signs of end-organ dysfunction (eg, decreased mental function, urinary output) may be present.
- Initial vital sign assessment should include BP measurements in both arms to evaluate possible thoracic aortic aneurysm or dissection. Vital signs should be regularly updated with continuous noninvasive physiologic monitoring.
- Neck examination may reveal jugular venous distention, which may be prominent. This finding is evidence of RV failure.
- LV dysfunction, characterized by florid pulmonary edema, can be auscultated as crackles with or without wheezing.
- Careful cardiac examination may reveal mechanical causes of cardiogenic shock.
  - Loud murmurs may indicate a valvular dysfunction, whereas muffled heart tones with jugular venous distention and pulsus paradoxus may suggest tamponade (Beck triad).
  - A gallop may also be heard. The presence of an S<sub>3</sub> heart sound is pathognomonic of congestive heart failure. The presence of pulmonary edema increases the likelihood of cardiogenic shock in the setting of hypotension.

**Causes:** The vast majority of cases of cardiogenic shock are due to acute myocardial ischemia.

- Mechanisms not related to acute infarction include the following:
  - Systolic - Beta-blocker overdose, calcium channel blocker overdose, myocardial contusion, respiratory acidosis, hypocalcemia, hypophosphatemia, and cardiotoxic drugs (eg, doxorubicin [Adriamycin])
  - Diastolic - Ventricular hypertrophy and restrictive cardiomyopathies
  - After load - Aortic stenosis, hypertrophic cardiomyopathy, dynamic outflow obstruction, aortic coarctation, and malignant hypertension

- Valvular/structural - Mitral stenosis, endocarditis, mitral or aortic regurgitation, atrial myxoma or thrombus, and tamponade
- Risk factors for the development of cardiogenic shock include preexisting myocardial damage or disease (eg, diabetes, advanced age, previous AMI), AMI (eg, Q-wave, large or anterior wall AMIs), and dysrhythmia.

### **Lab Studies:**

- No one test is completely sensitive or specific for cardiogenic shock. Laboratory studies are directed at the potential underlying cause.
- In most cases, the usual workup includes tests of all of the following, which usually are assessed in cases of suspected cardiac ischemia:
  - Cardiac enzymes (eg, creatine kinase, troponin, myoglobin)
  - CBC
  - Electrolytes
  - Coagulation profile (eg, prothrombin time, activated partial thromboplastin time)
  - An ABG may be useful to evaluate acid-base balance because acidosis can have a particularly deleterious effect on myocardial function. Elevated serum lactate level is an indicator of shock.
  - Brain natriuretic peptide (BNP) may be useful as an indicator of congestive heart failure and as an independent prognostic indicator of survival. A low BNP level may effectively rule out cardiogenic shock in the setting of hypotension; however, an elevated BNP level does not rule in the disease.

### **Imaging Studies:**

- A portable chest radiograph is helpful because it gives an overall impression of the cardiac size, pulmonary vascularity, and coexistent pulmonary pathology, and it provides a rough estimate of mediastinal and aortic sizes in the event that an aortic etiology is being considered.

### **Other Tests:**

- An ECG is helpful if it reveals an acute injury pattern consistent with an AMI. A normal ECG, however, does not rule out the possibility. ECGs are often most helpful when they can be compared with previous tracings.
- An echocardiogram obtained in the ED can be extremely useful.
  - It may be diagnostic and reveal akinetic or dyskinetic areas of ventricular wall motion.
  - It may reveal surgically correctable causes, such as valvular dysfunction and tamponade.

## Procedures:

- Placement of a central line may facilitate volume resuscitation, provide vascular access for multiple infusions, and allow invasive monitoring of central venous pressure and pulmonary capillary wedge pressure. Although not necessary for the diagnosis of cardiogenic shock, invasive monitoring with a pulmonary artery catheter may be helpful in guiding fluid resuscitation in situations in which LV preload is difficult to determine. Central venous pressure may also be used to guide fluid resuscitation. Cardiogenic shock may be indicated by a cardiac index of less than 1.8 L/min/m<sup>2</sup> with a pulmonary capillary wedge pressure greater than 18 mm Hg.

An intra-aortic balloon pump may be placed in the ED as a bridge to percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) to decrease myocardial workload.

**Prehospital Care:** Prehospital care is aimed at minimizing any further ischemia and shock.

- All patients require intravenous access, high-flow oxygen administered by mask, and cardiac monitoring.
- Twelve-lead electrocardiography performed in the field by appropriately trained paramedics may be useful in decreasing door to PCI times and/or thrombolytics because acute ST-segment elevation myocardial infarctions can be identified earlier. The ED physician, can thus be alerted, and may mobilize the appropriate resources.
- Inotropic medications should be considered in systems with appropriately trained paramedical personnel.

**Emergency Department Care:** ED care is aimed at making the diagnosis, preventing further ischemia, and treating the underlying cause. Treatment of the underlying cause is directed in the case of acute myocardial infarction (AMI) at coronary artery reperfusion. This is best accomplished with rapid transfer of the patient to a cardiac catheterization laboratory. The ED physician should be alert to the fact that the SHOCK trial demonstrated that PCI or coronary artery bypass are the treatments of choice and that they have been shown to markedly decrease mortality rates at 1 year. PCI should be initiated within 90 minutes of presentation; however, it remains helpful, as an acute intervention, within 12 hours of presentation. If such a facility is not immediately available, thrombolytics should be considered. However, this treatment is second best.

Treatment begins with assessment and management of the ABCs.

- The airway should be assessed for patency and breathing evaluated for effectiveness and increased work of breathing. Endotracheal intubation and mechanical ventilation should be considered for patients with excessive work of breathing. Positive pressure ventilation may improve oxygenation but may also compromise venous return, preload, to the heart. In any event, the patient should be treated with high-flow oxygen.
- Other interventions are directed at supporting myocardial perfusion and maximizing cardiac output. Intravenous fluids should be provided to maintain adequate preload. The administration of such fluids should be guided by central venous pressure or pulmonary capillary wedge pressure monitoring.
- Intravenous vasopressors provide inotropic support increasing perfusion of the ischemic myocardium and all body tissues. However, extreme heart rates should be avoided because



they may increase myocardial oxygen consumption, increase infarct size, and further impair the pumping ability of the heart.

- Dopamine may provide vasopressor support. With higher doses, it has the disadvantage of increasing the heart rate and myocardial oxygen consumption.
- Dobutamine, inamrinone (formerly amrinone), or milrinone may provide inotropic support. In addition to their positive inotropic effects, inamrinone and milrinone have a beneficial vasodilator effect, which reduces preload and afterload.
- Natreacor (nesiritide) may be considered. Although nesiritide has been shown to increase mortality and renal dysfunction, it continues to be studied as a treatment for acute congestive heart failure and currently retains Food and Drug Administration (FDA) approval. It should be used with caution in the setting of cardiogenic shock because it has been shown to cause hypotension.
- Nitrates and/or morphine are advised for the management of pain; however, they must be used with caution because these patients are in shock, and excessive use of either of these agents can produce profound hypotension. Neither of these options has been shown to improve outcomes in cardiogenic shock.
- The use of an intra-aortic balloon pump (IABP) is recommended for cardiogenic shock not quickly reversed with pharmacologic therapy. It is also recommended as a stabilizing measure combined with thrombolytic therapy when angiography and revascularization are not readily available. Counterpulsation of the IABP reduces LV afterload and improves coronary artery blood flow. Although this procedure is generally not performed in the ED, planning is essential, and early consultation with a cardiologist regarding this option is recommended. Although complications may occur in up to 30% of patients, extensive retrospective data support its use.

## Ventricular fibrillation

· Ventricular fibrillation (VF) begins as a quasiperiodic reentrant pattern of excitation in the ventricles with resulting poorly synchronized and inadequate myocardial contractions. The heart consequently immediately loses its ability to function as a pump. As the initial reentrant pattern of excitation breaks up into multiple smaller wavelets, the level of disorganization increases. Sudden loss of cardiac output with subsequent tissue hypoperfusion creates global tissue ischemia; brain and myocardium are most susceptible. VF is the primary cause of sudden cardiac death (SCD).

## History

- VF often occurs without forewarning. The following symptoms, while not necessarily specific for SCD or VF, may develop before any major cardiac event:
  - Chest pain and other angina equivalents
  - Dyspnea
  - Easy fatigue

- Palpitations
- Syncope
- Immediately preceding acute cardiac arrest, possible increase in heart rate, presence of premature ventricular contractions (PVCs), or period of VT

## Physical

- No pulse or respiration
- 
- Unconsciousness
- 
- Wide and chaotic QRS complexes on cardiac monitor

## Prehospital Care

Because of the critical importance of early defibrillation, prehospital care is vital for arrests due to VF that occur outside the hospital. Interventions that impact survival and outcome of resuscitation include the following:

- Witnessed or early recognition of an arrest
- Early activation of emergency medical services (EMS) system
- Bystander CPR slows the degeneration of VF and improves survival.
- Automated external defibrillator (AED) application and defibrillation by trained personnel in the field
  - AEDs have revolutionized prehospital VF management because they decrease the time to defibrillation. This is accomplished by having the units prepositioned in the field where cardiac arrests are likely to occur (eg, airports, casinos, jails, malls, stadiums, industrial parks), eliminating the need for rhythm-recognition training and increasing the number of trained personnel and laypeople that can defibrillate at the scene.
  - AEDs are programmed to recognize 3 shockable rhythms: coarse ventricular fibrillation, fine ventricular fibrillation, and rapid ventricular tachycardia. Modern units have a sensitivity greater than 95% and specificity approaching 100% for the 3 shockable rhythms. The greatest difficulty is in distinguishing fine ventricular fibrillation from asystole.
  - AEDs can also be used for children. A pediatric dose-attenuating system should be used, if available, for children up to the age of 8 years, and a conventional AED can be used for children at or older than 8 years or with a corresponding weight of at least 25 kg (55 lb).
- Early access to trained EMS personnel capable of performing CPR, defibrillation, and advanced cardiac life support (ACLS)

## Complete heart block

Complete heart block, also referred to as third-degree heart block, or third-degree atrioventricular (AV) block, is a disorder of the cardiac conduction system, where there is no conduction through the AV node. Therefore, complete disassociation of the atrial and ventricular activity exists. The ventricular escape mechanism can occur anywhere from the AV node to the bundle-branch Purkinje system. It is important to realize, however, that not all patients with AV dissociation have complete heart block. For example, patients with accelerated junctional rhythms have AV dissociation, but not complete heart block, if the escape rate is faster than the intrinsic sinus rate.

Electrocardiographically, complete heart block is represented by QRS complexes being conducted at their own rate and totally independent of the P waves.

### Physical

- The physical examination will be notable for bradycardia, which can be quite severe.
- 
- Signs of congestive heart failure as a result of decreased cardiac output may be present and include the following:
  - 
  - Tachypnea or respiratory distress
  - Rales
  - Jugular venous distention
- Patients may have signs of hypoperfusion, including the following:
  - 
  - Altered mental status
  - Hypotension
  - Lethargy
- In patients with concomitant myocardial ischemia or infarction, corresponding signs may be evident on examination:
  - 
  - Signs of anxiety such as agitation or unease
  - Diaphoresis
  - Pale or pasty complexion
  - Tachypnea
- Regularized atrial fibrillation is the classic sign of complete heart block due to digitalis toxicity. This rhythm occurs because of the junctional escape rhythm.

### Prehospital Care

- All patients should be rapidly transported to the nearest available facility, applying advanced life support (ACLS) with continuous cardiac monitoring, as per local protocols.
- 
- For any symptomatic patient, transcutaneous pacing is the treatment of choice.
- 
- In all patients, oxygen should be administered and intravenous access should be established.
- 
- Maneuvers that are likely to increase vagal tone (eg, Valsalva maneuvers, painful stimuli) should be avoided.
-

- Atropine can be administered but should be given cautiously, because it is likely to be ineffective in a wide complex QRS rhythm and can be dangerous if the patient is having a concurrent MI.

## Hypovolemic shock

Hypovolemic shock refers to a medical or surgical condition in which rapid fluid loss results in multiple organ failure due to inadequate circulating volume and subsequent inadequate perfusion. Most often, hypovolemic shock is secondary to rapid blood loss (hemorrhagic shock).

Acute external blood loss secondary to penetrating trauma and severe GI bleeding disorders are 2 common causes of hemorrhagic shock. Hemorrhagic shock can also result from significant acute internal blood loss into the thoracic and abdominal cavities.

Two common causes of rapid internal blood loss are solid organ injury and rupture of an abdominal aortic aneurysm. Hypovolemic shock can result from significant fluid (other than blood) loss. Two examples of hypovolemic shock secondary to fluid loss include refractory gastroenteritis and extensive burns. The remainder of this article concentrates mainly on hypovolemic shock secondary to blood loss and the controversies surrounding the treatment of this condition. The reader is referred to other articles for discussions of the pathophysiology and treatment for hypovolemic shock resulting from losses of fluid other than blood.

The many life-threatening injuries experienced during the wars of the 1900s have significantly affected the development of the principles of hemorrhagic shock resuscitation. During World War I, W.B. Cannon recommended delaying fluid resuscitation until the cause of the hemorrhagic shock was repaired surgically. Crystalloids and blood were used extensively during World War II for the treatment of patients in unstable conditions. Experience from the Korean and Vietnam wars revealed that volume resuscitation and early surgical intervention were paramount for surviving traumatic injuries resulting in hemorrhagic shock. These and other principles helped in the development of present guidelines for the treatment of traumatic hemorrhagic shock. However, recent investigators have questioned these guidelines, and today, controversies exist concerning the optimal treatment of hemorrhagic shock.

### History:

- In a patient with possible shock secondary to hypovolemia, the history is vital in determining the possible causes and in directing the workup. Hypovolemic shock secondary to external blood loss typically is obvious and easily diagnosed. Internal bleeding may not be as obvious as patients may complain only of weakness, lethargy, or a change in mental status.
- Symptoms of shock, such as weakness, lightheadedness, and confusion, should be assessed in all patients.

- In the patient with trauma, determine the mechanism of injury and any information that may heighten suspicion of certain injuries (eg, steering wheel damage or extensive passenger compartment intrusion in a motor vehicle accident).
- If conscious, the patient may be able to indicate the location of pain.
- Vital signs, prior to arrival in the ED, should also be noted.
- Chest, abdominal, or back pain may indicate a vascular disorder.
- The classic sign of a thoracic aneurysm is a tearing pain radiating to the back. Abdominal aortic aneurysms usually result in abdominal, back pain, or flank pain.
- In patients with GI bleeding, inquiry about hematemesis, melena, alcohol drinking history, excessive nonsteroidal anti-inflammatory drug use, and coagulopathies (iatrogenic or otherwise) is very important.
  - The chronology of vomiting and hematemesis should be determined.
  - The patient who presents with hematemesis after multiple episodes of forceful vomiting is more likely to have Boerhaave syndrome or a Mallory-Weiss tear, whereas a patient with a history of hematemesis from the start is more likely to have peptic ulcer disease or esophageal varices.
- If a gynecologic cause is being considered, gather information about the following: last menstrual period, risk factors for ectopic pregnancy, vaginal bleeding (including amount and duration), vaginal passage of products of conception, and pain. All women of childbearing age should undergo a pregnancy test, regardless of whether they believe that they are pregnant. A negative pregnancy test typically excludes ectopic pregnancy as a diagnosis.

**Physical:** The physical examination should always begin with an assessment of the airway, breathing, and circulation. Once these have been evaluated and stabilized, the circulatory system should be evaluated for signs and symptoms of shock.

Do not rely on systolic BP as the main indicator of shock; this practice results in delayed diagnosis. Compensatory mechanisms prevent a significant decrease in systolic BP until the patient has lost 30% of the blood volume. More attention should be paid to the pulse, respiratory rate, and skin perfusion. Also, patients taking beta-blockers may not present with tachycardia, regardless of the degree of shock.

Classes of hemorrhage have been defined, based on the percentage of blood volume loss. However, the distinction between these classes in the hypovolemic patient often is less apparent. Treatment should be aggressive and directed more by response to therapy than by initial classification.

- Class I hemorrhage (loss of 0-15%)
  - In the absence of complications, only minimal tachycardia is seen.
  - Usually, no changes in BP, pulse pressure, or respiratory rate occur.
  - A delay in capillary refill of longer than 3 seconds corresponds to a volume loss of approximately 10%.

- Class II hemorrhage (loss of 15-30%)
  - Clinical symptoms include tachycardia (rate >100 beats per minute), tachypnea, decrease in pulse pressure, cool clammy skin, delayed capillary refill, and slight anxiety.
  - The decrease in pulse pressure is a result of increased catecholamine levels, which causes an increase in peripheral vascular resistance and a subsequent increase in the diastolic BP.
- Class III hemorrhage (loss of 30-40%)
  - By this point, patients usually have marked tachypnea and tachycardia, decreased systolic BP, oliguria, and significant changes in mental status, such as confusion or agitation.
  - In patients without other injuries or fluid losses, 30-40% is the smallest amount of blood loss that consistently causes a decrease in systolic BP.
  - Most of these patients require blood transfusions, but the decision to administer blood should be based on the initial response to fluids.
- Class IV hemorrhage (loss of >40%)
  - Symptoms include the following: marked tachycardia, decreased systolic BP, narrowed pulse pressure (or immeasurable diastolic pressure), markedly decreased (or no) urinary output, depressed mental status (or loss of consciousness), and cold and pale skin.
  - This amount of hemorrhage is immediately life threatening.
- In the patient with trauma, hemorrhage usually is the presumed cause of shock. However, it must be distinguished from other causes of shock. These include cardiac tamponade (muffled heart tones, distended neck veins), tension pneumothorax (deviated trachea, unilaterally decreased breath sounds), and spinal cord injury (warm skin, lack of expected tachycardia, neurological deficits).
- The 4 areas in which life-threatening hemorrhage can occur are as follows: chest, abdomen, thighs, and outside the body.
  - The chest should be auscultated for decreased breath sounds, because life-threatening hemorrhage can occur from myocardial, vessel, or lung laceration.
  - The abdomen should be examined for tenderness or distension, which may indicate intraabdominal injury.
  - The thighs should be checked for deformities or enlargement (signs of femoral fracture and bleeding into the thigh).
  - The patient's entire body should then be checked for other external bleeding.
- In the patient without trauma, the majority of the hemorrhage is in the abdomen. The abdomen should be examined for tenderness, distension, or bruits. Look for evidence of an

aortic aneurysm, peptic ulcer disease, or liver congestion. Also check for other signs of bruising or bleeding.

- In the pregnant patient, perform a sterile speculum examination. However, with third-trimester bleeding, the examination should be performed as a "double set-up" in the operating room. Check for abdominal, uterine, or adnexal tenderness.

**Causes:** The causes of hemorrhagic shock are traumatic, vascular, GI, or pregnancy related.

### **Lab Studies:**

- After the history is taken and the physical examination is performed, further workup depends on the probable cause of the hypovolemia, as well as on the stability of the patient's condition.
- Initial laboratory studies should include analysis of the CBC, electrolyte levels (eg, Na, K, Cl, HCO<sub>3</sub>, BUN, creatinine, glucose levels), prothrombin time, activated partial thromboplastin time, ABGs, urinalysis (in patients with trauma), and a urine pregnancy test. Blood should be typed and cross-matched.

### **Imaging Studies:**

- Patients with marked hypotension and/or unstable conditions must first be resuscitated adequately. This treatment takes precedence over imaging studies and may include immediate interventions and immediately taking the patient to the operating room.
- The workup for the patient with trauma and signs and symptoms of hypovolemia is directed toward finding the source of blood loss.
- The atraumatic patient with hypovolemic shock requires ultrasonographic examination in the ED if an abdominal aortic aneurysm is suspected. If GI bleeding is suspected, a nasogastric tube should be placed, and gastric lavage should be performed. An upright chest radiograph should be obtained if a perforated ulcer or Boerhaave syndrome is a possibility. Endoscopy can be performed (usually after the patient has been admitted) to further delineate the source of bleeding.
- A pregnancy test should be performed in all female patients of childbearing age. If the patient is pregnant and in shock, surgical consultation and the consideration of bedside pelvic ultrasonography should be immediately performed in the ED. Hypovolemic shock secondary to an ectopic pregnancy is common. Hypovolemic shock secondary to an ectopic pregnancy in a patient with a negative pregnancy test, although rare, has been reported.
- If thoracic dissection is suspected because of the mechanism and initial chest radiographic findings, the workup may include transesophageal echocardiography, aortography, or CT scanning of the chest.
- If a traumatic abdominal injury is suspected, a FAST (Focused Abdominal Sonography for Trauma) ultrasound exam may be performed in the stable or unstable patient. Computed Tomography (CT) scanning typically is performed in the stable patient.
- If long-bone fractures are suspected, radiographs should be obtained.

**Prehospital Care:** The treatment of patients with hypovolemic shock often begins at an accident scene or at home. The prehospital care team should work to prevent further injury, transport the patient to the hospital as rapidly as possible, and initiate appropriate treatment in the field. Direct pressure should be applied to external bleeding vessels to prevent further blood loss.

- Prevention of further injury applies mostly to the patient with trauma. The cervical spine must be immobilized, and the patient must be extricated, if applicable, and moved to a stretcher. Splinting of fractures can minimize further neurovascular injury and blood loss.
- Although in selected cases stabilization may be beneficial, rapid transport of sick patients to the hospital remains the most important aspect of prehospital care. Definitive care of the hypovolemic patient usually requires hospital, and sometimes surgical, intervention. Any delay in definitive care, eg, such as delayed transport, is potentially harmful.
- Most prehospital interventions involve immobilizing the patient (if trauma is involved), securing an adequate airway, ensuring ventilation, and maximizing circulation.
  - In the setting of hypovolemic shock, positive-pressure ventilation may diminish venous return, diminish cardiac outcome, and worsen the shock state. While oxygenation and ventilation are necessary, excessive positive-pressure ventilation can be detrimental for a patient suffering hypovolemic shock.
  - Appropriate treatment usually can be initiated without delaying transport. Some procedures, such as starting intravenous (IV) lines or splinting of extremities, can be performed while a patient is being extricated. However, procedures in the field that prolong transportation should be delayed. Benefits to giving IV fluids prior to departure from the scene are not clear; however, IV lines and fluid resuscitation should be started and continued once the patient is en route to definitive care.
- In recent years, there has been considerable debate regarding the use of military antishock trousers (MAST). MAST were introduced in the 1960s and, based mostly on anecdotal reports of success, their use became standard therapy in the prehospital treatment of hypovolemic shock in the late 1970s. By the 1980s, the American College of Surgeons Committee on Trauma included their use in the standard of care for all patients with trauma and signs or symptoms of shock. Since that time, studies have failed to show improved outcome with the use of MAST. The American College of Surgeons Committee on Trauma no longer recommends the use of MAST.

## **Congestive heart failure (CHF) AND PULMONARY EDEMA**

Congestive heart failure (CHF) is an imbalance in pump function in which the heart fails to maintain the circulation of blood adequately. The most severe manifestation of CHF, pulmonary edema, develops when this imbalance causes an increase in lung fluid secondary to leakage from pulmonary capillaries into the interstitium and alveoli of the lung.

The New York Heart Association's functional classification of CHF is one of the most useful. Class I describes a patient who is not limited with normal physical activity by symptoms. Class II occurs when ordinary physical activity results in fatigue, dyspnea, or other symptoms. Class III is characterized by a marked limitation in normal physical activity. Class IV is defined by symptoms at rest or with any physical activity.

### **Physical:**



- Findings such as peripheral edema, jugular venous distention, and tachycardia are highly predictive of CHF. Overall specificity of physical examination has been reported at 90%; however, this same study reported a sensitivity of only 10-30%.
- Tachypnea, using accessory muscles of respiration
- Hypertension
- Pulsus alternans (alternating weak and strong pulse indicative of depressed left ventricle [LV] function)
- Skin may be diaphoretic or cold, gray, and cyanotic.
- Jugular venous distention (JVD) frequently is present.
- Wheezing or rales may be heard on lung auscultation.
- Apical impulse frequently is displaced laterally.
- Cardiac auscultation may reveal aortic or mitral valvular abnormalities, S<sub>3</sub> or S<sub>4</sub>.
- Lower extremity edema also may be noted, especially in the subacute process.

### **Prehospital Care:**

- Prehospital notification by emergency medical services (EMS) personnel should alert ED staff of a patient presenting with signs and symptoms of CHF and pulmonary edema. They should receive on-line medical advice for patients with high-risk presentations.
- Begin treatment with the ABCs. Administer supplemental oxygen, initially 100% nonrebreather facemask.
- Utilize cardiac monitoring and continuous pulse oximetry.
- Obtain intravenous access, as well as a prehospital ECG, if available.
- Provide nitroglycerin sublingual or spray for active chest pain in the patient without severe hypotension and IV furosemide.

Use of diuretics, nitrates, analgesics, and inotropic agents are indicated for the treatment of CHF and pulmonary edema. Calcium channel blockers, such as nifedipine and nondihydropyridines, increase mortality and increase prevalence of recurrent CHF with chronic use. Conflicting evidence currently exists both in favor of and against the use of calcium channel blockers in the acute setting; at this time limit their acute use to patients with diastolic dysfunction and heart failure, a condition not easily determined in the emergency department.

Angiotensin converting enzyme (ACE) inhibitors, such as SL captopril or IV enalapril, may rapidly reverse hemodynamic instability and symptoms, possibly avoiding an otherwise imminent intubation. Haude compared 25 mg of SL captopril with 0.8 mg of sublingual nitroglycerin in 24 patients with class III and class IV CHF and found that captopril induces a more sustained and more pronounced improvement in hemodynamics. Annane gave 1 mg of IV enalapril to 20 patients presenting with acute class III and class IV CHF over 2 hours and demonstrated rapid

hemodynamic improvement with no significant adverse effects on cardiac output or hepatosplanchnic measurements.

Captopril may play a unique role in sustaining patients with renal failure and concomitant acute CHF while awaiting definitive therapy with dialysis. Since the information on this subject is still controversial and limited to small studies, the routine use of ACE inhibitors cannot be recommended at this time. ACE inhibitors remain a promising area in need of further study.

Beta-blockers, possibly by restoring beta-1 receptor activity or via prevention of catecholamine activity, appear to be cardioprotective in patients with depressed left ventricular function. The US Carvedilol Heart Failure study group demonstrated a two-thirds decrease in mortality in patients taking carvedilol with left ventricular ejection fractions of 35% or less. Beta-blockers, particularly carvedilol, have been shown to improve symptoms in patients with moderate-to-severe heart failure. The role of beta-blockers in the acute setting, however, is currently unclear; limit use until hemodynamic studies indicate that further deterioration will not occur.

Because differentiating CHF and asthma exacerbations is often difficult, treating both with the shotgun approach is often used, particularly as both may cause bronchospasm. Aerosolized beta-2 agonists, which are the more selective of beta-agonists, decrease tachycardia, dysrhythmias, and cardiac work while transiently enhancing cardiac function. Terbutaline has been shown to be successful in this setting, as well as albuterol, isoetharine, and bitolterol.

Limit roles of theophylline and aminophylline in the acute setting. They are positive inotropic agents mediated by an increase in catecholamines, and they dilate coronaries and exert mild diuretic effects. Nevertheless, they can exacerbate dysrhythmias (eg, multifocal atrial tachycardia [MAT], ischemia) by increasing cardiac work.

## **Lesson 6. RESPIRATORY EMERGENCY**

### **Asphyxia**

**Asphyxia can literally be translated from the Greek as meaning 'absence of pulse', but is usually the term given to deaths due to 'anoxia' or 'hypoxia'.**

The term 'asphyxia' is thought by some forensic pathologists to be a vague and confusing term. In its broadest sense it refers to a state in which the body becomes deprived of oxygen while in excess of carbon dioxide (ie. hypoxia and hypercapnoea). This results in a loss of consciousness and/or death. However, prior to any death the body usually reaches a low oxygen-high carbon dioxide state, and so an 'asphyxial' death is therefore one in which the oxygen deprived state has been achieved unnaturally.

When oxygen is not able to reach the lungs because of external occlusion of the mouth and/ or nose, or the airway at the level of the larynx is obstructed (eg by a bolus of food), the cause of the asphyxial death is 'obstruction of the airways'. There are no specific autopsy findings that would support the main types of airway obstruction deaths, and circumstantial evidence, physical evidence (eg plastic bags used by the deceased) and the scene of death would be relied on to support the diagnosis.

### **Exhaustion or Displacement of Environmental Oxygen (Suffocation)**

This may occur in tight or confined spaces, where toxic fumes are released from bedding etc in cots, or in drowning (the inhaled water displaces the oxygen).

This is 'pure' asphyxia and results in a fairly rapid, painless loss of consciousness, followed by death if not discovered. There are no diagnostic autopsy findings.

## Asthma

Asthma is a common disorder that accounts for almost 2 million visits to the Emergency department each year in the United States. On average, this represents approximately 2% of all ED visits. In urban centers, however, acute asthma may comprise up to 10% of all ED visits.

**History:** Specific historical factors are key in the assessment of acute asthma. The patient should be asked about the following aspects of their disease to help gauge the severity of this episode.

- Precipitating factors may include the following:
  - Viral upper respiratory infection
  - Allergen exposure (dustmite, animal dander, mold)
  - Smoke inhalation
  - Change in weather
- Current medications and compliance (eg, frequency of inhaled beta-agonist treatments, use and dose of inhaled corticosteroids)
- Past asthma-related healthcare utilization, including both the frequency of events in last 12 months and the length of time since most recent event:
  - Systemic corticosteroids for an asthma exacerbation
  - ED visits for asthma exacerbation
  - Overnight hospitalization or other admissions for asthma exacerbation
  - ICU admission for severe asthma exacerbation
  - Endotracheal intubation
- Duration of present symptoms (eg, hours to days): Duration of more than 2 days is associated with a higher admission rate than duration of less than 2 days. Sudden-onset exacerbations (ie,  $\leq 3$  hours since symptom onset) tend to be more severe but also tend to respond better to treatment in the ED and an inpatient setting.
- Degree of dyspnea, cough, wheezing; whether new productive cough is present
- Ask about a patient's baseline peak flow or personal best peak flow. Many patients know these values, and they can serve as a comparison against current peak flow and help set a goal for improvement in the ED.
- The clinician should address whether the condition is truly asthma. Many other causes of dyspnea, cough, and wheezing exist and include the following:

- Chronic obstructive pulmonary disease (COPD), which usually requires smoking more than 20 pack-years of cigarette smoking
- Bronchopulmonary dysplasia, cystic fibrosis, sarcoidosis, or other pulmonary disease
- History of heart disease (cardiac asthma)
- Presence of chest pain or pleuritis, which may suggest a complication of more severe exacerbations

### **Physical:**

- Level of alertness
- Ability to lie flat: Patients with mild acute asthma are able to lie flat. In more severe cases, the patient assumes a sitting position. As the severity increases, the patient increasingly assumes a hunched-over sitting position with the hands supporting the torso, termed the tripod position. If symptomatology becomes more severe, profuse diaphoresis occurs. The diaphoresis presents concomitantly with a rise in PCO<sub>2</sub> and hypoventilation. In the most severe form of acute asthma, the patient may struggle for air and/or be bradypneic and be profusely diaphoretic; almost no breath sounds may be heard, and the patient is willing to lie recumbent.
- Ability to speak/staccato speech
- Stridor
- Accessory muscle use - In children, also look for supraclavicular and intercostal retractions and nasal flaring as well as abdominal breathing.
- Central cyanosis
- Peripheral edema
- Subcutaneous emphysema
- Bilateral breath sounds
- Wheezing: Inspiration-expiration ratio reveals prolongation of the expiratory phase (eg, 1:1 mild, 1:3 severe). Wheezing may be absent both during a severe presentation with very poor air exchange or in mild exacerbations. In a situation with mild exacerbation, request rapid forced expiration to see if a wheeze becomes audible.
- Peak flow measurements: A peak flow value should be obtained early in the course of the ED visit to document severity as well as to serve as a baseline against which improvement may be measured.

**Prehospital Care:** Therapy for acute asthma can be initiated in the prehospital setting consistent with EMS providers' legally authorized scope of practice and local medical direction. The primary treatment approach is administration of supplemental oxygen and inhaled bronchodilators. The latter treatment most often involves inhaled beta2-agonists given by hand-held nebulizer or using a

metered-dose inhaler (MDI) with spacer (holding chamber). If these delivery devices are not available, subcutaneous epinephrine or terbutaline can be given for severe exacerbations.

When initiating bronchodilator use, EMS personnel should not delay patient transport to the appropriate medical facility—which remains a high priority. If necessary, and again consistent with the scope of practice and local medical direction, bronchodilator treatments may be repeated while transporting patients. Prolonged transport times (eg, in rural settings or during transport on congested urban streets) may necessitate multiple bronchodilator treatments before arrival to the medical facility. To improve prehospital care, ambulance services are encouraged to develop protocols for the management of acute asthma in children and adults. Recently, a model protocol was developed by a CDC-funded workgroup to help advance this process.

### **Emergency Department Care:**

- The mainstay of ED therapy for acute asthma is inhaled beta<sub>2</sub>-agonists. The most effective particle sizes are 1-5  $\mu$ m. Larger particles are ineffective because they are deposited in the mouth and central airways. Particles smaller than 1  $\mu$ m are too small to be effective since they move in the airways by Brownian motion and do not reach the lower airways.
- Standard delivery systems and routes are as follows:
  - Albuterol 2.5-5 mg every 20 minutes for 3 doses, then 2.5-10 mg every 1-4 hours as needed. Dilution of 2.5 mg in 3-4 mL of saline or use of premixed nebulizers is standard. Oxygen or compressed air delivery of the inhaled beta-agonists should be at a rate of 6-8 L/min. For children, use 0.15 mg/kg (minimum dose 2.5 mg) every 20 minutes for 3 doses then 0.15-0.3 mg/kg up to 10 mg every 1-4 hours as needed.
  - An equivalent method of beta-agonist delivery in mild-to-moderate exacerbations is the MDI used in conjunction with a spacer or holding chamber. For severe exacerbations, it is less clear if nebulized versus MDI/spacer delivery is truly equivalent. Each puff delivers a standard 90 mcg of albuterol. The dose is 4-8 puffs every 20 minutes up to 4 hours, then every 1-4 hours as needed. A potential advantage of the MDI/holding chamber is that it requires little or no assistance from the respiratory therapist once the patient understands how to use administer the medication; the patient can be discharged from the ED with the same spacer and albuterol canister. This modality is especially effective in areas where patients may be unable to afford their inhaled beta-agonists.
  - Continuous nebulization may be superior to the MDI/holding chamber method in a patient with severe exacerbations (eg, PEF <200 L/min). The dose of albuterol is 10-15 mg in 70 mL of isotonic saline. For children, this method is reserved for severe asthma at an albuterol dose of 0.5 mg/kg/h. Based on meta-analyses, there is no advantage of intravenous albuterol over inhaled albuterol, even in severe asthma. However, the role of parenteral beta-agonists in addition to inhaled beta-agonist treatments is uncertain.
- In general, 3-4 hours in the ED is adequate time to determine if a patient with acute asthma has improved symptomatically and demonstrates pulmonary flow rates sufficiently improved for safe discharge. To allow time for corticosteroids to take effect, extended treatment in a clinical holding area has been demonstrated to be effective. Such observation units have avoided 60% of admissions to the hospital for acute asthma by treating and

observing the patient for as long as 12 hours. These units are appropriate if nursing care and monitoring are adequate. They provide an excellent site for specialized asthma education.

Antibiotics should be administered only if bacterial sinusitis, bronchitis, or pneumonia is suspected clinically. Asthma exacerbation severity and therapeutic choices instituted should be evaluated according to the percent of predicted FEV1 or PEF. The 2002 National Asthma Education and Prevention Program (NAEPP) cutpoints are less than 50% (severe exacerbation), 50-79% (moderate exacerbation), and 80% or higher (mild exacerbation). Some experts believe that more appropriate cutpoints are less than 40% as “severe” (because that is the approximate percentage predicted where several adjunct therapies, such as continuous nebulization and intravenous magnesium, begin to work) and 70% or higher as “mild” (because that is the target PEF for discharge of patients from the ED).

*Corticosteroids* -- These anti-inflammatory agents have myriad effects, including restoration of beta2-agonist receptors in the bronchial smooth muscles and, therefore, improved response to beta2-agonists.

Corticosteroids are indicated in all patients with severe exacerbations and in the vast majority of patients with moderate exacerbations. If response to the first or second beta2-agonist inhaler treatment is incomplete, this too is an indication for corticosteroids in most patients.

Additional high-risk patients for whom corticosteroids may be recommended are those who require frequent ED visits, have been admitted with asthma exacerbations, have been intubated, are already on outpatient steroids, or have been experiencing an episode for longer than 2-3 days.

The onset of action of corticosteroids is approximately 4-6 hours. The bioavailability of orally and parenterally administered steroids is the same, and numerous randomized double-blind trials have demonstrated this equivalence. A primary reason to use intravenous corticosteroids is the adage to avoid medications by mouth when intubation is imminent. However, for most ED patients with acute asthma, the use of oral corticosteroids obviates

### **Complications:**

- Complications of severe asthma include the following:

- Respiratory distress/arrest
- Death

### **Prognosis:**

- The prognosis is excellent if compliant with proper therapies.
- Risk factors for death from asthma include labile asthma, history of more than 3 ED visits or more than 2 hospitalizations, either ICU admission or endotracheal intubation within the past year, recent withdrawal from corticosteroids, current use of systemic corticosteroids, comorbid conditions (eg, heart disease, psychiatric disease, drug abuse), and concomitant adverse socioeconomic conditions.

## Pneumonia

**Pneumonia** is an illness of the lungs and respiratory system in which the alveoli (microscopic air-filled sacs of the lung responsible for absorbing oxygen from the atmosphere) become inflamed and flooded with fluid. Pneumonia can result from a variety of causes, including infection with bacteria, viruses, fungi, or parasites. Pneumonia may also occur from chemical or physical injury to the lungs.

Typical symptoms associated with pneumonia include cough, chest pain, fever, and difficulty in breathing. Diagnostic tools include x-rays and examination of the sputum. Treatment depends on the cause of pneumonia; bacterial pneumonia is treated with antibiotics.

Pneumonia is a common illness which occurs in all age groups, and is a leading cause of death among the elderly and people who are chronically and terminally ill. Vaccines to prevent certain types of pneumonia are available. The prognosis depends on the type of pneumonia, the appropriate treatment, any complications, and the person's underlying health.

## Symptoms

**Pneumonia** fills the lung's alveoli with fluid, keeping oxygen from reaching the bloodstream. The alveolus on the left is normal, while the alveolus on the right is full of fluid from pneumonia.

People with infectious pneumonia often have a cough that produces greenish or yellow sputum and a high fever that may be accompanied by shaking chills. Shortness of breath is also common, as is pleuritic chest pain, a sharp or stabbing pain, either felt or worse during deep breaths or coughs. People with pneumonia may cough up blood, experience headaches, or develop sweaty and clammy skin. Other symptoms may include loss of appetite, fatigue, blueness of the skin, nausea, vomiting, mood swings, and joint pains or muscle aches. Less common forms of pneumonia can cause other symptoms. For instance, pneumonia caused by Legionella may cause abdominal pain and diarrhea, while pneumonia caused by tuberculosis or Pneumocystis may cause only weight loss and night sweats. In elderly people the manifestations of pneumonia may not be typical. Instead, they may develop new or worsening confusion or may experience unsteadiness leading to falls. Infants with pneumonia may have many of the symptoms above, but in many cases, they are simply sleepy or have decreased appetite.

## Physical examination

Individuals with symptoms of pneumonia need medical evaluation. Physical examination by a health care provider may reveal fever or sometimes low body temperature, an increased respiratory rate, low blood pressure, a fast heart rate, or a low oxygen saturation, which is the amount of oxygen in the blood as indicated by either pulse oximetry or blood gas analysis. People who are struggling to breathe, confused, or who have cyanosis (blue-tinged skin) require immediate attention.



**Pneumonia as seen on chest x-ray.** A: Normal chest x-ray. B: Abnormal chest x-ray with shadowing from pneumonia in the right lung (left side of image).

Listening to the lungs with a stethoscope (auscultation) can reveal several things. A lack of normal breath sounds, the presence of crackling sounds (rales), or increased loudness of whispered speech (whispered pectoriloquy) can identify areas of the lung that are stiff and full of fluid, called

"consolidation." The examiner may also feel the way the chest expands (palpation) and tap the chest wall (percussion) to further localize consolidation. The examiner may also palpate for increased vibration of the chest when speaking (tactile fremitus).<sup>[1]</sup>

### **Chest X-rays, sputum cultures, and other tests**

An important test for detecting pneumonia in unclear situations is a chest x-ray. Chest x-rays can reveal areas of opacity (seen as white) which represent consolidation. Pneumonia is not always seen on x-rays, either because the disease is only in its initial stages, or because it involves a part of the lung not easily seen by x-ray. In some cases, chest CT (computed tomography) can reveal pneumonia that is not seen on chest x-ray. X-rays can be misleading, because other problems, like lung scarring and congestive heart failure, can mimic pneumonia on x-ray. Chest x-rays are also used to evaluate for complications of pneumonia. (*See below.*)

If an individual is not getting better with antibiotics, or if the health care provider has concerns about the diagnosis, a culture of the person's sputum may be requested. Sputum cultures generally take at least two to three days, so they are mainly used to confirm that the infection is sensitive to an antibiotic that has already been started. A blood sample may similarly be cultured to look for infection in the blood (blood culture). Any bacteria identified are then tested to see which antibiotics will be most effective.

A complete blood count may show a high white blood cell count, indicating the presence of an infection or inflammation. In some people with immune system problems, the white blood cell count may appear deceptively normal. Blood tests may be used to evaluate kidney function (important when prescribing certain antibiotics) or to look for low blood sodium. Low blood sodium in pneumonia is thought to be due to extra anti-diuretic hormone produced when the lungs are diseased (SIADH). Specific blood serology tests for other bacteria (*Mycoplasma*, *Legionella* and *Chlamydophila*) and a urine test for *Legionella* antigen are available. Respiratory secretions can also be tested for the presence of viruses such as influenza, respiratory syncytial virus, and adenovirus.

### ***Community-acquired pneumonia***

Community-acquired pneumonia (CAP) is infectious pneumonia in a person who has not recently been hospitalized. CAP is the most common type of pneumonia. The most common causes of CAP differ depending on a person's age, but they include *Streptococcus pneumoniae*, viruses, the atypical bacteria, and *Haemophilus influenzae*. Overall, *Streptococcus pneumoniae* is the most common cause of community-acquired pneumonia worldwide. Gram-negative bacteria cause CAP in certain at-risk populations. CAP is the fourth most common cause of death in the United Kingdom and the sixth in the United States. An outdated term, walking pneumonia, has been used to describe a type of community-acquired pneumonia of less severity (hence the fact that the patient can continue to "walk" rather than require hospitalization). Walking pneumonia is usually caused by a virus or by atypical bacteria.

### ***Hospital-acquired pneumonia***

Hospital-acquired pneumonia, also called nosocomial pneumonia, is pneumonia acquired during or after hospitalization for another illness or procedure with onset at least 72 hrs after admission. The causes, microbiology, treatment and prognosis are different from those of community-acquired pneumonia. Up to 5% of patients admitted to a hospital for other causes subsequently develop pneumonia. Hospitalized patients may have many risk factors for pneumonia, including mechanical



ventilation, prolonged malnutrition, underlying heart and lung diseases, decreased amounts of stomach acid, and immune disturbances. Additionally, the microorganisms a person is exposed to in a hospital are often different from those at home. Hospital-acquired microorganisms may include resistant bacteria such as MRSA, Pseudomonas, Enterobacter, and Serratia. Because individuals with hospital-acquired pneumonia usually have underlying illnesses and are exposed to more dangerous bacteria, it tends to be more deadly than community-acquired pneumonia. Ventilator-associated pneumonia (VAP) is a subset of hospital-acquired pneumonia. VAP is pneumonia which occurs after at least 48 hours of intubation and mechanical ventilation.

## Treatment

Most cases of pneumonia can be treated without hospitalization. Typically, oral antibiotics, rest, fluids, and home care are sufficient for complete resolution. However, people with pneumonia who are having trouble breathing, people with other medical problems, and the elderly may need more advanced treatment. If the symptoms get worse, the pneumonia does not improve with home treatment, or complications occur, the person will often have to be hospitalized.

Amoxicillin is the antibiotic selected for most patients with **community-acquired pneumonia**, sometimes with added clarithromycin; patients allergic to penicillins are given erythromycin instead of amoxicillin. In North America, where the "atypical" forms of community-acquired pneumonia are becoming more common, azithromycin, clarithromycin, and the fluoroquinolones have displaced amoxicillin as first-line treatment. The duration of treatment has traditionally been seven to ten days, but there is increasing evidence that shorter courses (as short as three days) are sufficient.

Antibiotics **for hospital-acquired pneumonia** include vancomycin, third- and fourth-generation cephalosporins, carbapenems, fluoroquinolones, and aminoglycosides. These antibiotics are usually given intravenously. Multiple antibiotics may be administered in combination in an attempt to treat all of the possible causative microorganisms. Antibiotic choices vary from hospital to hospital because of regional differences in the most likely microorganisms, and because of differences in the microorganisms' abilities to resist various antibiotic treatments.

People who have difficulty breathing due to pneumonia may require extra oxygen. Extremely sick individuals may require intensive care treatment, often including intubation and artificial ventilation.

Viral pneumonia caused by influenza A may be treated with rimantadine or amantadine, while viral pneumonia caused by influenza A or B may be treated with oseltamivir or zanamivir. These treatments are beneficial only if they are started within 48 hours of the onset of symptoms. Many strains of H5N1 influenza A, also known as avian influenza or "bird flu," have shown resistance to rimantadine and amantadine. There are no known effective treatments for viral pneumonias caused by the SARS coronavirus, adenovirus, hantavirus, or parainfluenza virus.

## Complications

Sometimes pneumonia can lead to additional complications. Complications are more frequently associated with bacterial pneumonia than with viral pneumonia. The most important complications include:

## Respiratory and circulatory failure

Because pneumonia affects the lungs, often people with pneumonia have difficulty breathing, and it may not be possible for them to breathe well enough to stay alive without support. Non-invasive breathing assistance may be helpful, such as with a bilevel positive airway pressure machine. In other cases, placement of an endotracheal tube (breathing tube) may be necessary, and a ventilator may be used to help the person breathe.

Pneumonia can also cause respiratory failure by triggering acute respiratory distress syndrome (ARDS), which results from a combination of infection and inflammatory response. The lungs quickly fill with fluid and become very stiff. This stiffness, combined with severe difficulties extracting oxygen due to the alveolar fluid, create a need for mechanical ventilation.



**Pleural effusion.** Chest x-ray showing a pleural effusion. The A arrow indicates "fluid layering" in the right chest. The B arrow indicates the width of the right lung. The volume of useful lung is reduced because of the collection of fluid around the lung.

Sepsis and septic shock are potential complications of pneumonia. Sepsis occurs when microorganisms enter the bloodstream and the immune system responds by secreting cytokines. Sepsis most often occurs with bacterial pneumonia; *Streptococcus pneumoniae* is the most common cause. Individuals with sepsis or septic shock need hospitalization in an intensive care unit. They often require intravenous fluids and medications to help keep their blood pressure from dropping too low. Sepsis can cause liver, kidney, and heart damage, among other problems, and it often causes death.

## Pleural effusion, empyema, and abscess

Occasionally, microorganisms infecting the lung will cause fluid (a pleural effusion) to build up in the space that surrounds the lung (the pleural cavity). If the microorganisms themselves are present in the pleural cavity, the fluid collection is called an empyema. When pleural fluid is present in a person with pneumonia, the fluid can often be collected with a needle (thoracentesis) and examined. Depending on the results of this examination, complete drainage of the fluid may be necessary, often requiring a chest tube. In severe cases of empyema, surgery may be needed. If the fluid is not drained, the infection may persist, because antibiotics do not penetrate well into the pleural cavity.

Rarely, bacteria in the lung will form a pocket of infected fluid called an abscess. Lung abscesses can usually be seen with a chest x-ray or chest CT scan. Abscesses typically occur in aspiration pneumonia and often contain several types of bacteria. Antibiotics are usually adequate to treat a lung abscess, but sometimes the abscess must be drained by a surgeon or radiologist.

## Pneumothorax

In medicine (pulmonology), a **pneumothorax**, or **collapsed lung**, is a potential medical emergency caused by accumulation of air or gas in the pleural cavity, occurring as a result of disease or injury

## Aetiology

It can result from:

- A penetrating chest wound
- Barotrauma to the lungs
- Spontaneously (most commonly in tall slim young males and in Marfan syndrome)
- Chronic lung pathologies including emphysema, asthma
- Acute infections
- Acupuncture
- Chronic infections, such as tuberculosis
- Cancer
- Catamenial pneumothorax (due to endometriosis in the chest cavity)

Pneumothoraces are divided into tension and non-tension pneumothoraces. A tension pneumothorax is a medical emergency as air accumulates in the pleural space with each breath. The remorseless increase in intrathoracic pressure results in massive shifts of the mediastinum away from the affected lung compressing intrathoracic vessels. A non-tension pneumothorax by contrast is a less severe pathology because the air in the pneumothorax is able to escape.

The accumulation of blood in the thoracic cavity (hemothorax) exacerbates the problem, creating a pneumohemothorax.

## Signs and symptoms

Sudden shortness of breath, cyanosis (turning blue) and pain felt in the chest and/or back are the main symptoms. In penetrating chest wounds, the sound of air flowing through the puncture hole may indicate pneumothorax, hence the term "sucking" chest wound. The flopping sound of the punctured lung is also occasionally heard.

If untreated, hypoxia may lead to loss of consciousness and coma. In addition, shifting of the mediastinum away from the site of the injury can obstruct the superior and inferior vena cava resulting in reduced cardiac preload and decreased cardiac output. Untreated, a severe pneumothorax can lead to death within several minutes.

Spontaneous pneumothoraces are reported in young people with a tall stature. As men are generally taller than women, there is a preponderance among males. The reason for this association, while unknown, is hypothesized to be the presence of subtle abnormalities in connective tissue.

Pneumothorax can also occur as part of medical procedures, such as the insertion of a central venous catheter (an intravenous catheter) in the subclavian vein or jugular vein. While rare, it is considered a serious complication and needs immediate treatment. Other causes include mechanical ventilation, emphysema and rarely other lung diseases (pneumonia).

## Diagnosis

The absence of audible breath sounds through a stethoscope can indicate that the lung is not unfolded in the pleural cavity. This accompanied by hyperresonance (higher pitched sounds than normal) to percussion of the chest wall is suggestive of the diagnosis. If the signs and symptoms are doubtful, an X-ray of the chest can be performed, but in severe hypoxia, emergency treatment has to be administered first.

In a supine chest X-ray the deep sulcus sign is diagnostic<sup>[2]</sup>, which is characterized by a low lateral costophrenic angle on the affected side.<sup>[3]</sup> In layman's terms, the place where rib and diaphragm meet appears lower on an X-ray with a deep sulcus sign and suggests the diagnosis of pneumothorax.

## Differential Diagnosis

When presented with this clinical picture, other possible causes include:

- Acute Myocardial Infarction: presents with shortness of breath and chest pain, though MI chest pain is characteristically crushing, central and radiating to the jaw, left arm or stomach. Whilst not a lung condition, patients having an MI often happen to also have lung disease.
- Emphysema: here, delicate functional lung tissue is lost and replaced with air spaces, giving shortness of breath, and decreased air entry and increased resonance on examination. However, it is usually a chronic condition, and signs are diffuse (not localised as in pneumothorax).

## First Aid

### Chest wound

Penetrating wounds require immediate coverage with an occlusive dressing, field dressing, or pressure bandage made air-tight with petroleum jelly or clean plastic sheeting. The sterile inside of plastic bandage packaging is good for this purpose; however any airtight material, even the cellophane of a cigarette pack, can be used. A small opening, known as a flutter valve, needs to be left open, so the air can escape while the lung reinflates. Any patient with a penetrating chest wound must be closely watched at all times and may develop a tension pneumothorax or other immediately life-threatening respiratory emergency at any moment. They cannot be left alone.

### Blast injury or tension

If the air in the pleural cavity is due to a tear in the lung tissue (in the case of a blast injury or tension pneumothorax), it needs to be released. A thin needle can be used for this purpose, to relieve the pressure and allow the lung to reinflate.

### Pre-hospital care

Many paramedics can perform needle thoracocentesis to relieve intrathoracic pressure. Intubation may be required, even of a conscious patient, if the situation deteriorates. Advanced medical care and immediate evacuation are strongly indicated.

An untreated pneumothorax is an absolute contraindication of evacuation or transportation by flight.

## Clinical treatment

**Small pneumothoraces** often are managed with no treatment other than repeat observation via Chest X-rays, but most patients admitted will have oxygen administered since this has been shown to speed resolution of the pneumothorax.<sup>[4]</sup>

Pneumothoraces which are too small to require tube thoracostomy and too large to leave untreated, have been aspirated with a needle to remove the pressure, although this technique is usually reserved for tension pneumothoraces

**Larger pneumothoraces** may require tube thoracostomy, also known as chest tube placement. A tube is inserted into the chest wall outside the lung and air is extracted using a simple one way valve or vacuum and a water valve device, depending on severity. This allows the lung to re-expand within the chest cavity. The pneumothorax is followed up with repeated X-rays. If the air pocket has become small enough, the vacuum drain can be clamped temporarily or removed.

In case of penetrating wounds, these require attention, but generally only after the airway has been secured and a chest drain inserted. Supportive therapy may include mechanical ventilation.

Recurrent pneumothorax may require further corrective and/or preventive measures such as pleurodesis. If the pneumothorax is the result of bullae, then bullectomy (the removal or stapling of *bullae* or other faults in the lung) is preferred. Chemical pleurodesis is the injection of a chemical irritant that triggers an inflammatory reaction, leading to adhesion of the lung to the parietal pleura. Substances used for pleurodesis include talc, blood, tetracycline and bleomycin. Mechanical pleurodesis does not use chemicals. The surgeon "roughs" up the inside chest wall ("parietal pleura") so the lung attaches to the wall with scar tissue. This can also include a "parietal" pleurectomy, which is the removal of the "parietal" pleura; "parietal" pleura is the serous membrane lining the inner surface of the thoracic cage and facing the "visceral" pleura, which lies all over the lung surface. Both operations can be performed using keyhole surgery to minimise discomfort to the patient.

## Lesson 7. GASTROENTEROLOGY

### ABDOMINAL PAIN

The evaluation of patients presenting with abdominal pain poses a difficult challenge for the emergency physician. It will become an increasingly common problem because the elderly population in the United States is growing rapidly. The definition of elderly varies among authors, but for the purpose of this subject, age 60 years is a reasonable starting point.

Previous studies demonstrated that among elderly patients presenting to the ED with abdominal pain, at least 50% were hospitalized and 30-40% eventually had surgery for the underlying condition. These studies also showed that approximately 40% of these patients were misdiagnosed, contributing to an overall mortality of approximately 10%. However, note that no study examining the epidemiology of abdominal pain in elderly patients has been published since 1998 and that data was collected in 1994 (Marco, 1998).

In the period of time since the last of these studies was published, the availability and accuracy of emergency diagnostic techniques have improved dramatically. Computed tomography and ultrasonography were not widely used in most EDs before the mid 1990s. Today, it is relatively rare for a patient with significant abdominal pain to leave the ED without some type of advanced imaging. Diagnostic accuracy and presumably short-term mortality very likely have improved since the bulk of the studies on this subject were published.

Immune function tends to decrease with advancing age. Many elderly patients have underlying conditions such as diabetes or malignancy, further suppressing immunity. Elderly patients often have underlying cardiovascular and pulmonary disease, which decreases physiologic reserve and predisposes them to conditions such as abdominal aortic aneurysm (AAA) and mesenteric ischemia. Elderly patients also have a high incidence of asymptomatic underlying pathology. Up to one half of elderly patients have underlying cholelithiasis, one half have diverticula, and 5-10% have AAA.

Understanding that elderly patients may present very differently than their younger counterparts also is important. Elderly patients are more likely than younger patients to present with vague symptoms and have nonspecific findings on examination. Many elderly patients have a diminished sensorium, allowing pathology to advance to a dangerous point prior to symptom development. Elderly patients with acute peritonitis are much less likely to have the classic findings of an acute abdomen. They are less likely to have fever or leukocytosis. In addition, their pain is likely to be much less severe than expected for a particular disease. Because of these factors, many elderly patients with serious pathology initially are misdiagnosed with benign conditions such as gastroenteritis or constipation. They also are at greater risk of being admitted to the wrong service (eg, internal medicine when a surgeon may be required).

A careful history and physical examination as well as a high index of suspicion are crucial to prevent missed diagnoses.

**Pathophysiology:** Abdominal pain may be the presenting symptom in a wide range of diseases in elderly patients. Note that elderly patients with intra-abdominal pathology are more likely to present with symptoms other than abdominal pain, such as fever, fatigue, chest pain, or altered mental status.

### **Biliary tract disease**

- Biliary tract disease includes symptomatic cholelithiasis, choledocholithiasis, calculus and acalculous cholecystitis, and ascending cholangitis.
- In some studies, biliary tract disease is the most common diagnosis among elderly patients presenting with abdominal pain.
- Approximately 30-50% of patients older than 65 years have gallstones.
- The mortality rate of elderly patients diagnosed with cholecystitis is approximately 10%. Cholecystitis is acalculous in approximately 10% of elderly patients with the condition. Classically, the diagnosis requires the presence of right upper quadrant pain associated with fever and leukocytosis. Unfortunately, 25% of elderly patients may have no significant pain, and less than one half have fever, vomiting, or leukocytosis. The diagnosis therefore can be difficult in this age group, requiring a high index of suspicion.
- Complications of biliary tract disease include gallbladder perforation, emphysematous cholecystitis, ascending cholangitis, and gallstone ileus, which is responsible for approximately 2% of cases of small bowel obstruction in elderly patients.

### **Appendicitis**

- Appendicitis is a less common cause of abdominal pain in elderly patients than in younger patients, but the incidence among elderly patients appears to be rising. Only approximately 10% of cases of acute appendicitis occur in patients older than 60 years, whereas one half of all deaths from appendicitis occur in this age group.
- The rate of perforation in elderly patients is approximately 50%, 5 times higher than in younger adults. This is largely because 75% of elderly patients wait more than 24 hours to seek medical attention.

- The diagnosis can be difficult to make, since more than one half of patients in this age group do not present with fever or leukocytosis. Further confusing the picture, approximately one third do not localize pain to the right lower quadrant, and one fourth do not have appreciable right lower quadrant tenderness.
- Only 20% of elderly patients present with anorexia, fever, right lower quadrant pain, and leukocytosis. The initial diagnosis is incorrect in 40-50% of patients in this age range.
- All of the above factors contribute to delayed diagnosis and high complication rates. A 10-year retrospective review found that the diagnosis was delayed in 35% of patients (Lee, 2000). Again, a high index of suspicion is necessary to avoid missing this diagnosis.

### **Diverticulitis**

- The formation of diverticula in the colon is largely a product of diet and age and is relatively rare in those younger than 40 years. In the United States, diverticula are present in approximately 50-80% of patients older than 65 years.
- Diverticulitis results when diverticula become obstructed by fecal matter, resulting in lymphatic obstruction, inflammation, and perforation. By definition, diverticulitis involves at least microperforation of the colon.
- Approximately 85% of cases occur in the left colon. Right-sided diverticulitis is often more difficult to diagnose and generally is more benign.
- Elderly patients with diverticulitis are often afebrile, and an elevated WBC count is observed in less than one half. Only approximately 25% of patients have guaiac positive stool.

### **Mesenteric ischemia**

- Including mesenteric ischemia in the differential is important, even though it accounts for less than 1% of cases of abdominal pain in elderly patients.
- Mortality ranges from 70-90%, and any delay in diagnosis increases the risk of death.
- Patients classically present with severe abdominal pain despite having little tenderness on examination. Vomiting and diarrhea are often present.
- Risk factors for the development of mesenteric ischemia include atrial fibrillation, atherosclerotic disease, and low ejection fraction.
- Occasionally patients may present with recurrent episodes of postprandial abdominal pain, sometimes termed intestinal angina.

### **Bowel obstruction**

- Bowel obstruction accounts for approximately 12% of cases of abdominal pain in elderly patients. Obstruction is classified as blockage of either the small bowel or the large bowel, although the distinction can be difficult to make clinically.
- Cecal volvulus is relatively rare and typically presents clinically as small bowel obstruction. Sigmoid volvulus is much more common and often can be identified by plain abdominal radiography.
- Distension of the colon of more than 9 cm can signal impending perforation.
- Risk factors for sigmoid volvulus include inactivity and laxative use, both of which are common in elderly patients.

### **Abdominal aortic aneurysm**

- AAA is observed almost exclusively in elderly patients. Approximately 5% of men older than 65 years have AAA. The male-to-female ratio is 7:1.

- If the diagnosis of ruptured AAA is made in the hemodynamically stable patient, the mortality is approximately 25%. In patients presenting in shock, the mortality is 80%.
- Maintain a high index of suspicion, since many patients present with a clinical picture suggestive of renal colic or musculoskeletal back pain. Approximately 30% of patients with ruptured AAA are misdiagnosed initially.

### **Peptic ulcer disease**

- Peptic ulcer disease (PUD) deserves special mention, since the incidence among elderly patients is increasing. This may be due in part to the increasing availability and use of nonsteroidal anti-inflammatory drugs (NSAIDs). Users of NSAIDs are 5-10 times more likely to develop PUD than nonusers.
- Mortality of elderly patients with PUD is approximately 100 times higher than that of younger patients with PUD.
- Diagnosis of PUD in elderly patients can be difficult. Approximately 35% of elderly patients with PUD have no pain. The most common presenting symptom is melena.
- Complications include hemorrhage and perforation. In elderly patients perforation is often painless, and free air may be absent on plain radiographs in more than 60% of patients.

### **Malignancy**

- Among elderly patients discharged from the ED with a diagnosis of nonspecific abdominal pain, approximately 10% eventually are diagnosed with an underlying malignancy.

### **Gastroenteritis**

- Consider gastroenteritis a diagnosis of exclusion in elderly patients with vomiting and diarrhea. Vomiting and diarrhea can be caused by many illnesses. Reviews of cases of missed appendicitis reveal that approximately one half of patients initially were diagnosed with gastroenteritis.
- Even when more dangerous conditions have been excluded, realize that gastroenteritis can cause serious morbidity in elderly patients. Of all deaths due to gastroenteritis, approximately two thirds occur in patients older than 70 years.

**History:** Obtaining a careful history is especially important in elderly patients complaining of abdominal pain. Elderly patients are often less likely to volunteer key points in their symptom development and their medical history. Unfortunately, many elderly patients may be unable to give an adequate history due to predisposing conditions such as dementia or prior stroke.

- Key points in the history include the following:
  - Time of onset and course of the pain
  - Sudden or gradual onset
  - Location, quality, and severity of pain
  - Radiation (eg, to back, groin, shoulder)



- Aggravating or precipitating factors (eg, food, position, medication)
- Palliative factors
- Prior similar episodes
- Ability to pass stool or flatus
- Associated symptoms
  - § Fever, chills, or sweating
  - § Urinary symptoms (eg, dysuria, hematuria, hesitancy)
  - § Anorexia, nausea, vomiting, or diarrhea
  - § Melena or blood in the stool
  - § Dyspnea or chest pain
- Medical history can provide clues as to the possible etiology of the pain. The following are particularly important to elicit:
  - Diabetes
  - Cardiovascular disease (hypertension, coronary artery disease, atrial fibrillation, peripheral vascular disease)
  - Previous abdominal surgery
  - Smoking history
  - Alcohol use
  - NSAID use

**Physical:** A thorough physical examination can help to identify the underlying cause of abdominal pain. In general, findings on abdominal examination tend to be less pronounced than in younger patients. Give special attention to the following systems:

- Vital signs
  - Tachycardia or hypotension may be signs of ruptured AAA, septic shock, GI hemorrhage, or volume depletion.
  - Take a rectal temperature to detect fever or hypothermia.
- Pulmonary: Pneumonia occasionally may cause abdominal pain without respiratory symptoms.
- Cardiovascular
  - Acute myocardial infarction can present as epigastric pain with or without nausea and vomiting.

- The finding of atrial fibrillation or signs of diminished cardiac output should raise the consideration of mesenteric ischemia.
- Hypotension, even if transient, is an ominous sign and should elicit consideration of ruptured AAA, acute myocardial infarction, or septic shock.
- Abdominal examination
  - High-pitched bowel sounds often are associated with bowel obstruction. Absent bowel sounds may indicate adynamic ileus or advanced bowel obstruction.
  - A tympanitic abdomen may be observed with bowel obstruction.
  - Elderly patients with peritonitis may lack classic peritoneal signs of rebound and guarding.
  - A palpable mass may indicate malignancy or phlegmon from ruptured appendix or diverticulitis. A pulsatile mass should raise the consideration of AAA.
  - Carefully look for the presence of hernia at the umbilicus, in the groin, or near the site of prior surgical incisions.
- Genitourinary examination
  - Perform a rectal examination to identify tenderness, fecal impaction, and the presence of gross or occult blood. Failure to perform a rectal examination in patients with abdominal pain may be associated with an increased rate of misdiagnosis and should be considered a medicolegal pitfall.
  - Perform a pelvic examination in women regardless of whether the patient may have had a hysterectomy or is postmenopausal.

**Causes:** Causes of abdominal pain in elderly patients are as follows (see Pathophysiology for more information):

- Biliary tract disease
- Appendicitis
- Diverticulitis
- Mesenteric ischemia (risk factors include atrial fibrillation, atherosclerotic disease, and low ejection fraction)
- Bowel obstruction
  - Small bowel obstruction most often is caused by adhesions from previous surgery. In elderly patients, an incarcerated hernia causes approximately 30% of cases, and approximately 20% are caused by gallstone ileus.
  - Large bowel obstruction most often is caused by malignancy or volvulus.

- Abdominal aortic aneurysm
- Peptic ulcer disease
- Malignancy

## Gastroenteritis

### Lab Studies:

- Complete blood count
  - Generally perform a complete blood count (CBC).
  - Although an elevated white blood cell (WBC) count may indicate infection or inflammation, it has poor sensitivity and specificity. Do not make treatment decisions based on a normal WBC count in elderly patients.
- Serum chemistries
  - Comprehensive metabolic panel or basic metabolic panel with liver function tests can be useful in assessing renal function, diabetes, acidosis, biliary tract disease, and liver dysfunction.
  - An anion gap may be an indication of a serious intra-abdominal process; look for a gap and other signs of acidosis particularly with concern for ischemic bowel.
  - Again, maintain caution despite the presence of normal results of liver function tests, since elderly patients with acute cholecystitis may not demonstrate elevations.
- Serum lipase or amylase: These studies are useful as screening tests for pancreatitis. Little evidence supports obtaining both, and lipase is the superior test.
- Urinalysis
  - Urinalysis is essential to aid in excluding urinary tract infection and detecting the presence of hematuria. Hematuria can have many causes in elderly patients, including ruptured AAA.
  - In female patients, a catheterized specimen has higher specificity when evaluating for urinary tract infection.
- Blood cultures: Blood cultures are recommended for elderly patients presenting with abdominal pain associated with either fever or hypothermia or when sepsis is suspected.
- Prothrombin time (PT) and activated partial thromboplastin time (aPTT): Obtain these in patients in whom liver disease, sepsis, or GI bleeding is suspected and in those expected to require operative intervention.
- Arterial blood gases
  - This is indicated for patients in whom bowel ischemia, diabetic ketoacidosis, or sepsis is suspected.

- Arterial blood gas also is a rapid method of determining hematocrit in patients with GI bleeding or if ruptured AAA is suggested.
- Serum lactate: This is helpful in sepsis or unexplained high anion gap acidosis.
- Type and crossmatch: This is indicated in patients with GI bleeding, ruptured AAA, or in unstable patients.

### **Imaging Studies:**

- Imaging plays a larger role in the workup of elderly patients with abdominal pain than in younger patients. Preference of imaging modality may vary among institutions according to what is available.
- Plain film radiography
  - Although of limited utility in younger patients, an abdominal series may be helpful in elderly patients because of the wide differential diagnosis.
  - Plain film radiography can be useful in detecting bowel obstruction, adynamic ileus, nephrolithiasis, and perforation. Occasionally, gallstones may be observed, as well as late findings of mesenteric ischemia (ie, pneumatosis intestinalis). However, the overall sensitivity is very low and a negative abdominal series should not influence management.
- Abdominal ultrasonography
  - Generally, this is the initial study of choice when evaluating for biliary tract disease because of availability and speed.
  - Bedside ultrasonography is an excellent rapid screening test for AAA.
  - Some studies report that it is reasonably sensitive in detecting hydronephrosis and nephrolithiasis, but it is highly operator dependent and not considered the optimal test for urolithiasis.
- CT scan
  - CT plays an increasingly important role in the evaluation of elderly patients with abdominal pain, especially when the diagnosis is unclear.
  - CT scan is the study of choice for suspected diverticulitis, having a sensitivity of 93%, and is very sensitive in patients with possible appendicitis when the diagnosis is not clear.
    - § When performing CT scan to exclude diverticulitis, allow enough time for the oral contrast to reach the distal colon (usually 2-3 h).
    - § One study demonstrated that using CT scan with only water-soluble contrast administered by enema without intravenous (IV) or oral contrast had a sensitivity for diverticulitis of 99% and appeared to be safe.
    - § Avoid barium enema in patients with suspected diverticulitis.
  - In stable patients with suspected AAA, CT scanning with IV contrast is approximately 100% sensitive.

- Noncontrast helical CT scan is reported to be 95-100% sensitive in detecting nephrolithiasis and ureterolithiasis. Unfortunately, many elderly patients have vascular calcifications in the pelvis, making interpretation more difficult. The presence of ureteral dilatation or perinephric stranding can help establish the diagnosis.
- CT scanning combined with CT angiography is increasingly used in the evaluation of suspected mesenteric ischemia. In a 2000 position statement by the American Gastrointestinal Society, it was stated that CT was of limited use in the diagnosis of mesenteric ischemia. Subsequent studies have strongly advocated for the use of multidetector-row CT in the evaluation of mesenteric ischemia (Fleischmann, 2003; Cademartiri, 2004), including one prospective study that found an overall sensitivity of 96%, with specificity of 94% (Kirkpatrick, 2003). Multidetector-row CT scanning had the additional advantage of identifying an alternate diagnosis in 58% of patients without mesenteric ischemia.
- Chest radiography
  - Chest radiography is helpful in excluding pneumonia, which is a cause of abdominal pain.
  - It may demonstrate free intraperitoneal air under the diaphragm in patients with ruptured viscus. The lateral chest radiography has been demonstrated to be more sensitive in detecting free air.
- Angiography: Although this is difficult to obtain on an emergency basis in some institutions, angiography remains the study of choice for mesenteric ischemia.
- Nuclear medicine imaging (hepatic 2,6 dimethyliminodiacetic acid [HIDA] scan or diisopropyl iminodiacetic acid [DISIDA] scan): This is helpful for patients in whom cholecystitis is suspected when the diagnosis is not clear. HIDA and DISIDA scanning both provide a very high negative predictive value.

### **Other Tests:**

Electrocardiogram: Perform an ECG in all elderly patients with upper abdominal pain and in

**Prehospital Care:** Patients with severe pain, abnormal vital signs, or altered mental status should undergo the following:

- Large-bore IV placed with either normal saline or lactated Ringer solution (gauged fluid resuscitation by vital signs)
- Cardiac monitor and pulse oximetry
- Oxygen by nasal cannula or 100% face mask, depending on vital signs and pulse oximetry

### **Emergency Department Care:**

- Care in the emergency department is dictated by the severity of presentation. Assess ABCs and vital signs immediately. Place patients on a monitor and start an IV or heparin lock. Administer oxygen to patients who appear to be seriously ill.

- If the diagnosis of AAA is suggested, perform a rapid bedside ultrasound, if available.
- Administer IV boluses of normal saline or lactated Ringer solution to patients with suspected volume loss. Carefully hydrate patients with a history of renal disease or congestive heart failure to avoid volume overload.
- A Foley catheter may be helpful as a guide for volume resuscitation in patients who are sicker. Incontinence is not an indication for a Foley catheter.
- Keep all patients with abdominal pain as nothing by mouth (NPO) until surgical pathology is excluded.
- Place a nasogastric tube in patients in whom bowel obstruction, ileus, or upper GI bleeding is suspected.
- Maintain a low threshold for ordering additional tests such as CT scan or ultrasound.
- If biliary disease is suggested, dicyclomine (Bentyl) or glycopyrrolate (Robinul) may be administered for pain. NSAIDs are very effective for biliary colic but should be administered with caution to elderly patients.
- In patients with undifferentiated abdominal pain, administering small doses of opioids is reasonable. Several studies have demonstrated this to be safe and effective without decreasing diagnostic accuracy.
  - Morphine administered IV in doses of 2-4 mg is inexpensive and effective. Morphine has been demonstrated to cause spasm of the sphincter of Oddi and should be avoided in patients in whom biliary disease is suspected.
  - Meperidine (Demerol) has been the traditional opioid of choice in biliary tract disease because it causes less sphincter of Oddi spasm.
  - Depending on the practice environment, contacting the on-call surgeon prior to administering opioids may be reasonable.
- Initiate appropriate antibiotic coverage for patients in whom sepsis, cholecystitis, appendicitis, diverticulitis, or perforated viscus is suspected. Please refer to the article on the specific diagnosis for choice of antibiotics for a specific disease process (see [Differentials](#)).

### **Consultations:**

- In patients in whom ruptured AAA or mesenteric ischemia is suspected, consult a surgeon immediately.
- Consult a gastroenterologist immediately for patients with significant GI bleeding.
- When the diagnosis is uncertain, obtain surgical consultation. Discharge of an elderly patient with abdominal pain should be the exception rather than the rule.

## Lesson 8. NEPHROLOGY

### Acute nephritis

**Nephritis** is inflammation of the kidney. The word comes from the Greek *nephro-* meaning "of the kidney" and *-itis* meaning "inflammation". Nephritis is often caused by infections, toxins, and autoimmune diseases.

### Subtypes

- glomerulonephritis is inflammation of the glomeruli. (Often when the term "nephritis" is used without qualification, this is the condition meant.)
- interstitial nephritis or tubulo-interstitial nephritis is inflammation of the spaces between renal tubules.
- pyelonephritis is when a urinary tract infection has reached the pyelum (pelvis) of the kidney.
- Lupus nephritis is an inflammation of the kidney caused by systemic lupus erythematosus (SLE), a disease of the immune system.

**Glomerulonephritis**, also known as **glomerular nephritis** and abbreviated **GN'**, is a primary or secondary immune-mediated renal disease characterized by inflammation of the glomeruli, or small blood vessels in the kidneys. It may present with isolated hematuria and/or proteinuria (blood resp. protein in the urine); or as a nephrotic syndrome, a nephritic syndrome, acute renal failure, or chronic renal failure. They are categorised into several different pathological patterns, which are broadly grouped into non-proliferative or proliferative types. Diagnosing the pattern of GN is important because the outcome and treatment differs in different types. Primary causes are one which are intrinsic to the kidney, whilst secondary causes are associated with certain infections (bacterial, viral or parasitic pathogens), drugs, systemic disorders (SLE, vasculitis) or cancers.

**Pyelonephritis** is an ascending urinary tract infection that has reached the *pyelum* (pelvis) of the kidney (*nephros* in Greek). If the infection is severe, the term "**urosepsis**" is used interchangeably. It requires antibiotics as therapy. It is a form of nephritis. It can also be called *pyelitis*.

### Pathology

**Acute pyelonephritis** is an, *exudative purulent localized inflammation* of kidney and renal pelvis. The renal parenchyma presents in the interstitium abscesses (suppurative necrosis), consisting in purulent exudate (pus): neutrophils, fibrin, cell debris and central germ colonies (hematoxylinophils). Tubules are damaged by exudate and may contain neutrophil casts. In the early stages, glomeruli and vessels are normal.[1] Gross pathology often reveals pathognomonic radiations of hemorrhage and suppuration through the renale pelvis to the renale cortex. Chronic infections can result in fibrosis and scarring.

**Chronic pyelonephritis** is often caused by Xanthogranulomatous pyelonephritis.

### Causes

Ascending bacteria (such as E.coli) from lower urinary tract infections, mainly cystitis and prostatitis. true....

## Signs and symptoms

It presents with high spiking fever, backache, vomiting, dysuria (painful voiding), rigors and often also with confusion. There may be renal angle tenderness on physical examination.

## Diagnosis

Nitrite and leukocytes on a urine dipstick are often detected, which may be an indication for empirical treatment. Formal diagnosis is with culture of the urine and bloods.

In patients with recurrent ascending urinary tract infections, it may be necessary to exclude an anatomical abnormality, such as vesicoureteric reflux (urine from the bladder flowing back into the ureter).

## Treatment

Treatment is with antibiotics, which are often administered intravenously to improve the effect. Trimethoprim (or co-trimoxazole) or nitrofurantoin are often used first-line, although in full-blown pyelonephritis amoxicillin (with or without clavulanic acid), gentamycin (with or without ampicillin), fluoroquinolones (eg. ciprofloxacin) or a third generation cephalosporins are often favoured.

# RENAL CALCULI

Acute passage of a kidney stone from the renal pelvis through the ureter gives rise to pain at times so excruciating that it has been likened to the discomfort of childbirth. The often sudden, extremely painful episode of renal colic prompts more than 450,000 visits to EDs annually and places emergency physicians on the front line of management of acute nephrolithiasis. ED management is focused on excluding other serious diagnoses and providing adequate pain relief.

**Pathophysiology:** Most calculi arise in the kidney when urine becomes supersaturated with a salt that is capable of forming solid crystals. Symptoms arise as these calculi become impacted within the ureter as they pass toward the urinary bladder.

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## Emergency Department Care:



- Intravenous access should be obtained to facilitate delivery of analgesic and antiemetic medications.
- Intravenous hydration is controversial.
  - Some authorities believe that intravenous fluids hasten passage of the stone through the urogenital system. Others express concern that additional hydrostatic pressure exacerbates the pain of renal colic.
  - No data exist to support either theory. Intravenous hydration should be given to patients with clinical signs of dehydration or to those with a borderline serum creatinine level who must undergo IVP.
- Analgesia should be provided promptly.
  - The pain of renal colic is mediated by prostaglandin E2. Nonsteroidal anti-inflammatory drugs inhibit formation of this mediator, and ketorolac (the only parenteral NSAID approved by the FDA) has been proven in multiple studies to be as effective as opioid analgesics, with fewer adverse effects.
  - Opioid analgesics can be added in cases of incomplete pain control.
- Antiemetics should be administered as needed.
- Medical expulsive therapy
  - Multiple prospective randomized controlled studies (Dellabella, 2003; Dellabella, 2005; Porpiglia, 2004) have demonstrated that patients treated with oral alpha-blockers have an increased rate of spontaneous stone passage and a decreased time to stone passage. The best studied of these is tamsulosin, 0.4 mg administered daily.
  - Calcium channel blockers in combination with oral steroids have also proven efficacious in multiple studies. The most common regimen is 30-mg slow-release nifedipine daily plus oral corticosteroid such as prednisolone.
- Strain urine for stone collection.

### Consultations:

- Consult a urologist immediately in cases of ureterolithiasis with proximal UTI. Infected hydronephrosis is a true urologic emergency and requires hospital admission, intravenous antibiotics, and immediate drainage of the infected hydronephrosis via percutaneous nephrostomy or ureteral stent placement.
- Urologic consultation is also appropriate in patients who are unable to tolerate oral fluids and medications and in those with unrelenting pain, renal failure, renal transplant, a solitary functioning kidney, and history of prior stones that required invasive intervention.

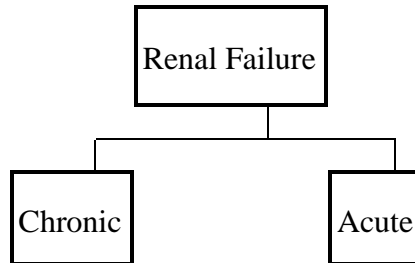
**Renal failure or kidney failure** is the condition in which the kidneys fail to function adequately.

Biochemically, it is typically detected by an elevated serum creatinine. In the science of physiology, renal failure is described as a decrease in the glomerular filtration rate

## Classification

Renal failure can broadly be divided into two categories (see flowchart below): acute renal failure and chronic renal failure.

### Renal failure classification



The type of renal failure (acute vs. chronic) is determined by the trend in the serum creatinine. Other factors which may help differentiate acute and chronic renal failure include the presence of anemia and the kidney size on ultrasound. Long-standing, i.e. chronic, renal failure generally leads to anemia and small kidney size.

## ACUTE RINAL FAILURE

Until recently, a systematic definition of acute renal failure (ARF) was lacking, which led to significant confusion both clinically and in the medical literature. In 2004, the Acute Dialysis Quality Initiative (ADQI) group published the RIFLE classification of ARF, based on changes from the patient's baseline either in serum creatinine level or glomerular filtration rate (GFR), urine output (UO), or both.

The RIFLE classification of ARF is as follows:

- Risk (R) - Increase in serum creatinine level X 1.5 or decrease in GFR by 25%, or UO <0.5 mL/kg/h for 6 hours
- Injury (I) - Increase in serum creatinine level X 2.0 or decrease in GFR by 50%, or UO <0.5 mL/kg/h for 12 hours
- Failure (F) - Increase in serum creatinine level X 3.0, decrease in GFR by 75%, or serum creatinine level  $\geq 4$  mg/dL; UO <0.3 mL/kg/h for 24 hours, or anuria for 12 hours
- Loss (L) - Persistent ARF, complete loss of kidney function >4 wk
- End-stage kidney disease (E) - Loss of kidney function >3 months

Since baseline serum creatinine level and GFRs are not readily available, the consensus committee recommends the use of the Modification of Diet in Renal Disease (MDRD) equation (see [Lab Studies](#)) to estimate the patients GFR/1.73 mm based upon: serum creatinine level, age, gender, and race. The proportional decrease in GFR should be calculated from 70 mL/min per 1.73 mm<sup>2</sup>, the agreed upon lower limit of normal.

ARF is a common entity in the ED. Emergency physicians play a critical role in recognizing early ARF, preventing iatrogenic injury, and reversing the course of ARF.

**Pathophysiology:** The driving force for glomerular filtration is the pressure gradient from the glomerulus to the Bowman space. Glomerular pressure is primarily dependent on renal blood flow

(RBF) and is controlled by combined resistances of renal afferent and efferent arterioles.

Regardless of the cause of ARF, reductions in RBF represent a common pathologic pathway for decreasing GFR. The etiology of ARF comprises 3 main mechanisms.

- Prerenal failure is defined by conditions with normal tubular and glomerular function; GFR is depressed by compromised renal perfusion.
- Intrinsic renal failure includes diseases of the glomerulus or tubule, which are associated with release of renal afferent vasoconstrictors.
- Postobstructive renal failure initially causes an increase in tubular pressure, decreasing the filtration driving force. This pressure gradient soon equalizes, and maintenance of a depressed GFR is then dependent upon renal afferent vasoconstriction.

Patients with chronic renal failure also may present with superimposed ARF from any of the aforementioned etiologies.

Depressed RBF eventually leads to ischemia and cell death. This initial ischemic insult triggers production of oxygen free radicals and enzymes that continue to cause cell injury even after restoration of RBF. Tubular cellular damage results in disruption of tight junctions between cells, allowing back leak of glomerular filtrate and further depressing effective GFR. In addition, dying cells slough off into the tubules, forming obstructing casts, which further decrease GFR and lead to oliguria.

During this period of depressed RBF, the kidneys are particularly vulnerable to further insults. This is when iatrogenic renal injury is most common. The following are common iatrogenic combinations:

- Preexisting renal disease (elderly, diabetic patients, jaundiced patients) and radiocontrast agents, aminoglycosides, atheroembolism, or cardiovascular surgery
- Angiotensin-converting enzyme (ACE) inhibitors and diuretics, small- and large-vessel renal arterial disease
- Nonsteroidal anti-inflammatory drugs (NSAIDs) and congestive heart failure (CHF), hypertension (HTN), or renal artery stenosis
- Hypovolemia and aminoglycosides, amphotericin, heme pigments, or radiologic contrast agents

Recovery from ARF is first dependent upon restoration of RBF. Early RBF normalization predicts better prognosis for recovery of renal function. In prerenal failure, restoration of circulating blood volume is usually sufficient. Rapid relief of urinary obstruction in postrenal failure results in a prompt decrease of vasoconstriction. With intrinsic renal failure, removal of tubular toxins and initiation of therapy for glomerular diseases decreases renal afferent vasoconstriction.

Once RBF is restored, the remaining functional nephrons increase their filtration and eventually hypertrophy. GFR recovery is dependent upon the size of this remnant nephron pool. If the number of remaining nephrons is below some critical value, continued hyperfiltration results in progressive glomerular sclerosis, eventually leading to increased nephron loss. A vicious cycle ensues; continued nephron loss causes more hyperfiltration until complete renal failure results. This has been termed the hyperfiltration theory of renal failure and explains the scenario in which progressive renal failure is frequently observed after apparent recovery from ARF.

**History:** Because ARF has such a long differential diagnosis, obtain a directed history along the lines of the pathophysiology of ARF (prerenal, intrinsic renal, postrenal failure).

- Prerenal failure

- Patients commonly present with symptoms related to hypovolemia, including thirst, decreased urine output, dizziness, and orthostatic hypotension.
- Look for a history of excessive fluid loss via hemorrhage, GI losses, sweating, or renal sources.
- Patients with advanced cardiac failure leading to depressed renal perfusion may present with orthopnea and paroxysmal nocturnal dyspnea.
- Insensible fluid losses can result in severe hypovolemia in patients with restricted fluid access and should be suspected in the elderly and in comatose or sedated patients.

- Intrinsic renal failure

- Patients can be divided into those with glomerular and those with tubular etiologies of ARF.
- Glomerular diseases: Nephritic syndrome of hematuria, edema, and HTN is synonymous with a glomerular etiology of ARF. Query about prior throat or skin infections. A history of an earlier episode resembling this symptom complex is often helpful in establishing a differential diagnosis.
- Tubular diseases: ATN should be suspected in any patient presenting after a period of hypotension secondary to cardiac arrest, hemorrhage, sepsis, drug overdose, or surgery.
- A careful search for exposure to nephrotoxins should include a detailed list of all current medications and any recent radiologic examinations (ie, exposure to radiologic contrast agents).
- Pigment-induced ARF should be suspected in patients with possible rhabdomyolysis (muscle tenderness, recent coma, seizures, drug abuse, alcohol, excessive exercise, limb ischemia) or hemolysis (recent blood transfusion).
- Allergic interstitial nephritis should be suspected with recent drug ingestion, fevers, rash, and arthralgias.

- Postrenal failure

- Postrenal failure usually occurs in older men with prostatic obstruction and symptoms of urgency, frequency, and hesitancy. Patients may present with asymptomatic high-grade urinary obstruction because of chronicity of their symptoms.
- History of prior gynecologic surgery or carcinoma often can be helpful in providing clues to the level of obstruction.
- Flank pain and hematuria should raise a concern about renal calculi or papillary necrosis as the source of urinary obstruction.

- Use of acyclovir, methotrexate, triamterene, indinavir, or sulfonamides implies the possibility of tubular obstruction by crystals of these medications.

### Physical:

- Hypotension and tachycardia are obvious clues to decreased renal perfusion. Evaluation for hypovolemia should include evaluations for orthostatic hypotension, mucosal membrane moisture, and tissue turgor.
- Acute fluid overload may lead to compromise of a patient's ability to oxygenate and ventilate.
- Patients also may present hypovolemic, with increased risk for iatrogenic complications of their renal failure. Physical examination should include a search for the following signs:
  - Skin
    - Livido reticularis, digital ischemia, butterfly rash, palpable purpura - Systemic vasculitis
    - Maculopapular rash - Allergic interstitial nephritis
    - Track marks (ie, intravenous drug abuse) - Endocarditis
  - Eyes
    - Keratitis, iritis, uveitis, dry conjunctivae - Autoimmune vasculitis
    - Jaundice - Liver diseases
    - Band keratopathy (ie, hypercalcemia) - Multiple myeloma
    - Signs of diabetes mellitus
    - Signs of hypertension
    - Atheroemboli (retinopathy)
  - Ears
    - Hearing loss - Alport disease and aminoglycoside toxicity
    - Mucosal or cartilage ulcerations - Wegener granulomatosis
  - Cardiac
    - Irregular rhythms (ie, atrial fibrillation) - Atheroemboli
    - Murmurs - Endocarditis
    - Increased jugulovenous distention, rales, S3 - CHF
  - Pulmonary
    - Rales - Goodpasture syndrome, Wegener granulomatosis
    - Hemoptysis - Wegener granulomatosis
  - Abdomen
    - Pulsatile mass (ie, aneurysm) - Atheroemboli

- Costovertebral angle tenderness - Nephrolithiasis, papillary necrosis
- Pelvic, rectal masses; prostatic hypertrophy; distended bladder - Urinary obstruction
- Limb ischemia, edema - Rhabdomyolysis

### **Causes:**

- Prerenal failure - Diseases that compromise renal perfusion
  - Decreased effective arterial blood volume - Hypovolemia, CHF, liver failure, sepsis
  - Renal arterial disease - Renal arterial stenosis (atherosclerotic, fibromuscular dysplasia), embolic disease (septic, cholesterol)
- Intrinsic renal failure - Diseases of the renal parenchyma, specifically involving the renal tubules, glomeruli, interstitium
  - ATN, ischemia, toxins (eg, aminoglycosides, radiocontrast, heme pigments, cisplatin, myeloma light chains, ethylene glycol)
  - Interstitial diseases - Acute interstitial nephritis, drug reactions, autoimmune diseases (eg, systemic lupus erythematosus [SLE]), infiltrative disease (sarcoidosis, lymphoma), infectious agents (Legionnaire disease, hantavirus)
  - Acute glomerulonephritis
  - Vascular diseases - Hypertensive crisis, polyarteritis nodosa, vasculitis
- Postrenal failure - Diseases causing urinary obstruction from the level of the renal tubules to the urethra
  - Tubular obstruction from crystals (eg, uric acid, calcium oxalate, acyclovir, sulfonamide, methotrexate, myeloma light chains)
  - Ureteral obstruction - Retroperitoneal tumor, retroperitoneal fibrosis (methysergide, propranolol, hydralazine), urolithiasis, papillary necrosis
  - Urethral obstruction - Benign prostatic hypertrophy; prostate, cervical, bladder, colorectal carcinoma; bladder hematoma; bladder stone; obstructed Foley catheter; neurogenic bladder; stricture

### **Lab Studies:**

- Urine output: Changes in urine output generally are poorly correlated with changes in GFR. Approximately 50-60% of all causes of ARF are nonoliguric. However, categories of anuria, oliguria, and nonoliguria may be useful in differential diagnosis of ARF.
  - Anuria (<100 mL/d) - Urinary tract obstruction, renal artery obstruction, rapidly progressive glomerulonephritis, bilateral diffuse renal cortical necrosis
  - Oliguria (100-400 mL/d) - Prerenal failure, hepatorenal syndrome

- Nonoliguria (>400 mL/d) - Acute interstitial nephritis, acute glomerulonephritis, partial obstructive nephropathy, nephrotoxic and ischemic ATN, radiocontrast-induced ARF, and rhabdomyolysis
- Urinalysis: Microscopic examination of urine is essential in establishing differential diagnosis.
  - Normal urinary sediment without hemoglobin, protein, cells, or casts generally consistent with prerenal and postrenal failure, HUS/thrombotic thrombocytopenic purpura (TTP), preglomerular vasculitis, or atheroembolism
  - Granular casts - ATN, glomerulonephritis, interstitial nephritis
  - RBC casts - Glomerulonephritis, malignant HTN
  - WBC casts - Acute interstitial nephritis, pyelonephritis
  - Eosinophiluria - Acute allergic interstitial nephritis, atheroembolism
  - Crystalluria - Acyclovir, sulfonamides, methotrexate, ethylene glycol toxicity, radiocontrast agents
- BUN: The urea concentration correlates poorly with the GFR. Because urea is highly permeable to renal tubules, urea clearance varies with urine flow rate.
  - Urea is filtered freely, but reabsorption along the tubule is a function of urine flow rate. During antidiuresis with urine flow rates less than 30 mL/h, urea clearance is as low as an estimated 30% of GFR. Under conditions of diuresis, with urine outputs greater than 100 mL/h, urea clearance can increase to 70-100% of GFR.
    - § This information can be used clinically to help differentiate prerenal failure from other etiologies of ARF.
    - § In prerenal conditions, low urine flow rates favor BUN reabsorption out of proportion to decreases in GFR, resulting in a disproportionate rise of BUN relative to creatinine, creating a serum BUN-creatinine ratio >20 in prerenal failure.
  - BUN concentration is dependent on nitrogen balance and renal function.
    - § BUN concentration can rise significantly with no decrement in GFR by increases in urea production with steroids, trauma, or GI bleeding.
    - § Tetracycline increases BUN by decreasing tissue anabolic rates.
    - § Basal BUN concentration can be depressed severely by malnutrition or advanced liver disease.
    - § Always first estimate basal BUN concentration when attempting to correlate changes in BUN with GFR. For example, in a patient with cirrhosis and a BUN of 12 mg/dL, a GFR in the normal range may be assumed. Only with the knowledge of a baseline BUN of 4 mg/dL does the real decrease in GFR become apparent.
- Creatinine: Serum creatinine provides the ED physician with the most accurate and consistent estimation of GFR. Correct interpretation of serum creatinine extends beyond just knowing normal values for the specific laboratory.
  - Creatinine measuring methods

- § Serum creatinine level varies by method of measurement, either Jaffe or iminohydrolase. Upper limit of normal creatinine can be 1.6-1.9 mg/dL or 1.2-1.4 mg/dL, respectively. This becomes important when patients present with changes in creatinine measured in different labs.
  - § Differing methods report markedly different results when interfacing with certain chemicals.
  - § Jaffe method of measuring creatinine reports falsely elevated serum creatinine in the presence of the following noncreatinine chromogens: glucose, fructose, uric acid, acetone, acetoacetate, protein, ascorbic acid, pyruvate, cephalosporin antibiotics. High levels of bilirubin cause reports of falsely low creatinine by the Jaffe method.
  - § Extremely high glucose levels and the antifungal agent flucytosine interfere with the iminohydrolase method.
- Serum creatinine is a reflection of creatinine clearance.
    - § Serum creatinine is a function of its production and excretion rates.
    - § Creatinine production is determined by muscle mass. Serum creatinine must always be interpreted with respect to patient's weight, age, and sex. The GFR can be estimated by the following formulas: The ADQI consensus committee on ARF favors the Modification of Diet in Renal Disease (MDRD) equation to estimate GFR (70 mL/min per 1.73 mm<sup>2</sup> is considered the lower limit of normal).
 

Cockcroft-Gault equation:  $GFR \text{ mL/min} = (140 - \text{age } y)(\text{weight kg})(0.85 \text{ if female})/(72 \times \text{serum creatinine mol/L})$

MDRD equation:  $GFR, \text{ in mL/min per } 1.73 \text{ mm}^2 = 186.3 \times ((\text{serum creatinine}) \exp[-1.154]) \times (\text{Age} \exp[-0.203]) \times (0.742 \text{ if female}) \times (1.21 \text{ if African American})$
    - § For example, GFR decreases by 1% per year after age 40, yet serum creatinine generally remains stable. Balance is achieved via a decrease in muscle mass with age, which matches the fall in GFR.
    - § Men generally have a higher muscle mass per kilogram of body weight and thus a higher serum creatinine than women.
  - Changes in serum creatinine reflect changes in GFR. Rate of change in serum creatinine is an important variable in estimating GFR. Stable changes in serum creatinine correlate with changes in GFR by the following relationships:
    - § Creatinine 1.0 mg/dL - Normal GFR
    - § Creatinine 2.0 mg/dL - 50% reduction in GFR
    - § Creatinine 4.0 mg/dL - 70–85% reduction in GFR
    - § Creatinine 8.0 mg/dL - 90–95% reduction in GFR
    - § As suggested by these data, knowledge of a patient's baseline creatinine becomes very important. Small changes with low baseline levels of creatinine are important clinically much more than large changes with high basal creatinine. Significant decrements in GFR can occur in the normal range of creatinine.



- § Certain diseases and medications can interfere with the correlation of serum creatinine with GFR. Acute glomerulonephritis causes increased tubular secretion of creatinine, falsely depressing the rise in serum creatinine when ARF occurs in acute glomerulonephritis. Trimethoprim and cimetidine cause decreased creatinine secretion and a falsely elevated creatinine with no change in GFR.
- Complete blood count
  - Leukocytosis is common in ARF.
  - Leukopenia and thrombocytopenia suggest SLE or TTP.
  - Anemia and rouleaux formation suggest multiple myeloma.
  - Microangiopathic anemia suggests TTP or atheroemboli.
  - Eosinophilia suggests allergic interstitial nephritis, polyarteritis nodosa, or atheroemboli.
  - Coagulation disturbances indicate liver disease or hepatorenal syndrome.
- Blood chemistry
  - Creatine phosphokinase (CPK) elevations are seen in rhabdomyolysis and myocardial infarction.
  - Elevations in liver transaminases are seen in rapidly progressive liver failure and hepatorenal syndrome.
  - Hypocalcemia (moderate) is common in ARF.
  - Hyperkalemia is a common complication of ARF.
- Urine chemical indices
  - Differentiation of prerenal azotemia from ATN takes on a special importance in early management of these patients.
  - Aggressive fluid resuscitation is appropriate in prerenal ARF. However, rapid fluid infusion in a patient with ATN who is unable to excrete the extra fluid could result in life-threatening volume overload.
  - To help with the differentiation of prerenal azotemia, analysis of urine may provide important clues. If possible, collect urine prior to any administration of diuretics.
  - Urine indices that suggest prerenal ARF include the following:
    - § Urine specific gravity  $>1.018$
    - § Urine osmolality (mOsm/kg  $H_2O$ )  $>500$
    - § Urine sodium (mEq/L)  $<15-20$
    - § Plasma BUN/creatinine ratio  $>20$
    - § Urine/plasma creatinine ratio  $>40$
  - Urine indices that suggest ATN include the following:
    - § Urine specific gravity  $<1.012$
    - § Urine osmolality (mOsm/kg  $H_2O$ )  $<500$
    - § Urine sodium (mEq/L)  $>40$
    - § Plasma BUN/creatinine ratio  $<10-15$
    - § Urine/plasma creatinine ratio  $<20$
- Calculation of fractional excretion of sodium (FeNa)

- $\text{FeNa} = (\text{urine Na}/\text{plasma Na})/(\text{urine creatinine}/\text{plasma creatinine})$
  - $\text{FeNa} < 1\% = \text{prerenal ARF}$
  - $\text{FeNa} > 1\% = \text{ATN}$
- Advantages of FeNa compared to other indices
    - Physiologic measure of sodium reabsorption
    - Measured creatinine and sodium clearances, accounting for filtration and reabsorption of sodium
    - FeNa increased before oliguric phase established and predictive of incipient ARF
  - Exceptions (intrinsic renal failure with  $\text{FeNa} < 1\%$ )
    - Urinary tract obstruction
    - Acute glomerulonephritis
    - Hepatorenal syndrome
    - Radiologic contrast-induced ATN
    - Myoglobinuric and hemoglobinuric ARF
    - Renal allograft rejection
    - Drug-related alterations in renal hemodynamics (eg, captopril, NSAIDs)

### **Imaging Studies:**

- Imaging studies in ARF are most important in the emergent workup of suspected postrenal azotemia. Please refer to Urinary Obstruction for a complete discussion of available imaging studies for this cause of ARF.
- Chest radiography
  - Obtain chest radiographs on a routine basis to look for evidence of volume overload.
  - Findings of lung infiltration can lead to pulmonary/renal syndromes, such as Wegener granulomatosis and Goodpasture syndrome, or evidence of pulmonary emboli from endocarditis or atheroembolic disease.

### **Other Tests:**

- Electrocardiography: Obtain routine ECGs to look for manifestations of hyperkalemia and arrhythmias, such as atrial fibrillation, related to atheroemboli.

### **Procedures:**

- Renal biopsy
  - Often helpful in finding specific cause of renal failure; however, not an ED procedure
  - Reserved for evaluation of ARF when cause cannot be determined
  - Especially important when glomerular causes of ARF are suspected

- Often helpful in finding specific cause of renal failure

**Prehospital Care:** Stabilize acute life-threatening conditions and initiate supportive therapy.

**Emergency Department Care:** Treatment of ARF ideally should begin before the diagnosis of ARF is firmly established. A high index of suspicion often is necessary to diagnose early ARF. Significant decreases in GFR frequently occur before indirect measures of GFR reveal a problem. All seriously ill medical patients (eg, elderly patients, diabetic patients, hypovolemic patients) should have ARF included early in their differential diagnosis.

- Physicians can play a pivotal role in reversing many of the underlying causes and preventing further iatrogenic renal injury if ARF is recognized early. After providing an adequate airway and ventilation, focus on fluid management of the ARF patient.
- Fluid management
  - Patients with ARF represent challenging fluid management problems.
  - Hypovolemia potentiates and exacerbates all forms of ARF.
  - Reversal of hypovolemia by rapid fluid infusion often is sufficient to treat many forms of ARF. However, rapid fluid infusion can result in life-threatening fluid overload in patients with ARF.
  - Accurate determination of a patient's volume status is essential and may require invasive hemodynamic monitoring if physical examination and laboratory results do not lead to a definite conclusion.
- Urinary catheter placement
  - Urinary obstruction often is an easily reversible cause of ARF.
  - Placement of a urinary catheter early in the workup of a patient with ARF not only allows diagnosis and treatment of urethral and bladder outlet urinary obstruction, and allows for accurate measurement of urine output.
  - If available, bedside ultrasonography can quickly identify a large and distended bladder.
  - Routine use of urinary catheters should be tempered by consideration of their inherent risks of introducing infections.

## Chronic renal failure

Chronic renal failure (CRF) can either develop slowly and show few initial symptoms, be the long term result of irreversible acute disease or be part of a disease progression. There are many causes of CRF. The most common cause is diabetes mellitus. End-stage renal failure (ESRF) is the ultimate consequence, in which case dialysis is required unless a donor for a renal transplant is found.

## Acute or chronic renal failure

Acute renal failure can be present on top of chronic renal failure. This is called acute-on-chronic renal failure (AoCRF). The acute part of AoCRF may be reversible and the aim of treatment, as with ARF, is to return the patient to their baseline renal function, which is typically measured by

serum creatinine. AoCRF, like ARF, can be difficult to distinguish from chronic renal failure, if the patient has not been monitored by a physician and no baseline (i.e., past) blood work is available for comparison. Use of the term *uremia*. Before the advancement of modern medicine, renal failure was often referred to as uremic poisoning. Uremia was the term used to describe the contamination of the blood with urine. Starting around 1847, this term was used to describe reduced urine output, now known as oliguria, that was thought to be caused by the urine mixing with the blood instead of being voided through the urethra.

## Lesson 9. ENDOCRINOLOGY

### Diabetes mellitus

**Diabetes mellitus** is a metabolic disorder characterized by hyperglycemia (high blood sugar) and other signs, as distinct from a single illness or condition. The World Health Organization recognizes three main forms of diabetes: *type 1*, *type 2*, and *gestational diabetes* (occurring during pregnancy), which have similar signs, symptoms, and consequences, but different causes and population distributions. Ultimately, all forms are due to the beta cells of the pancreas being unable to produce sufficient insulin to prevent hyperglycemia. Type 1 is usually due to autoimmune destruction of the pancreatic beta cells which produce insulin. Type 2 is characterized by tissue-wide insulin resistance and varies widely; it sometimes progresses to loss of beta cell function. Gestational diabetes is similar to type 2 diabetes, in that it involves insulin resistance; the hormones of pregnancy cause insulin resistance in those women genetically predisposed to developing this condition.

#### Acute complications

##### Diabetic ketoacidosis

*Diabetic ketoacidosis* (DKA) is an acute, dangerous complication and is always a *medical emergency*. Lack of insulin causes the liver to turn fat into ketone bodies, a fuel mainly for the brain. Large concentration of ketone bodies in the blood decreases the blood's pH, leading to most of the symptoms of DKA. On presentation at hospital, the patient in DKA is typically dehydrated and breathing both fast and deeply. Abdominal pain is common and may be severe. The level of consciousness is typically normal until late in the process, when lethargy (dulled or reduced level of alertness or consciousness) may progress to coma. Ketoacidosis can become severe enough to cause hypotension, shock, and death. Prompt proper treatment usually results in full recovery, though death can result from inadequate treatment, delayed treatment or from a variety of complications. Ketoacidosis occurs in type 1 and type 2 but is much more common in type 1.

**Emergency Department Care:** Maintain extreme vigilance for any concomitant process such as infection, cerebrovascular accident (CVA), MI, sepsis, or deep venous thrombosis (DVT).

- Fluid resuscitation is a critical part of treating DKA. Intravenous (IV) solutions replace extravascular and intravascular fluids and electrolyte losses. They also dilute both the glucose level and the levels of circulating counterregulatory hormones. Insulin is needed to help switch from a catabolic to an anabolic state, with uptake of glucose in tissues and the reduction of gluconeogenesis as well as free fatty acid and ketone production.
  - Administer 1 L of isotonic saline (or more if needed for significant hypovolemia) in the first hour. Further isotonic saline should be administered at a rate appropriate to maintain adequate blood pressure and pulse, urinary output, and mental status. If a

patient is severely dehydrated and significant fluid resuscitation is needed, switching to a balanced electrolyte solution (such as Normosol-R, in which some of the chloride in isotonic saline is replaced with acetate) may help to avoid the development of a hyperchloremic acidosis.

- After initial stabilization with isotonic saline, switch to half-normal saline at 200-1000 mL/h (half-normal saline matches losses due to osmotic diuresis).
- Pediatric protocols to minimize the risk of cerebral edema by reducing the rate of fluid repletion vary. Initial fluid repletion in pediatric patients should be 10-20 mL/kg over the first 1-2 hours with a maximum of 50 mL/kg over the first 4 hours. This is felt to reduce chances of cerebral edema.
- Potassium replacement
  - Add 20-40 mEq/L of KCl to each liter of fluid once  $K^+$  is under 5.5 mEq/L.
  - Potassium can be given as follows: two thirds as KCl, one third as  $KPO_4$ .
- Bicarbonate typically is not replaced, although some physicians do so when  $pH < 7$ . Administration of bicarbonate has been correlated with cerebral edema in children.
- Phosphate and magnesium replacements are not typically needed, since levels correct when patient resumes eating.
- Use data flow sheets to monitor timing of labs and therapy.

## Nonketotic hyperosmolar coma

While not generally progressing to coma, this *hyperosmolar nonketotic state* (HNS) is another acute problem associated with diabetes mellitus. It has many symptoms in common with DKA, but an entirely different cause, and requires different treatment. In anyone with very high blood glucose levels (usually considered to be above 300 mg/dl (16 mmol/l)), water will be osmotically drawn out of cells into the blood. The kidneys will also be "dumping" glucose into the urine, resulting in concomitant loss of water, and causing an increase in blood osmolality. If fluid is not replaced (by mouth or intravenously), the osmotic effect of high glucose levels combined with the loss of water will eventually result in very high serum osmolality (i.e. dehydration). The body's cells will become progressively dehydrated as water is taken from them and excreted. Electrolyte imbalances are also common, and dangerous. This combination of changes, especially if prolonged, will result in symptoms of lethargy (dulled or reduced level of alertness or consciousness) and may progress to coma. As with DKA urgent medical treatment is necessary, especially volume replacement. This is the 'diabetic coma' which more commonly occurs in type 2 diabetics.

Treatment is similar to ketoacidosis.

## Hypoglycemia

*Hypoglycemia*, or abnormally low blood glucose, is a complication of several diabetes treatments. It may develop if the glucose intake does not cover the treatment. The patient may become agitated, sweaty, and have many symptoms of sympathetic activation of the autonomic nervous system

resulting in feelings similar to dread and immobilized panic. Consciousness can be altered, or even lost, in extreme cases, leading to coma and/or seizures, or even brain damage and death. In patients with diabetes, this can be caused by several factors, such as too much or incorrectly timed insulin, too much exercise or incorrectly timed exercise (exercise decreases insulin requirements) or not enough food (actually an insufficient amount of glucose-producing carbohydrates in food). In most cases, hypoglycemia is treated with sugary drinks or food. In severe cases, an injection of glucagon (a hormone with the opposite effects of insulin) or an intravenous infusion of glucose is used for treatment, but usually only if the person is unconscious. In hospital, intravenous dextrose is often used.

**Prehospital Care:** Isotonic saline solution should be given as a bolus up to 1 L, depending on the patient's vital signs and other indicators of hypovolemia.

**Prehospital Care:** Treatment of hypoglycemia consists of correcting the glucose deficiency and directing further treatment to the underlying cause.

- EMS care generally consists of drawing serum glucose or Accucheck prior to administering D50 in the field. This procedure usually is performed in the case of an unconscious patient or a patient with altered mental status.
- Many advanced cardiac life support (ACLS)-trained and first responders are able to perform simple bedside glucose testing. This procedure should be part of the normal protocol for any EMS unit.
- When hypoglycemia is found and treated in the diabetic patient, the patient may awaken and not desire transport.
- Considering the multiple causes of a sudden episode of hypoglycemia in a patient with previously well-controlled diabetes, advising transport and ED evaluation is prudent.

### **Emergency Department Care:**

- The initial approach should include the following: ABCs, intravenous (IV) access, oxygen, monitoring, and Accucheck. Administration of glucose as part of the initial evaluation of altered mental status often corrects hypoglycemia.
- Treatment should not be withheld while waiting for a laboratory glucose value. Because the brain uses glucose as its primary energy source, neuronal damage may occur if treatment of hypoglycemia is delayed.
  - A hyperglycemic patient with an altered mental status may receive a bolus of glucose. This procedure is unlikely to harm the patient with high glucose; however, the delay in giving glucose to the hypoglycemic patient may be detrimental.
  - If an Accucheck can be performed immediately, awaiting the results of this test (available within 1 minute) before deciding whether to administer glucose is reasonable.
- Once the diagnosis of hypoglycemia is made, search carefully for the cause in the previously healthy patient.

- In the diabetic patient, search diligently for the cause (eg, medication changes, dietary changes, new metabolic changes, recent illness, occult infection) of the episode.

## Hyperthyroidism, thyroid storm, and Graves disease

Hyperthyroidism, thyroid storm, and Graves disease are conditions of excess thyroid hormone. The elevated level of thyroid hormones can result in clinical manifestations ranging from mild to severely toxic with resultant morbidity and mortality for affected patients.

### Hyperthyroidism

Hyperthyroidism presents as a constellation of symptoms due to elevated levels of circulating thyroid hormones. Because of the many actions of thyroid hormone on various organ systems in the body, the spectrum of clinical signs produced by the condition is broad. The presenting symptoms can be subtle and nonspecific, making hyperthyroidism difficult to diagnose in its early stages without the aid of laboratory data.

The term hyperthyroidism refers to inappropriately elevated thyroid function. Though often used interchangeably, the term thyrotoxicosis, which is an excessive amount of circulating thyroid hormone, is not the same as normal thyroid function, such as in instances of inappropriate exogenous thyroid hormone or excessive release of stored hormone from an inflamed thyroid gland.

### Graves disease

Graves disease (diffuse toxic goiter), the most common form of overt hyperthyroidism, is an autoimmune condition in which autoantibodies are directed against the thyroid-stimulating hormone (TSH) receptor. As a result, the thyroid gland is inappropriately stimulated with ensuing gland enlargement and increase of thyroid hormone production. Risk factors for Graves disease include family history of hyperthyroidism or various other autoimmune disorders, high iodine intake, stress, use of sex steroids, and smoking. The disease is classically characterized by the triad of goiter, exophthalmos, and pretibial myxedema.

### Thyroid storm

Thyroid storm is a rare and potentially fatal complication of hyperthyroidism. It typically occurs in patients with untreated or partially treated thyrotoxicosis who experience a precipitating event such as surgery, infection, or trauma. Thyroid storm must be recognized and treated on clinical grounds alone, as laboratory confirmation often cannot be obtained in a timely manner. Patients typically appear markedly hypermetabolic with high fevers, tachycardia, nausea and vomiting, tremulousness, agitation, and psychosis. Late in the progression of disease patients may become stuporous or comatose with hypotension.

**Pathophysiology:** In healthy patients, the hypothalamus produces thyrotropin-releasing hormone (TRH), which stimulates the anterior pituitary gland to secrete thyroid-stimulating hormone (TSH); this in turn triggers the thyroid gland to release thyroid hormone.

Thyroid hormone concentration is regulated by negative feedback by circulating free hormone primarily on the anterior pituitary gland and to a lesser extent on the hypothalamus. The secretion of TRH is also partially regulated by higher cortical centers.

The thyroid gland produces the prohormone thyroxine (T4), which is deiodinated primarily by the liver and kidneys to its active form, triiodothyronine (T3). The thyroid gland also produces a small amount of T3 directly. T4 and T3 exist in 2 forms: a free, unbound portion that is biologically active and a portion that is protein bound to thyroid-binding globulin (TBG). Despite consisting of less than 0.5% of total circulating hormone, free or unbound T4 and T3 levels best correlate with the patient's clinical status.

**History:** The clinical presentation of hyperthyroidism ranges from an array of nonspecific historical features to an acute life-threatening event. Historical features common to hyperthyroidism and thyroid storm are numerous and represent a hypermetabolic state with increased beta-adrenergic activity.

- Weight loss
  - Patients typically report an average loss of approximately 15% of their prior weight.
  - Basal metabolic rate is increased with a stimulation of lipolysis and lipogenesis.
- Palpitations
- Chest pain - Often occurs in the absence of cardiovascular disease
- Psychosis
- Menstrual irregularity
- Disorientation
- Tremor
- Nervousness, anxiety, or emotional lability
- Heat intolerance
- Increased perspiration
- Fatigue
- Weakness - Typically affects proximal muscle groups
- Edema
- Dyspnea
- Frequent bowel movements

**Physical:**

- Fever
- Tachycardia (often out of proportion to the fever)



- Diaphoresis (often profuse)
- Dehydration secondary to GI losses and diaphoresis
- Warm, moist skin
- Widened pulse pressure
- Congestive heart failure (may be a high output failure)
- Thyromegaly
  - Nontender, diffuse enlargement in Graves disease
  - Tender, diffusely enlarged gland in thyroiditis
  - Thyroid nodules, either single or multinodular goiter
- Exophthalmos
- Shock
- Atrial fibrillation
  - Typically in elderly patients
  - May be refractory to attempted rate control with digitalis
  - Converts after antithyroid therapy in 20-50% of patients
- Myopathy
- Thyroid bruit - Relatively specific for thyrotoxicosis
- Fine, resting tremor

**Causes:** Hyperthyroidism results from numerous etiologies, including autoimmune, drug-induced, infectious, idiopathic, iatrogenic, and malignancy.

- Autoimmune
  - Graves disease
  - Chronic thyroiditis (Hashimoto thyroiditis) - Although the primary cause of hypothyroidism, the disease process occasionally presents initially with thyrotoxicosis
  - Subacute thyroiditis (de Quervain thyroiditis) - Diffuse, painful inflammation of the thyroid producing a transient state leakage of stored hormone

- Postpartum thyroiditis - Presents similarly to subacute thyroiditis 2-6 months postpartum but typically painless with mild symptoms
- Drug-induced
  - Iodine-induced - Occurs after administration of either supplemental iodine to those with prior iodine deficiency or pharmacologic doses of iodine (contrast media, medications) in those with underlying nodular goiter
  - Amiodarone - Its high iodine content is primarily responsible for producing a hyperthyroid state, though the medication may itself induce autoimmune thyroid disease.
- Infectious
  - Suppurative thyroiditis - Often bacterial, results in a painful gland commonly in those with underlying thyroid disease or in immunocompromised individuals
  - Postviral thyroiditis
- Idiopathic
  - Toxic multinodular goiter - The second most common cause of hyperthyroidism, characterized by functionally autonomous nodules, typically after age 50 years
- Iatrogenic
  - Thyrotoxicosis factitia - A psychiatric condition in which high quantities of exogenous thyroid hormone are consumed
  - Surgery - Now uncommon secondary to preventative measures, manipulation of the thyroid gland during thyroidectomy historically caused a flood of hormone release, often resulting in highly toxic blood levels
- Malignancy
  - Toxic adenoma - A single, hyperfunctioning nodule within a normally functioning thyroid gland commonly among patients in their 30s and 40s
  - Thyrotropin-producing pituitary tumors
  - Struma ovarii - Ovarian teratoma with ectopic thyroid tissue
- Thyroid storm can be triggered by many different events, classically in patients with underlying Graves disease or toxic multinodular goiter.
  - Infection
  - Surgery
  - Cardiovascular events
  - Toxemia of pregnancy
  - Diabetic ketoacidosis, hyperosmolar coma, and insulin-induced hypoglycemia
  - Thyroidectomy
  - Discontinuation of antithyroid medication
  - Radioactive iodine

- Vigorous palpation of the thyroid gland in hyperthyroid patients

### **Emergency Department Care:**

- Do not delay treatment once thyroid storm is suspected.
- Patients with severe thyrotoxicosis must be placed on a cardiac monitor. The patient should be intubated if profoundly altered. Supplemental oxygen may be required. Aggressive fluid resuscitation may be indicated.
- Fevers are treated with cooling measures and antipyretics. However, aspirin should be avoided to prevent decreased protein binding and subsequent increases in free T3 and T4 levels. Only in the setting of subacute thyroiditis is aspirin indicated.
- Aggressive hydration of up to 3-5 L/d of crystalloid compensates for potentially profound GI and insensible losses.
- Appropriate electrolyte replacement should be directed by laboratory values.
- Atrial fibrillation due to thyroid storm may be refractory to rate control, and conversion to sinus rhythm may be impossible until after antithyroid therapy has been initiated.
- Intravenous glucocorticoids are indicated if adrenal insufficiency is suspected. Large doses of dexamethasone (2 mg q6h) inhibit hormone production and decrease peripheral conversion from T4 to T3.
- Antithyroid medications such as propylthiouracil (PTU) and methimazole (MMI) oppose synthesis of T4 by inhibiting the organification of tyrosine residues.
  - PTU also inhibits the conversion of T4 to active T3.
  - Clinical effects may be seen as soon as 1 hour after administration. Both agents are administered orally or via a nasogastric tube.
  - PTU and MMI inhibit the synthesis of new thyroid hormone but are ineffective in blocking the release of preformed thyroid hormone. Iodide administration serves this purpose well; however, it should be delayed until 1 hour after the loading dose of antithyroid medication to prevent the utilization of iodine in the synthesis of new thyroid hormone. Lithium may be used as an alternative in those with iodine allergy.
- Beta-adrenergic blocking agents are the mainstays of symptomatic therapy for thyrotoxicosis. Propranolol has been used with the greatest success due to the additional benefit of inhibition of peripheral conversion of T4 to T3.

## **Hypothyroidism**

Hypothyroidism is a clinical syndrome in which the deficiency or absence of thyroid hormone slows bodily metabolic processes. Symptoms can manifest in all organ systems and range in severity based on the degree of hormone deficiency. The disease typically progresses over months to years but can occur quickly following cessation of thyroid replacement medication or surgical removal of the thyroid gland.

The term myxedema refers to the thickened, nonpitting edematous changes to the soft tissues of patients in a markedly hypothyroid state. Myxedema coma, a rare, life-threatening condition, occurs late in the progression of hypothyroidism. The condition is seen typically in elderly women and is often precipitated by infection, medication, environmental exposure, or other metabolic-related stresses. Since rapid confirmatory laboratory tests are often unavailable, the diagnosis may be made on clinical grounds with treatment started promptly.

Treatment of **myxedema coma** requires potentially toxic doses of thyroid hormone, and mortality rates exceeding 20% have been reported even with optimum therapy.

**History:** The symptoms characteristic of hypothyroidism are numerous yet often vague and subtle, especially in early stages of the disease.

- Lethargy
- Generalized weakness
- Brittle or thinning hair
- Menstrual irregularity
- Menorrhagia
- Forgetfulness
- Fullness in throat
- Deep, husky voice secondary to mucopolysaccharide infiltration of the vocal cords
- Cold intolerance
- Weight gain
- Muscle/joint pain or weakness
- Inability to concentrate
- Headaches
- Constipation
- Emotional lability
- Depression
- Blurred vision
- Dry hair

**Physical:**

- Pseudomyotonic reflexes - Prolonged relaxation phase, usually at least twice as long as the contraction phase
- Hypothermia (especially in myxedema coma)
- Skin changes - Dry, cool, coarse, and thickened with a yellowish appearance
- Subcutaneous tissues - Nonpitting, waxy, dry edema, secondary to accumulation of polysaccharides
- Loss of axillary and pubic hair
- Pallor
- Loss of outer one third of eyebrows
- Abdominal distention
- Goiter
- Unsteady gait/ataxia
- Pericardial effusion
- Dull facial expression
- Coarsening or huskiness of voice
- Periorbital edema
- Bradycardia, narrow pulse pressure
- Macroglossia
- Thyroidectomy scar - In patients with altered mental status, suggests myxedema coma as a potential cause

**Prehospital Care:** Stabilize acute life-threatening conditions, and initiate supportive therapy.

**Emergency Department Care:** Patients with myxedema coma may present in extremis; implement initial resuscitative measures, including intravenous (IV) access, cardiac monitoring, and oxygen therapy, as indicated. Mechanical ventilation is indicated for patients with diminished respiratory drive or obtundation.

- Evaluate for life-threatening causes of altered mental status (eg, bedside glucose, pulse oximetry).
- If myxedema coma is suspected on clinical impression, start IV thyroid hormone treatment.
- Confirmatory tests often are not available to an ED physician.
- With a diagnosis of myxedema coma, initiate hormonal therapy.

- Investigate immediately for inciting events such as infection.
- Treat respiratory failure with appropriate ventilatory support.
  - The condition often requires mechanical ventilation.
  - Treat underlying pulmonary infection.
- Hypotension may respond to crystalloid infusion.
  - Occasionally, vasopressive agents are required.
  - In refractory cases, hypotension may resolve with thyroid hormone replacement.
- Treat hypothermia.
  - Most patients with myxedema coma respond to passive rewarming measures such as blankets and removal of cold or wet clothing; aggressive rewarming may lead to peripheral vasodilatation and hypotension. However, hemodynamically unstable patients with profound hypothermia require active rewarming measures.
  - Treat hyponatremia initially with water restriction; however, if sodium levels are less than 120 mEq/L or any seizures occur, hypertonic saline is indicated.
- Avoid medications such as sedatives, narcotics, and anesthetics. Metabolism of these agents may be slowed significantly, causing prolonged effects.

### Consultations:

- For patients with myxedema coma, consult a critical care intensivist regarding admission to an ICU and optimization treatment.
- An endocrinologist should be consulted to help confirm the diagnosis and assist in patient management after admission.

## HYPERPARATHYROIDISM

In cases of primary, tertiary and quinary hyperparathyroidism increased PTH consequently leads to increased serum calcium (hypercalcemia) due to:

1. increased bone resorption, allowing flow of calcium from bone to blood
2. reduced renal clearance of calcium
3. increased intestinal calcium absorption

By contrast, in secondary and quaternary hyperparathyroidism effectiveness of PTH is reduced. Alkaline phosphatase levels are elevated in all types of hyperparathyroidism.

In primary hyperparathyroidism, serum phosphorus levels are abnormally low as a result of decreased renal tubular phosphorus reabsorption. This contrasts with secondary hyperparathyroidism, in which serum phosphorus levels are generally elevated because of renal disease.

## Etiology

- Primary hyperparathyroidism results from a dysfunction in the parathyroid glands themselves, with oversecretion of PTH.
  - The most common cause is a benign parathyroid adenoma that loses its sensitivity to circulating calcium levels. Usually, only one of the four parathyroid glands is affected.
  - A less common cause is from multiple endocrine neoplasia (MEN).
- Secondary hyperparathyroidism is due to resistance to the actions of PTH, usually due to chronic renal failure. The bone disease in secondary parathyroidism along with renal failure is termed renal osteodystrophy.
- Tertiary, quartary and quintary hyperparathyroidism are rare forms that are caused by long lasting disorders of the calcium feedback control system.

## Signs and symptoms

Many patients presenting with hyperparathyroidism will have no signs or symptoms, with diagnosis being made on further investigation after a coincidental finding of hypercalcemia. It is, however, reported that many patients will report that they feel better after treatment for hyperparathyroidism. Of those patient that do present with symptoms, they are commonly associated with the effects of an increased level of calcium.

Since calcium is responsible for the electrical conduction within our nervous system, high blood calcium levels have a direct effect on the nervous system. Thus, most of the symptoms of parathyroid disease are "neurological" in origin. The most common symptom is fatigue and tiredness. Other very common symptoms are lack of energy, memory problems, depression, problems with concentration, and problems sleeping. Other manifestations of hyperparathyroidism usually involve the kidney (stones) and the skeletal system (bone pain due to the development of osteoporosis).

The symptoms of hyperparathyroidism can be classically remembered by the rhyme "moans" (complaints of not feeling well), "groans" (abdominal pain, GERD), "stones" (kidney), "bones" (bone pain), and "psychiatric overtones" (lethargy, fatigue, depression, memory problems).

Almost all patients with hyperparathyroidism will develop osteoporosis. If untreated, this osteoporosis can be extreme. Unfortunately, medicines are usually not useful for treating the osteoporosis associated with hyperparathyroidism until the parathyroid tumor is removed. Osteoporosis associated with hyperparathyroidism is caused by the high parathyroid hormone that is secreted by the overactive parathyroid gland(s). This excess parathyroid hormone (PTH) acts directly on the bones to remove calcium from the bones. Thus, the high calcium in the blood comes from the bones. Removing the offending parathyroid gland will usually cause a significant improvement in the osteoporosis, often reversing this process back to normal bone density over several years.

Other symptoms include: headaches, gastroesophageal reflux, decreased sex drive, thinning hair, hypertension, and heart palpitations which are often due to bouts of atrial fibrillation.

Almost all patients will have symptoms if their calcium is high and the right questions are asked. Removing the parathyroid tumor which is causing the excess parathyroid hormone will eliminate the symptoms in most patients within several days or weeks. Often it is life-changing when the parathyroid tumor is removed.

## Diagnosis

The gold standard of diagnosis is the PTH immunoassay. Once an elevated PTH has been confirmed, goal of diagnosis is to determine whether the hyperparathyroidism is primary or secondary in origin by obtaining a serum calcium level:

Tertiary hyperparathyroidism has a high PTH and a high serum calcium. It is differentiated from primary hyperparathyroidism by a history of chronic kidney failure and secondary hyperparathyroidism.

## Treatment

Treatment is first and foremost directed at hypercalcemia, if symptomatic patients are sent for surgery to remove the parathyroid tumor (parathyroid adenoma). (see hypercalcemia) Most experts now believe that almost all patients with hyperparathyroidism should be evaluated for surgery. Watching and waiting has been falling out of vogue since it is being realized that the disease will rarely stay the same. It will almost always progress as the tumor grows.

Calcium regulation is critical for normal cell function, neural transmission, membrane stability, bone structure, blood coagulation, and intracellular signaling. The essential functions of this divalent cation continue to be elucidated, particularly in head injury/stroke and cardiopulmonary effects. Depending on the cause, unrecognized or poorly treated hypocalcemic emergencies can lead to significant morbidity or death.

## HYPOCALCIEMIA

### Pathophysiology

Metabolic and endocrine emergencies require an understanding of normal physiology.

Calcium regulation is maintained by parathyroid hormone (PTH), vitamin D, and calcitonin through complex feedback loops. These compounds act primarily at bone, renal, and GI sites. Calcium also is affected by magnesium and phosphorus.

### History

- The patient may complain of muscle cramping, shortness of breath secondary to bronchospasm, tetanic contractions, distal extremity numbness, and tingling sensations.
- 
- Chronic manifestations include cataracts, dry skin, coarse hair, brittle nails, psoriasis, chronic pruritus, and poor dentition.
- 
- Acute hypocalcemia may lead to syncope, congestive heart failure (CHF), and angina due to the multiple cardiovascular effects.



- 
- The patient's past medical history should be explored for pancreatitis, anxiety disorders, renal or liver failure, gastrointestinal disorders, and hyperthyroidism or hyperparathyroidism.
- 
- The patient may have a recent history of thyroid, parathyroid, or bowel surgeries or recent neck trauma.
- 
- Inquire about recent radiocontrast, estrogen, loop diuretics, bisphosphonates, calcium supplements, antibiotics, and anti-epileptics.
- 
- Evaluate for appropriate dietary intake.

## Physical

Neuromuscular and cardiovascular findings predominate. Neural hyperexcitability due to acute hypocalcemia causes smooth and skeletal muscle contractions. The patient should be examined for the following:

- Dry skin and psoriasis (if long-term hypocalcemia)
- 
- Perioral anesthesia, cataracts, papilledema, and laryngeal stridor
- 
- Scars over thyroid region
- 
- Recent trauma or surgery to the neck
- 
- Cardiopulmonary effects
  - 
  - Wheezing, dysphagia, stridor, bradycardia, rales, and S<sub>3</sub> may be noted.
  - 
  - Acute hypocalcemia causes prolongation of the QT interval, which may lead to ventricular dysrhythmias. It also causes decreased myocardial contractility, leading to CHF, hypotension, and angina. Cardiomyopathy and ventricular tachycardia may be reversible with treatment.
  - 
  - Smooth muscle contraction may lead to laryngeal stridor, dysphagia, and bronchospasm.
- 
- Smooth muscle contraction causes biliary colic, intestinal colic, and dysphagia.
- 
- Diarrhea and/or gluten intolerance (celiac sprue) may result in significant malabsorption and electrolyte abnormalities.
- 
- Preterm labor or detrusor dysfunction may result from smooth muscle contraction.
- 
- Peripheral nervous system findings include tetany, focal numbness, and muscle spasms.
- 
- Classic peripheral neurologic findings include the Chvostek sign and Trousseau sign.
-

- Chvostek sign: Tap over the facial nerve about 2 cm anterior to the tragus of the ear. Depending on the calcium level, a graded response will occur: twitching first at the angle of the mouth, then by the nose, the eye, and the facial muscles.
- 
- Trousseau sign: Inflation of a blood pressure cuff above the systolic pressure causes local ulnar and median nerve ischemia, resulting in carpal spasm.
- 
- Irritability, confusion, hallucinations, dementia, extrapyramidal manifestations, and seizures may occur.
  - 
  - Calcification of basal ganglia, cerebellum, and cerebrum may occur.
  - 
  - Seizures often occur in individuals with preexistent epileptic foci when the excitation threshold is lowered.

## Causes

The causes of hypocalcemia include hypoalbuminemia, hypomagnesemia, hyperphosphatemia, multifactorial enhanced protein binding and anion chelation, medication effects, surgical effects, PTH deficiency or resistance, and vitamin D deficiency or resistance.

## Prehospital Care

Standard advanced cardiac life support (ACLS) procedures should be initiated in the patient whose condition is unstable. No specific therapy, other than supportive care, is recommended.

## Emergency Department Care

Most hypocalcemic emergencies are mild and require only supportive treatment and further laboratory evaluation. On occasion, severe hypocalcemia may result in seizures, tetany, refractory hypotension, or arrhythmias that require a more aggressive approach.

- Mild hypocalcemia (when symptoms are not life threatening)
  - 
  - Confirm ionized hypocalcemia and check other pertinent laboratory tests.
  - 
  - If the cause is not obvious, send for a PTH level.
  - 
  - Depending on the PTH level, the endocrinologist may do further laboratory workup, particularly an evaluation of vitamin D levels.
  - 
  - Oral repletion may be indicated for outpatient treatment; patients requiring intravenous (IV) repletion should be admitted. (Recommended dose of elemental calcium in healthy adults is 1-3 g/d.)
- 
- Severe hypocalcemia (life-threatening symptoms)
  - 
  - Supportive treatment often is required prior to directed treatment of hypocalcemia (ie, IV replacement, oxygen, monitoring). Be aware that severe hypocalcemia often is associated with other life-threatening conditions.
  -

- Check ionized calcium and other pertinent screening laboratory tests.
- 
- IV replacement is recommended in severe cases. Doses of 100-300 mg of elemental calcium (calcium gluconate – 10 mL contains 90 mg elemental calcium; calcium chloride – 10 mL contains 272 mg elemental calcium) should be given over 5-10 minutes. This dosage raises the ionized level to 0.5-1.5 mmol and should last 1-2 hours. Caution should be used when giving CaCl intravenously (see Medication).
- 
- Calcium infusion drips should be started at 0.5 mg/kg/h and increased to 2 mg/kg/h as needed, with an arterial line placed for frequent measurement of ionized calcium.

## Consultations

Depending on the clinical situation, multiple consultations may be necessary, including internist, endocrinologist, intensivist, surgeon, oncologist, nephrologist, dietitian, and/or toxicologist.

## Addison's disease

(also known as **chronic adrenal insufficiency**, **hypocortisolism** or **hypocorticism**) is a rare endocrine disorder in which the adrenal gland produces insufficient amounts of steroid hormones (glucocorticoids and often mineralocorticoids). It may develop in children as well as adults, and may occur as the result of a large number of underlying causes. The condition is named after Dr Thomas Addison, the British physician who first described the condition in his 1855 *On the Constitutional and Local Effects of Disease of the Suprarenal Capsules*. The adjective "Addisonian" is used for features of the condition, as well as patients with Addison's disease.<sup>[1]</sup>

The condition is generally diagnosed with blood tests, medical imaging and additional investigations.<sup>[1]</sup> Treatment is with replacement of the hormones (oral hydrocortisone and fludrocortisone). If the disease is caused by an underlying problem, this is addressed. Regular follow-up and monitoring for other health problems is necessary.<sup>[1]</sup>

## Symptoms

The symptoms of Addison's disease develop insidiously, and it may take some time to be recognised. The most common symptoms are fatigue, muscle weakness, vomiting, diarrhoea, headache, sweating, changes in mood and personality and joint and muscle pains. Some have marked cravings for salty foods due to the urinary losses of sodium.<sup>[1]</sup>

## Clinical signs

On examination, the following may be noticed:<sup>[1]</sup>

- Low blood pressure that falls further when standing (orthostatic hypotension)
- Darkening (hyperpigmentation) of the skin, including areas not exposed to the sun; characteristic sites are skin creases (e.g. of the hands) and the inside of the cheek (buccal mucosa).
- Signs of conditions that often occur together with Addison's: goitre and vitiligo

## Addisonian crisis

An "Addisonian crisis" is a constellation of symptoms that indicate severe adrenal insufficiency. This may be the result of either previously undiagnosed Addison's disease, a disease process suddenly affecting adrenal function (such as adrenal haemorrhage, or in a patient with known Addison's disease who has suffered an intercurrent problem (e.g. infection, trauma). Additionally, this situation may develop in those on long-term oral glucocorticoids who have suddenly ceased taking their medication.

Untreated, an Addisonian crisis can be fatal. It is a medical emergency, usually requiring hospitalization. Characteristic symptoms are:<sup>[citation needed]</sup>

- Sudden penetrating pain in the legs, lower back or abdomen
- Severe vomiting and diarrhea, resulting in dehydration
- Low blood pressure
- Loss of consciousness/Syncope
- Hypoglycemia
- Confusion, psychosis
- Convulsions

## Diagnosis

### Features suggesting diagnosis

Routine investigations may show:<sup>[1]</sup>

- Hypoglycemia, low blood sugar (worse in children)
- Hyponatraemia (low blood sodium levels)
- Hyperkalemia (raised blood potassium levels), due to loss of production of the hormone aldosterone
- Eosinophilia and lymphocytosis (increased number of eosinophils or lymphocytes, two types of white blood cells)

## Treatment

### Maintenance treatment

Treatment for Addison's disease involves replacing the missing cortisol (usually in the form of hydrocortisone tablets) in a dosing regimen that mimics the physiological concentrations of cortisol. Treatment must usually be continued for life. In addition, many patients require fludrocortisone as replacement for the missing aldosterone. Caution must be exercised when the person with Addison's disease becomes unwell, has surgery or becomes pregnant. Medication may need to be increased during times of stress, infection, or injury.

### Addisonian crisis

Treatment for an acute attack, an Addisonian crisis, usually involves intravenous (into blood veins) injections of:

- Cortisone (cortisol)

- Saline solution (basically a salt water, same clear IV bag as used to treat dehydration)
- Glucose

## Hyperaldosteronism,

also **aldosteronism**, is a medical condition where too much aldosterone is produced by the adrenal glands, which can lead to lowered levels of potassium in blood.

## Symptoms

It can be asymptomatic, but the following symptoms can be present

- Fatigue
- Headache
- High blood pressure
- Hypokalemia
- Intermittent or temporary paralysis
- Muscle spasms
- Muscle weakness
- Numbness
- Polyuria
- Polydipsia

## Cushing's syndrome

(also called **hypercortisolism** or **hyperadrenocorticism**) is a rare endocrine disorder caused by high levels of cortisol in the blood. Cortisol is released from the adrenal gland in response to ACTH being released from the pituitary gland. High levels of cortisol can also be induced by the administration of drugs. **Cushings disease**, or more properly termed *secondary hyperadrenocorticism*, is very similar to Cushing's syndrome in that all physiologic manifestations of the conditions are the same. Both diseases are characterized by elevated levels of cortisol in the blood, but the cause of elevated cortisol differs between the diseases. Cushing's disease specifically refers to a tumor in the pituitary gland that stimulates excessive release of cortisol from the adrenal gland by releasing large amounts of ACTH. It was discovered by American physician, surgeon and endocrinologist Harvey Cushing (1869-1939) and reported by him in 1932.

## Signs and symptoms

Symptoms include rapid weight gain, particularly of the trunk and face with sparing of the limbs (central obesity), a round face often referred to as a "moon face", excess sweating, telangiectasia (dilation of capillaries), thinning of the skin (which causes easy bruising) and other mucous membranes, purple or red striae (also caused by thinning of the skin) on the trunk, buttocks, arms, legs or breasts, proximal muscle weakness (hips, shoulders), and hirsutism (facial male-pattern hair growth). A common sign is the growth of fat pads along the collar bone and on the back of the neck (known as a buffalo hump). The excess cortisol may also affect other endocrine systems and cause, for example, reduced libido, impotence, amenorrhoea and infertility. Patients frequently suffer various psychological disturbances, ranging from euphoria to frank psychosis. Depression and anxiety, including panic attacks, are common.

Other signs include persistent hypertension (due to the aldosterone-like effects) and insulin resistance, leading to hyperglycemia (high blood sugars) which can lead to diabetes mellitus. Untreated Cushing's syndrome can lead to heart disease and increased mortality. Cushing's syndrome due to excess ACTH may also result in hyperpigmentation of the skin, due to its ability to stimulate melanocyte receptors.

## Diagnosis

When Cushing's is suspected, a dexamethasone suppression test (administration of dexamethasone and frequent determination of cortisol and ACTH levels) and 24-hour urinary measurement for cortisol have equal detection rates (Raff & Findling 2003). Dexamethasone is a glucocorticoid and simulates the effects of cortisol, including negative feedback on the pituitary gland. When dexamethasone is administered and a blood sample is tested, high cortisol would be indicative of Cushing's syndrome because there is an ectopic source of cortisol or ACTH (eg: adrenal adenoma) that is not inhibited by the dexamethasone. A low cortisol reading would be indicative of Cushing's disease because the dexamethasone inhibited the pituitary adenoma so that its' output of ACTH decreased, resulting in decreased cortisol levels. A novel approach, recently cleared by the US FDA, is sampling cortisol in saliva over 24 hours, which may be equally sensitive, as late night levels of salivary cortisol are high in Cushingoid patients. Other pituitary hormones may need to be determined, and performing physical examination directed for any visual field defect may be necessary if a pituitary lesion is suspected (which may compress the optic chiasm causing typical bitemporal hemianopia).

When these tests are positive, CT scanning of the adrenal gland and MRI of the pituitary gland are performed to detect the presence of an adrenal or pituitary adenoma. These should be performed when other tests are positive, to decrease likelihood of incidentalomas (incidental discovery of harmless lesions in both organs). Scintigraphy of the adrenal gland with iodocholesterol scan is occasionally necessary. Very rarely, determining the cortisol levels in various veins in the body by venous catheterisation working towards the pituitary (petrosal sinus sampling) is necessary.

## Pheochromocytoma

A **phaeochromocytoma** (**pheochromocytoma** in the US) is a neuroendocrine tumor of the medulla of the adrenal glands originating in the chromaffin cells, which secretes excessive amounts of catecholamines, usually adrenaline and noradrenaline (epinephrine and norepinephrine in the US). Extra-adrenal paragangliomas (often described as extra-adrenal pheochromocytomas) are closely related, though less common, tumors that originate in the ganglia of the sympathetic nervous system and are named based upon the primary anatomical site of origin.

## Diagnosis

The diagnosis can be established by measuring catecholamines and metanephrines in plasma or through a 24-hour urine collection. Care should be taken to rule out other causes of adrenergic (adrenalin-like) excess like hypoglycemia, stress, exercise, and drugs affecting the catecholamines like methyldopa, dopamine agonists, or ganglion blocking antihypertensives. Various foodstuffs (e.g. vanilla ice cream) can also affect the levels of urinary metanephrine and VMA (vanillyl mandelic acid). Imaging by computed tomography or a T2 weighted MRI of the head, neck, and

chest, and abdomen can help localize the tumor. Tumors can also be located using Iodine-131 meta-iodobenzylguanidine (I131 MIBG) imaging.

One diagnostic test used in the past for a pheochromocytoma is to administer clonidine, a centrally-acting alpha-2 agonist used to treat high blood pressure. Clonidine mimics catecholamines in the brain, causing it to reduce the activity of the sympathetic nerves controlling the adrenal medulla. A healthy adrenal medulla will respond to the Clonidine suppression test by reducing catecholamine production; the lack of a response is evidence of pheochromocytoma.

Another test is for the clinician to press gently on the adrenal gland. A pheochromocytoma will often release a burst of catecholamines, with the associated signs and symptoms quickly following. This method is not recommended because of possible complications arising from a potentially massive release of catecholamines.

Pheochromocytomas occur most often during young-adult to mid-adult life. Less than 10% of pheochromocytomas are malignant (cancerous), bilateral or pediatric.

These tumors can form a pattern with other endocrine gland cancers which is labeled multiple endocrine neoplasia (MEN). Pheochromocytoma may occur in patients with MEN 2 and MEN 3. VHL (Von Hippel Lindau) patients may also develop these tumors.

Patients experiencing symptoms associated with pheochromocytoma should be aware that it is rare. However, it often goes undiagnosed until autopsy; therefore patients might wisely choose to take steps to provide a physician with important clues, such as recording whether blood pressure changes significantly during episodes of apparent anxiety.

## Acromegaly

**Acromegaly** (from Greek *akros* "extreme" or "extremities" and *megalos* "large" - extremities enlargement) is a hormonal disorder that results when the pituitary gland produces excess growth hormone (hGH). Most commonly it is a benign hGH producing tumor derived from a distinct type of cells (somatotrophs) and called **pituitary adenoma**.

Acromegaly most commonly affects middle-aged adults and can result in serious illness and premature death. Because of its insidious pathogenesis and slow progression, the disease is hard to diagnose in the early stages and is frequently missed for many years.

## Symptoms

Features that result from high level of hGH or expanding tumor include:

- Soft tissue swelling of the hands and feet
- Brow and lower jaw protrusion
- Enlarging hands
- Enlarging feet
- Arthritis and carpal tunnel syndrome
- Teeth spacing increase
- Macroglossia [enlarged tongue]

- Heart failure
- Compression of the optic chiasm leading to loss of vision in the outer visual fields (typically bitemporal hemianopia)
- Headache
- Diabetes mellitus
- Hypertension
- Increased palmar sweating and sebum production over the face (seborrhea) are clinical indicators of active growth hormone (GH) producing pituitary tumours. These symptoms can also be used to monitor the activity of the tumour after surgery although biochemical monitoring is confirmatory.

## Causes

### Pituitary adenoma

In over 90 percent of acromegaly patients, the overproduction of GH is caused by a benign tumor of the pituitary gland, called an adenoma. These tumors produce excess GH and, as they expand, compress surrounding brain tissues, such as the optic nerves. This expansion causes the headaches and visual disturbances that are often symptoms of acromegaly. In addition, compression of the surrounding normal pituitary tissue can alter production of other hormones, leading to changes in menstruation and breast discharge in women and impotence in men because of reduced testosterone production.

There is a marked variation in rates of GH production and the aggressiveness of the tumor. Some adenomas grow slowly and symptoms of GH excess are often not noticed for many years. Other adenomas grow rapidly and invade surrounding brain areas or the sinuses, which are located near the pituitary. In general, younger patients tend to have more aggressive tumors.

Most pituitary tumors arise spontaneously and are not genetically inherited. Many pituitary tumors arise from a genetic alteration in a single pituitary cell which leads to increased cell division and tumor formation. This genetic change, or mutation, is not present at birth, but is acquired during life. The mutation occurs in a gene that regulates the transmission of chemical signals within pituitary cells; it permanently switches on the signal that tells the cell to divide and secrete GH. The events within the cell that cause disordered pituitary cell growth and GH oversecretion currently are the subject of intensive research.

### Other tumors

In a few patients, acromegaly is caused not by pituitary tumors but by tumors of the pancreas, lungs, and adrenal glands. These tumors also lead to an excess of GH, either because they produce GH themselves or, more frequently, because they produce GHRH, the hormone that stimulates the pituitary to make GH. In these patients, the excess GHRH can be measured in the blood and establishes that the cause of the acromegaly is not due to a pituitary defect. When these non-pituitary tumors are surgically removed, GH levels fall and the symptoms of acromegaly improve.

In patients with GHRH-producing, non-pituitary tumors, the pituitary still may be enlarged and may be mistaken for a tumor. Therefore, it is important that physicians carefully analyze all "pituitary tumors" removed from patients with acromegaly in order not to overlook the possibility that a tumor elsewhere in the body is causing the disorder.



## Diagnosis

If acromegaly is suspected, medical imaging and medical laboratory investigations are generally used together to confirm or rule out the presence of this condition.

### Hormonal

IGF1 provides the most sensitive and useful lab test for the diagnosis of acromegaly. A single value of the Growth hormone (GH) is not useful in view of its pulsatility (levels in the blood vary greatly even in healthy individuals). GH levels taken 2 hours after a 75 gram glucose tolerance test are helpful in the diagnosis: GH levels are suppressed below 1 µg/L in normal people, and levels higher than this cutoff are confirmatory of acromegaly.

Other pituitary hormones have to be assessed to address the secretory effects of the tumour as well as the mass effect of the tumor on the normal pituitary gland. They include TSH (thyroid stimulating hormone), gonadotropic hormones (FSH,LH), ACTH (adrenocorticotrophic hormone), prolactin.

### Radiological

An MRI of the brain focussing on the sella turcica after gadolinium administration allows for clear delineation of the pituitary and the hypothalamus and the location of the tumour. Treatment

The goals of treatment are to reduce GH production to normal levels, to relieve the pressure that the growing pituitary tumor exerts on the surrounding brain areas, to preserve normal pituitary function, and to reverse or ameliorate the symptoms of acromegaly. Currently, treatment options include surgical removal of the tumor, drug therapy, and radiation therapy of the pituitary.

### Surgery

Surgery is a rapid and effective treatment, of which there are two alternative methods. The first method, a procedure known as **transsphenoidal surgery**, involves the surgeon reaching the pituitary through an incision in the nose and, with special tools, removing the tumor tissue. The second method is the removal of the tumor via a craniotomy, during which a *bone flap* is removed from the patient's skull to allow access to the tumor from the front and side. Once the tumor has been removed, the section of bone is replaced. Transsphenoidal surgery is a less invasive procedure with a shorter recovery time than a craniotomy, yet the likelihood of successfully removing the entire tumor is lower. Consequently, transsphenoidal surgery is often used as a first option, with craniotomy and other treatments being used to remove any remaining tumor.

Even when surgery is successful and hormone levels return to normal, patients must be carefully monitored for years for possible recurrence. More commonly, hormone levels may improve, but not return completely to normal. These patients may then require additional treatment, usually with medications.

## Diabetes insipidus

**Diabetes insipidus (DI)** is a disease characterized by excretion of large amounts of severely diluted urine, which cannot be reduced when fluid intake is reduced. It denotes inability of the kidney to

concentrate urine. DI is caused by a deficiency of antidiuretic hormone (ADH), also known as vasopressin, or by an insensitivity of the kidneys to that hormone.

## Signs and symptoms

Excessive urination and extreme thirst (especially for cold water) are typical for DI. Symptoms of diabetes insipidus are quite similar to those of untreated diabetes mellitus, with the distinction that the urine is not sweet and there is no hyperglycemia (elevated blood glucose). Blurred vision is a rarity.

The extreme urination continues throughout the day and the night. In children, DI can interfere with appetite, eating, weight gain, and growth as well. They may present with fever, vomiting, or diarrhea. Adults with untreated DI may remain healthy for decades as long as enough water is drunk to offset the urinary losses. However, there is a continuous risk of dehydration.

## Diagnosis

In order to distinguish DI from other causes of excess urination, blood glucose, bicarbonate and calcium need to be tested. Electrolytes can show substantial derangement; hyponatremia (excess sodium levels) are common in severe cases. Urinalysis shows low electrolyte levels, and measurement of urine osmolality (or specific gravity) is generally low.

A *fluid deprivation test* helps determine whether DI is caused by:

1. excessive intake of fluid
2. a defect in ADH production
3. a defect in the kidneys' response to ADH

This test measures changes in body weight, urine output, and urine composition when fluids are withheld. Sometimes measuring blood levels of ADH during this test is also necessary.

To distinguish between the main forms, desmopressin stimulation is also used; desmopressin can be taken by injection, a nasal spray, or a tablet. While taking desmopressin, a patient should drink fluids or water only when thirsty and not at other times, as this can lead to sudden fluid accumulation in central nervous system. If desmopressin reduces urine output and increases osmolality, the pituitary production of ADH is deficient, and the kidney responds normally. If the DI is due to renal pathology, desmopressin does not change either urine output or osmolality.

If central DI is suspected, testing of other hormones of the pituitary, as well as magnetic resonance imaging (MRI), is necessary to discover if a disease process (such as a prolactinoma, or histiocytosis, syphilis, tuberculosis or other tumor or granuloma) is affecting pituitary function.

Habit drinking (in its severest form termed psychogenic polydipsia) is the most common imitator of diabetes insipidus at all ages. While many adult cases in the medical literature are associated with mental disorders, most patients with habit polydipsia have no other detectable disease. The distinction is made during the water deprivation test, as some degree of urinary concentration above isosmolar is eventually obtained before the patient becomes dehydrated.

## Treatment

Central DI and gestational DI respond to desmopressin. In dipsogenic DI, desmopressin is not usually an option. Desmopressin will be ineffective in nephrogenic DI. Instead, the diuretic hydrochlorothiazide (HCT or HCTZ) or indomethacin can improve NDI; HCT is sometimes combined with amiloride to prevent hypokalemia. Again, adequate hydration is important for patients with DI, as they may become dehydrated easily.

## Lesson 10. HAEMATOLOGY EMERGENC ES

### HEMORRHAGIC SHOCK

Shock is a state of inadequate perfusion, which does not sustain the physiologic needs of organ tissues. Many conditions, including blood loss but also including nonhemorrhagic states such as dehydration, sepsis, impaired autoregulation, obstruction, decreased myocardial function, and loss of autonomic tone, may produce shock or shocklike states.

**Pathophysiology:** In hemorrhagic shock, blood loss exceeds the body's ability to compensate and provide adequate tissue perfusion and oxygenation. This frequently is due to trauma, but it may be caused by spontaneous hemorrhage (eg, GI bleeding, childbirth), surgery, and other causes.

Most frequently, clinical hemorrhagic shock is caused by an acute bleeding episode with a discrete precipitating event. Less commonly, hemorrhagic shock may be seen in chronic conditions with subacute blood loss.

Physiologic compensation mechanisms for hemorrhage include initial peripheral and mesenteric vasoconstriction to shunt blood to the central circulation. This is then augmented by a progressive tachycardia. Invasive monitoring may reveal an increased cardiac index, increased oxygen delivery (ie,  $DO_2$ ), and increased oxygen consumption (ie,  $VO_2$ ) by tissues. Lactate levels, acid-base status, and other markers also may provide useful indicators of physiologic status. Age, medications, and comorbid factors all may affect a patient's response to hemorrhagic shock.

Failure of compensatory mechanisms in hemorrhagic shock can lead to death. Without intervention, a classic trimodal distribution of deaths is seen in severe hemorrhagic shock. An initial peak of mortality occurs within minutes of hemorrhage due to immediate exsanguination. Another peak occurs after 1 to several hours due to progressive decompensation. A third peak occurs days to weeks later due to sepsis and organ failure.

**History:** History taking should address the following:

- Specific details of the mechanism of trauma or other cause of hemorrhage are essential.
- Inquire about a history of bleeding disorders and surgery.
- Prehospital interventions, especially the administration of fluids, and changes in vital signs should be determined. Emergency medical technicians or paramedics should share this information.

**Prehospital Care:**

- The standard care consists of rapid assessment and expeditious transport to an appropriate center for evaluation and definitive care.
- Intravenous access and fluid resuscitation are standard. However, this practice has become controversial.
  - For many years, aggressive fluid administration has been advocated to normalize hypotension associated with severe hemorrhagic shock. Recent studies of urban patients with penetrating trauma have shown that mortality increases with these interventions; these findings call these practices into question.
  - Reversal of hypotension prior to the achievement of hemostasis may increase hemorrhage, dislodge partially formed clots, and dilute existing clotting factors. Findings from animal studies of uncontrolled hemorrhage support these postulates. These provocative results raise the possibility that moderate hypotension may be physiologically protective and should be permitted, if present, until hemorrhage is controlled.
  - These findings should not yet be clinically extrapolated to other settings or etiologies of hemorrhage. The ramifications of permissive hypotension in humans remain speculative, and safety limits have not been established yet.

### **Emergency Department Care:**

- Management of hemorrhagic shock should be directed toward optimizing perfusion of and oxygen delivery to vital organs.
- Diagnosis and treatment of the underlying hemorrhage must be performed rapidly and concurrently with management of shock.
- Supportive therapy, including oxygen administration, monitoring, and establishment of intravenous access (eg, 2 large-bore catheters in peripheral lines, central venous access), should be initiated.
  - Intravascular volume and oxygen-carrying capacity should be optimized.
  - In addition to crystalloids, some colloid solutions, hypertonic solutions, and oxygen-carrying solutions (eg, hemoglobin-based and perfluorocarbon emulsions) are used or being investigated for use in hemorrhagic shock.
  - Blood products may be required.
- Determination of the site and etiology of hemorrhage is critical to guide further interventions and definitive care.
- Control of hemorrhage may be achieved in the ED, or control may require consultations and special interventions.

**Consultations:** Consult a general or specialized surgeon, gastroenterologist, obstetrician-gynecologist, radiologist, and others as required.

## ACUTE ANEMIA

Anemia is characterized by a reduction in the number of circulating red blood cells (RBCs), the amount of hemoglobin, or the volume of packed red blood cells (hematocrit). Anemia is classified as acute or chronic. Acute anemia denotes a precipitous drop in the RBC population due to hemolysis or acute hemorrhage. In the emergency department (ED), acute hemorrhage is by far the most common etiology. This article also discusses other causes of acute anemia.

### Pathophysiology

The function of the RBC is to deliver oxygen from the lungs to the tissues and carbon dioxide from the tissues to the lungs. This is accomplished by using hemoglobin, a tetramer protein composed of heme and globin. Anemia impairs the ability of the RBCs to transport oxygen and carbon dioxide.

Physiologic response to anemia varies according to acuity and the type of insult. Gradual onset may allow for compensatory mechanisms to take place. With anemia due to acute blood loss, a reduction in oxygen-carrying capacity occurs along with a decrease in intravascular volume, with resultant hypoxia and hypovolemia. Hypovolemia leads to hypotension, which is detected by stretch receptors in the carotid bulb, aortic arch, heart, and lungs. These receptors transmit impulses along afferent fibers of the vagus and glossopharyngeal nerves to the medulla oblongata, cerebral cortex, and pituitary gland.

In the medulla, sympathetic outflow is enhanced while parasympathetic activity is diminished. Increased sympathetic outflow leads to norepinephrine release from sympathetic nerve endings and discharge of epinephrine and norepinephrine from the adrenal medulla. Sympathetic connection to the hypothalamic nuclei increases ADH secretion from the pituitary gland. ADH increases free water reabsorption in the distal collecting tubules. In response to decreased renal perfusion, juxtaglomerular cells in the afferent arterioles release renin in the renal circulation, leading to increased angiotensin I, which is converted by angiotensin-converting enzyme to angiotensin II.

Angiotensin II has a potent pressor effect on arteriolar smooth muscle. Angiotensin II also stimulates the zona glomerulosa of the adrenal cortex to produce aldosterone. Aldosterone increases sodium reabsorption from the proximal tubules of the kidney, thus increasing intravascular volume. The primary effect of the sympathetic nervous system is to maintain perfusion to the tissues by increasing systemic vascular resistance (SVR). The augmented venous tone increases the preload and, hence, the end-diastolic volume, which increases stroke volume. Therefore, stroke volume, heart rate, and SVR all are maximized by the sympathetic nervous system. Oxygen delivery is enhanced by the increased blood flow.

In states of hypovolemic hypoxia, the increased venous tone due to sympathetic discharge is thought to dominate the vasodilator effects of hypoxia. Counterregulatory hormones (eg, glucagon, epinephrine, cortisol) are thought to shift intracellular water to the intravascular space, perhaps because of the resultant hyperglycemia. This contribution to the intravascular volume has not been clearly elucidated.

### History

- Elicit a thorough and focused history while assessing ABCs and initiating resuscitation. In the critically ill patient, the emergency physician should attempt to obtain a focused history

(per the mnemonic AMPLE: allergies; medications, including over-the-counter drugs such as NSAIDs; past medical and surgical history; last meal; and events preceding incident).

- .
  - For noncommunicative patients, caretakers, paramedics, or primary physicians are a valuable source of information.
  - 
  - For injured patients, question paramedics about the circumstances of the accident, mechanism of the injury, initial vital signs, estimated blood loss in the field, prehospital treatment initiated, and response.
  - 
  - Patients with chronic illnesses are often knowledgeable about their condition and can provide information about prior complications and treatments. A call to their primary care physician may provide additional information and may help with disposition.
  -
- .
  - Important specific queries should address GI and menstrual histories (where applicable).
  - .
    - Specific questions about menstrual timing, frequency, and duration of vaginal bleeding in premenopausal females are required. Denial of the possibility of pregnancy should not preclude a beta-human chorionic gonadotropin (beta-hCG) test in premenopausal females with acute anemia.
    - 
    - When concern for GI hemorrhage exists, obtain a full GI history including stool color, consistency, and frequency. Black, tarry, malodorous, and frequent stools characterize upper GI bleeding proximal to the ligament of Treitz. Maroon, lumpy, irregular stools characterize lower GI bleeding.
    -
- .
  - Consider constitutional symptoms of chronic illnesses (eg, weight loss, night sweats, rashes, bowel changes).
- .
  - Consider family history of malignancy or hematologic problems.

## Physical

- . Initial evaluation
  - Monitor initial vital signs and address any abnormality. Periodic measurement of vital signs and examinations of appropriate organ systems are helpful in assessing ongoing hemorrhage.
  - 
  - In patients with multiple traumas, presume that every body cavity contains blood until investigation suggests otherwise. The chest, abdomen, pelvis, and extremities must undergo thorough physical examination with imaging, as clinically indicated.
- .
  - Cutaneous findings
    - In early hemorrhagic shock, capillary refill time may increase and the skin may feel cool to touch. With progressive shock, the skin is cold to touch, and it appears pale and mottled.
    -

- Flank ecchymosis (Grey-Turner sign) suggests retroperitoneal hemorrhage, while umbilical ecchymosis (Cullen sign) suggests intraperitoneal or retroperitoneal bleeding. Both are rare findings in acute states.
- 
- Patients with jaundice may have liver disease, hemoglobinopathies, or other forms of hemolysis. Purpura and petechiae suggest platelet disorders, and hemarthrosis may be due to hemophilia. Diffuse bleeding from intravenous sites and mucous membranes may be due to disseminated intravascular coagulation (DIC). In patients with alcoholic liver disease, spider angiomas, caput medusae, umbilical hernias, and hemorrhoids may be appreciated.
- .
- Neurologic findings
  - Agitation may present secondary to acute blood loss.
  - 
  - When blood loss exceeds 40% of total volume, the patient may lose consciousness.
- .
- Cardiovascular and respiratory findings
  - With chronic anemia, a hyperdynamic heart, with a prominent point of maximal impulse (PMI), a systolic flow murmur and, occasionally, an S<sub>3</sub>, may be heard.
  - 
  - Advanced trauma life support classifies shock into 4 levels.
    - § In class I (<15% blood loss), mild tachycardia may be present, but blood pressure is normal.
    - §
    - § In class II (15-30% blood loss), tachycardia, tachypnea, and a decreased pulse pressure are seen.
    - §
    - § Class III (30-40% blood loss) always leads to a measurable decrease in blood pressure as well as a significant tachycardia and a narrow pulse pressure.
    - §
    - § Class IV (40% and greater blood loss) leads to patient demise unless prompt resuscitative measures are taken. Marked tachycardia and significantly decreased blood pressure are common findings.
    - §
    - § Blood loss greater than 50% leads to loss of pulse and blood pressure.
  - 
  - Tachypnea may occur with blood loss greater than 15% of total volume (class II).
  - 
  - Patients with exacerbations of chronic anemia occasionally may present with signs and symptoms of congestive heart failure.
- .
- Genitourinary findings: Urinary output is decreased in class III shock and is negligible in class IV shock.
- .
- Other findings
  - Organomegaly is a common finding in patients with chronic blood disorders.
  -

- A palpable spleen and an enlarged hepatic inferior border (more than 3 cm below the right midclavicular costal margin) may suggest chronic anemia.

## Causes

The common pathway in life-threatening acute anemia is a sudden reduction in the oxygen-carrying capacity of the blood. Depending on the etiology, this may occur with or without reduction in the intravascular volume. It is generally accepted that an acute drop in hemoglobin to a level of 7-8 g/dL is symptomatic, while levels of 4-5 g/dL may be tolerated in chronic anemia, as the body is able to gradually replace the loss of intravascular volume.

## TREATMENT

### Prehospital Care

- Initial care of patients includes supplemental oxygen, intravenous fluid resuscitation, applying direct pressure to any external hemorrhage, fracture splinting, and rapid transport.
- 
- Recent prehospital studies suggest that trauma patients should receive minimal fluid resuscitation. This remains unproven and controversial.
- 
- The military antishock treatment (MAST) suit is occasionally used in the prehospital setting for trauma patients with pelvis and lower extremity injuries. It is contraindicated in patients with pulmonary edema or a ruptured diaphragm. It is also contraindicated in pregnant patients.

## HEMOCOAGULATION DESORDERS

### Hemophilia

Genetic deficiencies and a rare autoimmune disorder may lower plasma clotting factor levels of coagulation factors needed for a normal clotting process. When a blood vessel is injured, a temporary scab does form, but the missing coagulation factors prevent fibrin formation which is necessary to maintain the blood clot. Therefore, there is no increase in bleeding time with hemophilia because platelets are intact, allowing the formation of these temporary hemostatic plugs (clots). However, "late" bleeding is affected, because these hemostatic plugs are not able to be maintained.

The bleeding with external injury is normal, but incidence of late re-bleeding and internal bleeding is increased, especially into muscles, joints, or bleeding into closed spaces. Major complications include hemarthrosis, hemorrhage, Gastrointestinal bleeding, and menorrhagia.

### Treatment

Though there is no cure for haemophilia, it can be controlled with **regular injections** of the deficient clotting factor, i.e. factor VIII in haemophilia A or factor IX in haemophilia B. Some haemophiliacs develop antibodies (inhibitors) against the replacement factors given to them, so the amount of the factor has to be increased or non-human replacement products must be given, such as porcine factor VIII Troy.



If a patient becomes refractory to replacement coagulation factor as a result of circulating inhibitors, this may be overcome with recombinant human factor VII (NovoSeven®), which is registered for this indication in many countries.

In western countries, common standards of care fall into one of two categories: prophylaxis or on-demand. Prophylaxis involves the infusion of clotting factor on a regular schedule in order to keep clotting levels sufficiently high to prevent spontaneous bleeding episodes. On-demand treatment involves treating bleeding episodes once they arise.

As a direct result of the contamination of the blood supply in the late 1970s and early/mid 1980s with viruses such as Hepatitis and HIV, new methods were developed in the production of clotting factor products. The initial response was to heat treat (pasteurize) plasma-derived factor concentrate, followed by the development of monoclonal factor concentrates which use a combination of heat treatment and affinity chromatography to inactivate any viral agents in the pooled plasma from which the factor concentrate is derived. The Lindsay Tribunal in Ireland investigated, among other things, the slow adoption of the new methods.

Since 1993 (Dr. Mary Nugent), recombinant factor products (which are typically cultured in Chinese hamster ovary (CHO) tissue culture cells and involve little, if any human plasma products) have become available and are widely used in wealthier western countries. While recombinant clotting factor products offer higher purity and safety, they are, like concentrate, extremely expensive, and not generally available in the developing world. In many cases, factor products of any sort are difficult to obtain in developing countries.

## Disseminated intravascular coagulation

**Disseminated intravascular coagulation (DIC)**, also called **consumptive coagulopathy**, is a pathological process in the body where the blood starts to coagulate throughout the whole body. This depletes the body of its platelets and coagulation factors, and there is a paradoxically increased risk of hemorrhage. It occurs in critically ill patients, especially those with Gram-negative sepsis (particularly meningococcal sepsis) and acute promyelocytic leukemia

### Causes

There are a variety of causes of DIC, all usually causing the release of chemicals into the blood that instigates the coagulation.

- Sepsis, particularly with gram-negative bacteria.
- Obstetric complications (most common cause), with chemicals from the uterus being released into the blood, or from amniotic fluid embolisms, and eclampsia can be causes. Another obstetric condition which can cause DIC is *abruptio placentae*.
- Tissue trauma such as burns, accidents, surgery or shock.
- Liver disease
- Incompatible blood transfusion reactions or massive blood transfusion (more than the total circulatory volume)
- Malignant cancers, or widespread tissue damage (e.g. burns), or hypersensitivity reactions all can produce the chemicals leading to a DIC.
- Viral hemorrhagic fevers bring about their frank effects, paradoxically, by causing DIC.

- Envenomation by some species of venomous snakes, such as those belonging to the genus *Diagnosis*

Although numerous blood tests are often performed on patients prone to DIC, the important measures are: full blood count (especially the platelet count), fibrin degradation products or D-dimer tests (markers of fibrinolysis), bleeding time and fibrinogen levels. Decreased platelets, elevated FDPs or D-dimers, prolonged bleeding time and decreased fibrinogen are markers of DIC.

## Treatment

The underlying cause must be treated initially. Anticoagulants are only given when indicated (development of thrombotic renal complications) as patients with DIC are prone to bleeding. Platelets may be transfused if counts are very low, and fresh frozen plasma may be administered.

DIC results in lower fibrinogen (as it has all been converted to fibrin), and this can be tested for in the hospital lab. A more specific test is for "fibrin split products" (FSPs) or "fibrin degradation products" (FDPs) which are produced when fibrin undergoes degradation when blood clots are dissolved by fibrinolysis.

In some situations, infusion with antithrombin may be necessary. A new development is drotrecogin alfa (Xigris®), a recombinant activated protein C product. Activated Protein C (APC) deactivates clotting factors V and VIII, and the presumed mechanism of action of drotrecogin is the cessation of the intravascular coagulation. Due to its high cost, it is only used strictly on indication in intensive care patients.<sup>[1]</sup>

The prognosis for those with DIC, depending on its cause, is often grim, leading the initials to be known colloquially as "death is coming".<sup>[2]</sup>

## TROMBOCYTOPENIA

### Signs and symptoms

Often, low platelet levels do not lead to clinical problems; rather, they are picked up on a routine full blood count. Occasionally, there may be bruising, particularly purpura in the forearms, nosebleeds and/or bleeding gums.

It is vital that a full medical history is elicited, to ensure the low platelet count is not due to a secondary process. It is also important to ensure that the other blood cell types red blood cells, and white blood cells, are not also suppressed.

### Diagnosis

Laboratory tests might include: full blood count, liver enzymes, renal function, vitamin B12 levels, folic acid levels, erythrocyte sedimentation rate, and peripheral blood smear.

If the cause for the low platelet count remains unclear, bone marrow biopsy is often undertaken, to differentiate whether the low platelet count is due to *decreased production* or *peripheral destruction*.

## ITP (VERLGOF DISEASE0

In many cases, ITP is self-limited, and does not require treatment. Platelet counts less than ten thousand per mm<sup>3</sup> usually require treatment (less than fifty thousand requires treatment, less than ten thousand is a potentially dangerous situation) and patients with significant bleeding and thrombocytopenia due to ITP are also usually treated. The threshold for treating ITP has decreased since the 1990s, and hematologists recognize that patients rarely bleed with platelet counts greater than ten thousand, though there are documented exceptions to this observation. Treatments for ITP include:

- Prednisone and other corticosteroids
- Intravenous gamma globulin
- Splenectomy
- Danazol
- Rituximab

Thrombopoietin analogues have been tested extensively for the treatment of ITP. These agents had previously shown promise but had been found to stimulate antibodies against endogenous thrombopoietin or lead to thrombosis.

A medication known as AMG 531 was found to be safe and effective for the treatment of ITP in refractory patients.<sup>[5]</sup> AMG 531 is a peptide that bears no sequence homology with endogenous human thrombopoietin, so it is not as likely to lead to neutralizing antibodies as previous peptide thrombopoietin analogues.<sup>[6]</sup>

## Treatment

Prednisone in a dose of 1 mg/kg/d for 2 weeks and then tapered over 2 more weeks has been shown to improve gastrointestinal and joint symptoms. Although this regimen did not decrease the incidence of renal disease, it did lessen the severity of nephritis in some patients.

Other treatment regimens have included IV or oral steroids with or without any of the following: azathioprine, cyclophosphamide, cyclosporine, dipyridamole, plasmapheresis, high-dose IV immunoglobulin G (IVIg), danazol, or fish oil. A recent study of 12 patients with severe HSP nephritis indicated that patients did well with a treatment of methylprednisolone at 30 mg/kg/d for 3 days followed by oral corticosteroids at 2 mg/kg/d for 2 months, cyclophosphamide at 2 mg/kg/d for 2 months, and dipyridamole at 5 mg/kg/d for 6 months.

## Lesson 11.

## ALLERGOLGY AND IMMUNOLOGY EMERGENCES

## Allergy

### ANAPHYLAXIS

Anaphylaxis refers to a severe allergic reaction in which prominent dermal and systemic signs and symptoms manifest. The full-blown syndrome includes urticaria (hives) and/or angioedema with hypotension and bronchospasm. The classic form, described in 1902, involves prior sensitization to an allergen with later re-exposure, producing symptoms via an immunologic mechanism. An

anaphylactoid reaction produces a very similar clinical syndrome but is not immune-mediated. Treatment for both conditions is similar, and this article uses the term anaphylaxis to refer to both conditions unless otherwise specified.

**Pathophysiology:** Rapid onset of increased secretion from mucous membranes, increased bronchial smooth muscle tone, decreased vascular smooth muscle tone, and increased capillary permeability occur after exposure to an inciting substance. These effects are produced by the release of mediators, which include histamine, leukotriene C4, prostaglandin D2, and tryptase.

In the classic form, mediator release occurs when the antigen (allergen) binds to antigen-specific immunoglobulin E (IgE) attached to previously sensitized basophils and mast cells. The mediators are released almost immediately when the antigen binds. In an anaphylactoid reaction, exposure to an inciting substance causes direct release of mediators, a process that is not mediated by IgE. Increased mucous secretion and increased bronchial smooth muscle tone, as well as airway edema, contribute to the respiratory symptoms observed in anaphylaxis. Cardiovascular effects result from decreased vascular tone and capillary leakage. Histamine release in skin causes urticarial skin lesions.

The most common inciting agents in anaphylaxis are parenteral antibiotics (especially penicillins), IV contrast materials, Hymenoptera stings, and certain foods (most notably, peanuts). Oral medications and many other types of exposures also have been implicated. Anaphylaxis also may be idiopathic.

### History:

- Anaphylactic reactions almost always involve the skin or mucous membranes. More than 90% of patients have some combination of urticaria, erythema, pruritus, or angioedema.
- The upper respiratory tract commonly is involved, with complaints of nasal congestion, sneezing, or coryza. Cough, hoarseness, or a sensation of tightness in the throat may presage significant airway obstruction.
- Eyes may itch and tearing may be noted. Conjunctival injection may occur.
- Dyspnea is present when patients have bronchospasm or upper airway edema. Hypoxia and hypotension may cause weakness, dizziness, or syncope. Chest pain may occur due to bronchospasm or myocardial ischemia (secondary to hypotension and hypoxia).
- GI symptoms of cramplike abdominal pain with nausea, vomiting, or diarrhea also occur but are less common, except in the case of food allergy.
- In a classic case of anaphylaxis, the patient or a bystander provides a history of possible exposures that may have caused the rapid onset of skin and other manifestations. This history often is partial; exposure may not be recalled, or it may not be considered significant by the patient or physician. For example, when queried about medications, a patient may not mention over-the-counter (OTC) products. The clinician may not realize that, while reactions are usually rapid in onset, they also may be delayed.

### Physical:

- General

- Physical examination of patients with anaphylaxis depends on affected organ systems and severity of attack. Vital signs may be normal or significantly disordered with tachypnea, tachycardia, and/or hypotension.
- Place emphasis on determining the patient's respiratory and cardiovascular status.
- Frank cardiovascular collapse or respiratory arrest may occur in severe cases. Anxiety is common unless hypotension or hypoxia causes obtundation. Shock may occur without prominent skin manifestations or history of exposure; therefore, anaphylaxis is part of the differential diagnosis for patients who present with shock and no obvious cause.
- General appearance and vital signs vary according to severity of attack and affected organ system(s). Patients commonly are restless due to severe pruritus from urticaria. Anxiety, tremor, and a sensation of cold may result from compensatory endogenous catecholamine release. Severe air hunger may occur when the respiratory tract is involved. If hypoperfusion or hypoxia occurs, the patient may exhibit a depressed level of consciousness or may be agitated and/or combative. Tachycardia usually is present, but bradycardia may occur in very severe reactions.

#### · Skin

- The classic skin manifestation is urticaria (ie, hives). Lesions are red and raised, and they sometimes have central blanching. Intense pruritus occurs with the lesions. Lesion borders usually are irregular and sizes vary markedly. Only a few small or large lesions may become confluent, forming giant urticaria. At times, the entire dermis is involved with diffuse erythema and edema. Hives can occur anywhere on the skin.
- In a local reaction, lesions occur near the site of a cutaneous exposure (eg, insect bite). The involved area is erythematous, edematous, and pruritic. If only local skin reaction (as opposed to generalized urticaria) is present, systemic manifestations (eg, respiratory distress) are less likely. Local reactions, even if severe, are not predictive of systemic anaphylaxis on re-exposure.
- Lesions typical of angioedema also may manifest in anaphylaxis. The lesions involve mucosal surfaces and deeper skin layers. Angioedema usually is nonpruritic and associated lesions are nonpitting. Lesions most often appear on the lips, palms, soles, and genitalia.

#### · Pulmonary

- Upper airway compromise may occur when the tongue or oropharynx is involved. When the upper airway is involved, stridor may be noted. The patient may have a hoarse or quiet voice and may lose speaking ability as the edema progresses. Complete airway obstruction is the most common cause of death in anaphylaxis.
- Wheezing is common when patients have lower airway compromise due to bronchospasm or mucosal edema.
- In angioedema, due to ACE inhibitors, marked edema of the tongue and lips may obstruct the airway.

- Cardiovascular

- Cardiovascular examination is normal in mild cases. In more severe cases, compensatory tachycardia occurs due to loss of vascular tone.
- Intravascular volume depletion may take place as a consequence of capillary leakage. These mechanisms also lead to development of hypotension.
- Relative bradycardia has been reported.

**Causes:**

- A wide variety of substances can cause anaphylaxis. Anaphylaxis also may be idiopathic.
- In the classic form of anaphylaxis, a foreign protein is the inciting agent (eg, antigen). On initial exposure, the antigen elicits generation of an IgE antibody. The antibody residue binds to mast cells and basophils. On re-exposure, the antigen binds to the antibody, and the receptors are activated. Clinical manifestations result from release of immune response mediators such as histamine, leukotrienes, tryptase, and prostaglandins. The same mechanism occurs when a nonimmunogenic foreign substance binds as a so-called hapten to a native carrier protein, creating an immunogenic molecule. Factors influencing severity of a reaction include degree of host sensitivity and dose, route, and rate of administration of the offending agent.
- Parenteral exposures tend to result in faster and more severe reactions. Most severe reactions occur soon after exposure. The faster a reaction develops, the more severe it is likely to be. While most reactions occur within hours, symptoms may not occur for as long as 3-4 days after exposure.
- Drugs
  - Penicillin and cephalosporin antibiotics are the most commonly reported medical agents in anaphylaxis. This prevalence is a function of the immunogenicity and overuse of these agents. Because of their molecular and immunologic similarity, cross-sensitivity may exist. Reports often assert that 10% of patients allergic to a penicillin antibiotic are allergic to cephalosporins. A recent report suggests that actual incidence of cross-reactivity is lower (perhaps 1%), with most reactions considered mild. A more recent review indicated that patients with a history of allergy to penicillin seem to have a higher risk (by a factor of about 3) of subsequent reaction to any drug and that the risk of an allergic reaction to cephalosporins in patients with a history of penicillin allergy may be up to 8 times as high as the risk in those with no history of penicillin allergy (ie, at least part of the observed "cross reactivity" may represent a general state of immune hyperresponsiveness, rather than true cross-reactivity).
  - Reactions tend to be more severe and rapid in onset when the antibiotic is administered parenterally.
  - Anaphylaxis may occur in a patient with no prior history of drug exposure.
  - History of penicillin or cephalosporin allergy often is unreliable and is not predictive of future reactions. Up to 85% of patients reporting an allergic reaction to penicillin do not react on subsequent exposure. When a drug in either class is the drug of choice for a patient with a life-threatening emergency, a number of options exist.

When the history is indefinite, the drug may be administered under close observation; however, when possible, obtain the patient's informed consent. Immediate treatment measures for anaphylaxis should be available. Alternatively, when the history is more convincing, a desensitization or prophylactic pretreatment protocol may be instituted or another agent selected.

- Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) commonly are implicated in allergic reactions and anaphylaxis. Bronchospasm is common in patients with reactive airway disease and nasal polyps. Cross-reactivity may occur between the various NSAIDs.
- Intravenous radiocontrast media
  - IV administered radiocontrast media causes an anaphylactoid reaction that is clinically identical to true anaphylaxis and is treated in the same way. The reaction is not related to prior exposure. Shellfish or "iodine allergy" is not a contraindication to use of IV contrast and does not mandate a pretreatment regimen. As with any "allergic" patient, give consideration to use of low molecular weight (LMW) contrast.
  - The term iodine allergy is a misnomer. Iodine is an essential trace element present throughout the body. No one is allergic to iodine. Patients who report iodine allergy usually have had either a prior contrast reaction or a shellfish allergy. Manage these patients as indicated earlier.
  - Approximately 1-3% of patients who receive hyperosmolar IV contrast experience a reaction. Use of LMW contrast decreases incidence of reactions to approximately 0.5%. Personnel, medications, and equipment needed for treatment of allergic reactions always should be available when these agents are administered. Obtain consent before administration.
  - Reactions to radiocontrast usually are mild (most commonly urticarial), with only rare fatalities reported. Risk of a fatal reaction has been estimated at 0.9 cases per 100,000 exposures.
  - Mucosal exposure (eg, GI, genitourinary [GU]) to radiocontrast agents has not been reported to cause anaphylaxis; therefore, a history of prior reaction is not a contraindication to GI or GU use of these agents.
  - Pretreatment with antihistamines or corticosteroids and use of LMW agents lead to lower rates of anaphylactoid reactions to IV contrast. Consider these measures for patients who have prior history of reaction, since rate of recurrence is estimated at 17-60%. Patients who are atopic and/or asthmatic also are at increased risk of reaction. In addition, allergic reaction is more difficult to treat in those taking beta-blockers.
- Hymenoptera stings
  - Hymenoptera stings are a common cause of allergic reaction and anaphylaxis. An uncertain but enormous number of exposures occur; accurate reaction rates are difficult to estimate. In the United States, Hymenoptera envenomations result in fewer than 100 reported deaths per year.

- Local reaction and urticaria without other manifestations of anaphylaxis are much more common than full-blown anaphylaxis. Generalized urticaria is a risk factor for subsequent anaphylaxis; but a local reaction, even if severe, is not a risk factor for anaphylaxis.
- Caution patients treated and released from the ED after an episode of anaphylaxis or generalized urticaria from Hymenoptera envenomation to avoid future exposure when possible. Consider referral to an allergist for desensitization, particularly when further exposure is likely. Additionally, consider prescribing a treatment kit with an epinephrine auto-injector and oral antihistamine. Both are effective measures in preventing or ameliorating future reactions.

## · Allergies

- Food allergy is common. Symptoms usually are mild and limited to the GI tract, but full-blown anaphylaxis can occur. Fatalities are rare compared to number of exposures; however, the number of exposures is so high that foods may be the commonest cause of anaphylaxis. Anaphylaxis due to foods may be an underrecognized cause of sudden death and an unappreciated cause of diagnosed anaphylaxis. Commonly implicated foods include nuts (especially peanuts), legumes, fish and shellfish, milk, and eggs.
- Latex allergy is an increasingly recognized problem in medical settings, where use of gloves and other latex products is ubiquitous. Most reactions are cutaneous or involve the mucous membranes. Anaphylactic reactions occur and have been reported with seemingly benign procedures (eg, Foley catheter insertion, intraperitoneal exposure to gloves during surgery).

### Lab Studies:

- The diagnosis of anaphylaxis is clinical and does not rely on laboratory testing. When typical symptoms are noted in association with a likely exposure, diagnosis is virtually certain. Ancillary testing may help assess severity of reaction, although this is primarily a clinical judgment. When unclear, ancillary testing may help establish the diagnosis.
- The only potentially useful test at the time of reaction is measurement of serum mast cell tryptase. Tryptase is released from mast cells in both anaphylactic and anaphylactoid reactions. Levels are usually raised in severe reactions. Mast cell tryptase is raised transiently with blood levels reaching a peak approximately an hour after reaction onset.
  - Tryptase levels may aid in later diagnosis and treatment.
  - Consider the test in cases for which diagnosis of anaphylaxis is uncertain.
  - The utility of this test awaits full evaluation.
- Cardiac monitoring in patients with severe reactions and in those with underlying cardiovascular disease is important, particularly when adrenergic agonists are used in treatment. Pulse oximetry also is useful.

### Imaging Studies:



- Imaging studies are not generally useful in the diagnosis and management of anaphylaxis, although they may be used as diagnostic aids when diagnosis is unclear.

### Other Tests:

- Sensitivity testing
  - Testing for sensitivity to penicillin antibiotics may be useful when a penicillin or cephalosporin antibiotic is the drug of choice for a serious infection in a patient who has a history of severe allergic reaction. Obtain informed consent, and ensure that resuscitative equipment is immediately available. Protocols for acute testing for allergy to penicillin or cephalosporin antibiotics involve administration of increasing IV doses of the chosen antibiotic, while observing the patient for pruritus, flushing, urticaria, dyspnea, hypotension, or other manifestations of anaphylaxis. If no manifestations are observed, a full dose of the antibiotic may be administered safely.
  - A suggested protocol for IV testing begins with 0.001 mg of the chosen drug. At 10-min intervals, incrementally increase the dose (eg, 0.001 mg, 0.005 mg, 0.01 mg, 0.05 mg, 0.1 g, 0.5 mg, 1 mg, 10 mg, 50 mg, 100 mg, full dose), while observing the patient. Many other protocols exist. In most circumstances, perform desensitization on an inpatient basis. If the necessary resources are available, desensitization may be performed in the ED.

### Procedures:

- Intravenous contrast reaction prevention
  - Patients with a history of severe reactions to IV contrast material may require use of contrast in an urgent or emergency situation. Alternatives (eg, spiral CT scan for ureteral stone, Doppler ultrasound for deep venous thrombosis [DVT]) should be considered but are not always feasible. In these circumstances, a prophylactic regimen of corticosteroids and antihistamines may be used. The precise efficacy of these regimens is difficult to evaluate, but they generally are considered effective. One author states that the recurrence rate for patients with a previous reaction was reduced from 17-60% to 9% when conventional contrast material was used; the rate was reduced to less than 1% when low osmolality material was employed after a pretreatment regimen.
  - The use of H<sub>2</sub> blockers has not been shown to decrease the risk of reaction to IV contrast. One study suggests H<sub>2</sub> blockers actually appear to increase the risk.
  - A widely quoted protocol for prevention of reactions to IV contrast suggests the following:
    - § Use low osmolality contrast.
    - § Administer hydrocortisone (200 mg IV); wait 2 hours if clinically appropriate.
    - § Administer diphenhydramine (50 mg IM) immediately before the procedure.
- Desensitization regimens
  - Desensitization regimens for penicillin and cephalosporin antibiotic allergy have been shown effective. Because these regimens are lengthy (approximately 6 h), they

have limited applicability to the ED. When patients wait for long periods in the ED or in an observation unit, consider desensitization regimens.

- A typical desensitization regimen involves administering the antibiotic of choice in an initial dose of 0.01 mg. While observing the patient, double the dose every 10-15 minutes until a full dose has been administered.
- Desensitization regimens do not protect against non-IgE-mediated reactions that may be severe or even life threatening (eg, Stevens-Johnson syndrome).
- While theoretically attractive, premedication regimens have not been clinically shown to decrease incidence or severity of IgE-mediated allergic reactions to antibiotics

### **Prehospital Care:**

- Prehospital patients with symptoms of severe anaphylaxis should first receive standard interventions. Interventions include high-flow oxygen, cardiac monitoring, and IV access. These measures are appropriate for an asymptomatic patient who has a history of serious reaction and has been re-exposed to the inciting agent. Additional treatment depends upon the condition of the patient and the severity of the reaction. Measures beyond basic life support (BLS) are not necessary for patients with purely local reactions.
- Immediately assess airway patency due to the potential for compromise secondary to edema or bronchospasm. Active airway intervention may be difficult due to laryngeal or oropharyngeal edema. In this circumstance, it may be preferable to defer intubation attempts, and instead ventilate with a bag/valve/mask apparatus while awaiting medications to take effect. In extreme circumstances, cricothyrotomy or catheter jet ventilation may be lifesaving. Inhaled beta-agonists are used to counteract bronchospasm and should be administered to patients who are wheezing.
- The IV line should be of large caliber due to the potential requirement for large-volume IV fluid resuscitation. Isotonic crystalloid solutions (ie, normal saline, Ringer lactate) are preferred. A keep vein open (KVO) rate is appropriate for patients with stable vital signs and only cutaneous manifestations. If hypotension or tachycardia is present, administer a fluid bolus of 20 mg/kg for children and 1 L for adults. Further fluid therapy depends on patient response. Large volumes may be required in the profoundly hypotensive patient.
- Administer epinephrine to patients with systemic manifestations of anaphylaxis. With mild cutaneous reactions, an antihistamine alone may be sufficient, thus the potential adverse effects of epinephrine can be avoided. Patients on beta-blocker medications may not respond to epinephrine. In these cases, glucagon may be useful. The Medication section describes dosage, routes of administration, and contraindications for medications discussed in this section. Antihistamines (eg, H1 blockers), such as diphenhydramine (Benadryl) are important and should be administered for all patients with anaphylaxis or generalized urticaria.
- Corticosteroids are used in anaphylaxis primarily to decrease the incidence and severity of delayed or biphasic reactions. Corticosteroids may not influence the acute course of the disease; therefore, they have a lower priority than epinephrine and antihistamines.

### **Emergency Department Care:**

- ED care begins with standard monitoring and treatment, including oxygen, cardiac monitoring, and a large-bore IV with isotonic crystalloid solution. Further intervention depends on severity of reaction and affected organ system(s).
- Rapidly assess airway patency in patients with systemic signs or symptoms. If required, intubation may be difficult to achieve because of upper airway or facial edema. Standard rapid sequence induction (RSI) techniques can be used but may cause loss of the airway in a patient whose airway anatomy is altered by edema. Epinephrine may rapidly reverse airway compromise, and bag/valve/mask ventilation may be effective in the interim when intubation is not possible. Surgical airway intervention using standard cricothyrotomy is an option when orotracheal intubation or bag/valve/mask ventilation is not effective.
  - Wheezing or stridor indicates bronchospasm or mucosal edema. Treatment with epinephrine and inhaled beta-agonists is effective for these indications.
  - Recommendations to treat refractory bronchospasm with corticosteroids have been made because of their effectiveness in reactive airway disease. As in asthma therapy, onset of action is delayed for several hours. Aminophylline also has been recommended for bronchospasm in anaphylaxis and may be more rapidly effective than corticosteroids.
- Hypotension in anaphylaxis usually is due to vasodilatation and capillary fluid leakage. Epinephrine is the primary pharmacologic treatment for these findings. H1-blocking antihistamines also may have a role in reversing hypotension. Some authors also recommend H2-blocking agents. Large volume fluid resuscitation with isotonic crystalloid often is needed to support the circulation in patients with cardiovascular manifestations of anaphylaxis.
  - Refractory hypotension first should be treated with large volumes of crystalloid and repeated doses of epinephrine or a continuous epinephrine infusion. If this is not effective, other pressors with alpha-adrenergic activity, such as levarterenol (Levophed) or dopamine, may be considered. Cases of effective use of military antishock trousers (MAST) for refractory hypotension have been reported.
  - Mediators of anaphylaxis are not considered to have direct myocardial toxicity. In patients with preexisting heart disease, ischemic myocardial dysfunction may occur due to hypotension and hypoxia. Epinephrine still may be necessary in patients with severe anaphylaxis, but remember the potential for exacerbating ischemia. If pulmonary congestion or evidence of cardiac ischemia is present, fluid resuscitation should be approached more cautiously.
  - Patients taking beta-blockers may be resistant to the effects of epinephrine. Larger than usual doses may be needed. Glucagon may be effective in this circumstance, because it increases intracellular cyclic adenosine monophosphate (cAMP) levels by a mechanism that does not depend upon beta-receptors.
- Cutaneous effects of anaphylaxis are uncomfortable but not life threatening. Patients often respond promptly to epinephrine and H1 antihistamines. Some authors state that corticosteroids help prevent recurrence of symptoms (both cutaneous and systemic) that may occur 6-8 hours after successful treatment (so-called biphasic reaction). H2 blockers may have an added effect.

- GI symptoms in anaphylaxis respond to H1 antihistamines and epinephrine.

### **Consultations:**

- Acute manifestations of anaphylaxis usually respond to ED treatment. In refractory cases, consult with an allergist, cardiologist, pulmonologist, or other intensivist.
- Consultation with an allergist (when available) is appropriate when desensitization to an antibiotic is contemplated.
- When a patient at high risk for contrast reaction is under consideration for a contrast study, consultation with the radiologist regarding pretreatment and choice of contrast agent is appropriate.
- Refer patients who are treated and released from the ED after an episode of anaphylaxis or generalized urticaria to their primary care physician or to an allergist for follow-up. At that time, consideration can be given to skin testing and possible desensitization.

## **BEE AND HYMENOPTERA STINGS**

Hymenoptera stings account for more deaths in the United States than any other envenomation. Order Hymenoptera includes *Apis* species, ie, bees (European, African), vespids (wasps, yellow jackets, hornets), and ants. Although most deaths result from immunologic mechanisms, some are from direct toxicity. Severe anaphylactoid reactions occur occasionally when toxins directly stimulate mast cells. While the vast majority of stings cause only minor problems, stings cause a significant number of deaths.

**Pathophysiology:** Target organs are the skin, vascular system, and respiratory system. Pathology is similar to other immunoglobulin E (IgE)–mediated allergic reactions. Urticaria, vasodilation, bronchospasm, laryngospasm, and angioedema are prominent symptoms of the reaction. Respiratory arrest may result in refractory cases.

### **Frequency:**

- **In the US:** Ants sting 9.3 million people each year. Other Hymenoptera account for more than 1 million stings annually.

### **History:**

- A patient's reaction to a Hymenoptera sting determines the treatment required. Reactions may be graded as local, urticaria without systemic symptoms, and generalized. Emergency physicians should attempt to determine degree of reaction based on both patient history and a physical examination.
- Rapid onset of symptoms is the rule; 50% of deaths occur within 30 minutes of the sting, and 75% occur within 4 hours.
- Fatal allergic reactions can occur as the first generalized reaction. Far more common, however, is a fatal reaction following a previous, milder generalized reaction. The shorter the interval since the last sting, the more likely it is that a severe reaction will take place.
- Large local reactions do not predispose patients to generalized reactions. Local reactions may be life threatening if local swelling at the sting site compromises the airway. Local reactions to stings can cause peripheral nerve block.

- Local reactions may produce the following:
  - Pain occurs immediately after sting.
  - Edema is marked and may extend to 10 cm from site of envenomation.
  - The insect frequently is seen by patient and may be identified from the description.
  - Bleeding may occur at site of sting.
  - Pruritus is common.
  - Vasodilation may produce a sensation of warmth.
  - The stinging apparatus may have been seen in the wound and removed prior to presentation.
  - Nausea or vomiting may occur without generalization.
  - Visceral pain may occur with stings in the gastrointestinal (GI) tract after ingestion of the insect.
- Urticaria may occur with or without the symptoms noted in local reaction.
- Generalized reactions may produce the following symptoms:
  - Urticaria
  - Confluent red rash
  - Shortness of breath, wheezing
  - Edema in airway, tongue, or uvula
  - Weakness, syncope
  - Anxiety, confusion
  - Chest pain

**Physical:**

- Local reactions may include the following:
  - Erythema, edema, warmth, tenderness
  - Drainage from site of sting
  - Compromised distal circulation as result of edema
  - Distal sensation loss from stings over peripheral nerve

- Corneal ulceration from corneal stings
- With bee stings, stinging apparatus visible at sting site
- Ant stings: Vesicles from fire ants, classic arc of fire ant stings, and ant stings on mucous membranes or conjunctival surfaces cause dramatic swelling in patients who are sensitive.
- Urticaria or generalized redness may develop without systemic symptoms.
- Generalized reactions may include the following symptoms:
  - Urticaria
  - Vomiting
  - Wheezing
  - Tachypnea
  - Hypotension
  - Laryngoedema, lingual edema, uvular edema
  - Delirium, shock
  - Respiratory arrest

### **Causes:**

- Hymenoptera are social creatures that typically sting to protect their colony, nest, or hive. Most stings are incited by proximity to the colony. Noisy or vigorous activity (eg, lawn mowers, weed eaters), bright or dark colors, and perfumes also may incite stings. In addition, these insects can release defense pheromones that attract other insects and induce them to sting. These pheromones are released during stinging or when an insect is smashed. Hymenoptera frequently are swallowed, and their stings can cause painful swelling in the mouth or esophagus.
- Although bee and wasp venom varies from species to species, all venom is composed primarily of proteins, peptides, and amines. Toxic components include phospholipase, histamine, bradykinin, acetylcholine, dopamine, and serotonin. In addition, mast cell degranulating (MCD) peptide and mastoparan are peptides that can cause degranulation of mast cells and result in an anaphylactoid reaction. Molecule size and the presence of protein enhance the antigen properties of venom, making it a potent activator of the immune system. Most significant reactions are mediated through true IgE allergic mechanisms that activate mast cell degranulation.
- Anaphylactoid reactions may occur. However, venom load may be sufficient to cause fatal injury without the added effects of the endogenous system. This may result from as few as 30 vespid stings or 200 honeybee stings. Since the compounds are similar in anaphylactic and toxic reactions, pathology and treatment also are similar.

- Bees and wasps sting through a modified ovipositor. They puncture the skin with a hollow stinger and then inject venom. Bees leave their barbed stinger in the skin along with its stinging apparatus, killing the bee. Vespids have smooth or less-barbed stingers and can sting more than once. Vespids are responsible for almost twice as many allergic reactions as honeybees. Retained stingers can cause granuloma formation and subsequent epidermal necrosis.
- A "killer" bee is an Africanized honeybee (*Apis mellifera scutellata*), the offspring of aggressive wild African honeybees and domesticated European honeybees. Aggressive defensive behavior is dominant in these offspring. This variety displays increased group defense behavior. One pheromone, isoamylacetate, has been isolated as a mediator of this activity. Africanized bees defend their hive up to a 150-yard radius, 3 times the distance of European bees.
  - As of May 2000, Africanized bees have migrated from their western-hemisphere origin in Brazil to Texas, Arizona, California, New Mexico, and Nevada, according to the US Department of Agriculture.
  - Multiple stings from these species are more common. Hymenoptera fly at only 4 mph, allowing most victims to flee after only a few stings. Overwhelming numbers of stings usually occur in young patients or in those slowed by physical limitations or intoxication.
- In addition to reaction to stings, bee venom may be encountered as a result of apiotherapy. In this Chinese treatment, ointment containing bee venom may be applied to skin or eye and result in an immunologic reaction.
- Ant stings
  - Ants account for one half of all insects. While many ant species sting, the most aggressive in the United States are imported fire ants, *Solenopsis invicta*. These ants fiercely guard their territory and attack intruders in large numbers, inflicting thousands of stings and bites to victims unable to escape. Fire ant venom is 95% alkaloid, which is unique among ants. A fire ant typically bites with its mandibles, then swivels its abdomen and stings repeatedly in an arc about the bite site. Their stings develop into sterile pustules and then rupture, leaving crusted wounds that may become infected secondarily. Patients have survived as many as 5000 fire ant stings. Brazilian fire ants, *S invicta*, have nearly eradicated native ant species in their range from Florida to Texas and north to Arkansas and South Carolina. *S invicta* is found in South and North America in areas where mean high temperatures are 15°C or higher.
  - Stings from other ants often closely resemble those of wasps and bees, although with less tissue destruction and less severity. Harvester ants, *Pogonomyrmex* species, inject venom containing a hemolysin. This sting frequently creates an ecchymotic area surrounding the sting site. Some species of field ants truly bite with the mandible and spray the acidic toxin into the wound without injecting venom. Formic acid, a component of ant venom uncommon in bee or wasp stings, is derived from the superfamily name Formicidae. Ant stings cause generalized reactions less often than stings from flying Hymenoptera.

### Prehospital Care:

- Prehospital care must assess severity immediately and provide immediate appropriate treatment, because the most endangered patients die within 30 minutes of a sting.
- Local reactions can be life threatening if swelling occludes the airway. Initiate invasive measures to secure the airway if this occurs. Otherwise, the following local care measures suffice:
  - Diphenhydramine limits the size of the local reaction.
  - Clean wound and remove stinger if present.
  - Apply ice or cool packs.
  - Elevate extremity to limit edema.
- Manage generalized reactions similarly to anaphylaxis, even in the absence of shock. Check airway and ventilatory status. Treatment should include an initial intravenous (IV) bolus of 10-20 mL/kg isotonic crystalloids in addition to diphenhydramine and epinephrine.
- If the patient has not removed the stinger, it should be removed as soon as possible by the first caregiver on the scene. Delay increases venom load, so the fastest removal technique is the best. Pinching and traction is an acceptable technique.

**Emergency Department Care:**

- Corticosteroids and cimetidine may be given IV; vasopressors such as dopamine can be used to provide vascular support.
- Patients developing respiratory arrest require ventilatory support.
- Blood products may be required in the event of disseminated intravascular coagulation (DIC).

**Consultations:**

- Refer all patients with generalized reactions to an allergist as soon as possible, because risk of fatal reaction is inversely related to length of time since the last sting.