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**Chapter 38**

## HYPERTHERMIA AND HYPOTHERMIA SYNDROMES

The human body is a metabolic furnace that generates enough heat, even at rest, to raise the body temperature by *1°C* every hour . This, of course, is not allowed to happen thanks to a thermoregulatory system that promotes the transfer of excess body heat to the surrounding environment. This system is so effective that the daily variation in body temperature is only +/- 0.6°C (2). This chapter describes what happens when the regulation of body temperature is faulty, allowing the temperature to rise or fall to extreme and life-threatening levels.

### *Heat Exchange through the Skin*

The external surface of the body acts like a radiator (with a built-in thermostat) that discharges excess heat into the surroundings. About 90% of the excess heat generated by metabolism is dissipated through the skin, with the remainder being lost in exhaled gas.

### *Mechanisms of Heat Exchange*

Heat exchange between the body and its surroundings is accomplished in several ways, as described next.

### *Radiation*

*Radiation* refers to the loss of heat via infrared heat rays (a type of electromagnetic wave) that radiate out from the skin. These waves emanate from all objects that exist above absolute zero temperature, and the intensity of radiation increases as the temperature of the object increases.

Under normal conditions, radiation accounts for about 60% of the heat loss from the human body (3).

*Conduction*

*Conduction* is the transfer of heat from an object of higher temperature to an object of lower temperature. This is the behavior of heat as kinetic energy, which imparts motion to molecules and results in the transfer of heat from a hotter to a colder object. Heat transfer by conduction alone is responsible for only about 15% of heat loss from the body (2).

*Convection*

When heat is lost from the skin, it warms the air just above the skin surface. This increase in surface temperature limits the further loss of body heat by conduction. However, when an air current from a fan (or a gust of wind) is passed across the skin, it displaces the warm layer of air above the skin and replaces it with cooler air, and this process facilitates the continued loss of body heat by conduction. The same effect is produced by increases in blood flow just underneath the skin. The action of currents (air and blood) to promote heat loss is known as *convection.*

*Evaporation*

The transformation of water from liquid to gaseous phase requires heat (called the latent heat of vaporization), and when water or sweat evaporates from the surface of the body, the heat that is utilized is body heat. Normally, evaporation accounts for about 20% of the loss of body heat (mostly as a result of insensible fluid losses from the lungs). Evaporation plays a much greater role in the adaptation to thermal stress (see next).

*Response to Thermal Stress*

The maintenance of body temperature in conditions of thermal stress (hot weather, strenuous exercise, or both) is primarily achieved by enhanced blood flow to the skin (convective heat loss) and the loss of sweat (evaporative heat loss).

*The Role of Sweating*

The evaporation of sweat from the skin is responsible for at least 70% of the loss of body heat during periods of thermal stress. The evaporation of one liter of sweat from the skin is accompanied by the loss of 580 kilocalories (kcal) of heat from the body (3). This is about one-quarter of the daily heat production by an average-sized adult at rest. Thermal sweating (as opposed to "nervous sweating") can achieve rates of 1 to 2 liters per hour (3), which means that over 1,000 kcal of heat can be lost hourly during profuse sweating. **It** is important to emphasize that sweat must evaporate to ensure loss of body heat. Wiping sweat off the skin will not result in heat loss, so this practice should be discouraged during strenuous exercise.

### *Hyperthermia and Fever*

The terms *hyperthermia* and *fever* both indicate an elevated body temperature, but hyperthermia is the result of abnormal temperature regulation, while fever is the result of a normal thermoregulatory system operating at a higher set point. In both conditions, extreme elevation in body temperature (>40°C or 104°F) is called *hyperpyrexia.* This chapter will describe specific conditions that result in elevated body temperatures as a result of abnormal thermoregulation (i.e., hyperthermia syndromes). The conditions associated with fever will be described in the next chapter. (Also included in the next chapter is an explanation of how to convert between degrees Celsius and degrees Fahrenheit.)

## HEAT-RELATED ILLNESS

Heat-related illnesses are conditions where the thermoregulatory system is no longer able to maintain a constant body temperature in response to thermal stress (from exercise, the environment, or both). There are a number of minor heat-related illnesses, such as heat cramps and heat rash (prickly heat), but the following descriptions are limited to the major heat-related illnesses: *heat exhaustion* and *heat stroke.* The comparative features of these conditions are shown in Table 38.1.

### *Heat Exhaustion*

Heat exhaustion is the most common form of heat-related illness, and is the result of volume depletion. Patients with heat exhaustion experience flu-like symptoms that include hyperthermia (usually below 39°C or 102°F), muscle cramps, nausea, and malaise. The hallmark of this condition is volume depletion, which is accompanied by tachycardia but no other signs of hemodynamic compromise. The volume loss can be accompanied by hypernatremia (from net loss of free water) or hyponatremia (usually seen when salt and water losses are replaced with water alone). There is no evidence of significant neurologic impairment.

TABLE 38.1 Comparative Features of Heat Exhaustion and Heat Stroke

| Feature | Heat Exhaustion | Heat Stroke |
|---|---|---|
| Body Temperature | <39°C | >=41°C |
| CNS Dysfunction | Mild | Severe |
| Sweat Production | Yes | Occasionally |
| Dehydration | Yes | Yes |
| Multiorgan Dysfunction (e.g., rhabdomyolysis, acute renal failure) | No | Yes |

The management of heat exhaustion includes volume repletion and other general supportive measures. Cooling measures to reduce body temperature are not necessary.

*Heat Stroke*

Heat stroke is a life-threatening condition characterized by extreme elevations in body temperature (> =41°C or 106°F), severe neurologic dysfunction (e.g., delirium, ataxia, coma, and seizures), severe volume depletion with hypotension, and multiorgan involvement that includes rhabdomyolysis (a condition of widespread skeletal muscle injury), acute renal failure, disseminated intravascular coagulopathy (DIC), and marked elevation in serum transaminases (presumably from the liver). The inability to produce sweat (anhidrosis) is a common feature of heat stroke, but it is not frequent enough to be of value in distinguishing heat stroke from heat exhaustion (4). There are two types of heat stroke, one related to environmental temperatures (classic heat stroke) and the other related to strenuous exercise (exertional heat stroke).

Classic heat stroke is the result of exposure to high environmental temperatures, usually in a confined space. This type of heat stroke is usually seem in elderly and debilitated people and in people who are taking psychiatric medications, have a history of alcohol and drug abuse, and have advanced heart failure.

Exertional heat stroke is the result of strenuous physical activity in a hot environment, and is typically seen in athletes and military recruits. Exertional heat stroke tends to be more severe, with a higher incidence of multiorgan dysfunction than seen in classic heat stroke.

*Cooling Methods*

Immediate cooling to reduce body temperature is essential in heat stroke to reduce the risk of progressive or permanent organ injury (5). External cooling is the easiest and quickest way to reduce the body temperature. This is accomplished by placing ice packs in the groin and axilla, and covering the upper thorax and neck with ice. Cooling blankets are then placed over the entire length of the body. The one drawback with external cooling is the risk of shivering when the skin temperature falls below 30°C (86°F) (5). Shivering is counterproductive because it raises body temperature. If shivering does occur, a switch to one of the internal cooling techniques is indicated.

The most effective external cooling method is evaporative cooling, which involves spraying the skin with cool water (at 15°C or 59°F) and then fanning the skin to promote evaporation of the water. This method can reduce the body temperature at a rate of O.3°C (O.6°F) per minute (6). Evaporative cooling is used mostly in the field, and is particularly effective when the weather is hot and dry (which enhances evaporation from the skin).

Internal cooling can be achieved with a cold-water lavage of the stomach, bladder, or rectum. These methods produce a more rapid reduction in body temperature than external cooling with ice and cooling

blankets, but they can be more labor-intensive. Internal cooling is usually reserved for cases where external cooling is ineffective or produces unwanted shivering.
Body cooling should be continued until the body temperature reaches 38°C 100.4°F). While this is taking place, blood samples should be obtained to check for multiorgan dysfunction, including rhabdomyolysis, renal insufficiency, hepatocellular injury, and coagulopathy. Hypovolemia is common in heat stroke, so volume resuscitation is usually necessary.

*Rhabdomyolysis*
Skeletal muscle seems particularly vulnerable to thermal stress because rhabdomyolysis is a common complication of hyperthermia syndromes, including heat stroke (particularly the exertional type), malignant hyperthermia, and neuroleptic malignant syndrome (the latter two conditions are described later in the chapter). Disruption of myocytes in skeletal muscle leads to the release of creatine kinase (CK) into the bloodstream, and the measurement of CK levels in plasma is used to determine the presence and severity of rhabdomyolysis (7,8). There is no standard CK level for the diagnosis of rhabdomyolysis, but CK levels that are five times higher than normal (or about 1,000 Units/liter) have been used to identify rhabdomyolysis in clinical studies (7). Plasma CK levels above 15,000 Units/L indicate severe rhabdomyolysis and an increased risk of myoglobinuric renal failure (7).

*Myoglobinuria and Renal Failure*
Acute renal failure occurs in about one-third of patients with rhabdomyolysis (8). The culprit is myoglobin, which is released from injured myocytes and is eventually filtered by the glomeruli in the kidneys. Once in the renal tubules, myoglobin can damage the renal tubular epithelium, particularly when the pH of the fluid in the renal tubules is low (acid pH). The final result can be a condition of acute renal failure that resembles acute tubular necrosis (ATN).
An ordinary urine dipstick test for blood can be used as a simple screening test for myoglobin in the urine. This test uses a colorimetric reaction to detect the iron moiety in myoglobin or hemoglobin. A negative test result is evidence against the presence of myoglobin in the urine. A positive test result is not specific for myoglobin (and could indicate hemoglobin in the urine), and should be combined with urine microscopy to search for red blood cells. A positive dipstick test for blood in urine *plus* the absence of red blood cells on urine microscopy is evidence of myoglobinuria.
When myoglobin is detected in the urine, aggressive volume resuscitation is an effective means of preventing or limiting the development of myoglobinuric renal failure. Alkalinizing the urine (with acetazolamide or intravenous bicarbonate infusions) can also reduce the potential for myoglobin to damage the renal tubules, but this measure adds little to the beneficial effects of volume infusion.

## DRUG-INDUCED HYPERTHERMIA SYNDROMES

The heat-related illnesses just described are characterized by thermal stress in the em·ironment. The illnesses described in this section are charactenzed by thermal stress in the interior of the body. The source of the thermal stress in each case is drug-induced increases in metabolic heat production. Three specific hyperthermia syndromes are described: malignant hyperthermla, neuroleptic malignant syndrome, and the serotonin syndrome.

### *Malignant Hyperthermia*

Malignant hyperthermia (MH) is an uncommon disorder that occurs in approximately 1 in 15,000 episodes of general anesthesia and affects approximately 1 in 50,000 adults (9). **It** is an inherited disorder with an autosomal dominant pattern and it is characterized by excessive release of calcmm from the sarcoplasmic reticulum in skeletal muscle in response to halogenated inhalational anesthetic agents (e.g., halothane, Isoflurane, servoflurane, and desflurane) and depolarizing neuromuscular blockers (e g , succinylcholine) (9). The calcium influx into the cell cytoplasm somehow leads to uncoupling of oxidative phosphorylation and a marked rise in metabolic rate.

### *Clinical Manifestations*

The clinical manifestations of MH include muscle rigidity, increased body temperature, depressed consciousness, and autonomic instability. The first sign of MH may be a sudden and unexpected rise in end-tidal  (reflecting the underlying hypermetabolism) in the operating room (9,10) This is followed (within minutes to a few hours) by generalized muscle rigidity, which can progress rapidly to widespread myonecrosis (rhabdomyolysis) and subsequent myoglobinuric renal failure. The heat generated by the muscle rigidity is responsible for the marked rise in body temperature (often above 40°C or 104°F) in MH. The altered mental status in MH can range from confusion and agitation to obtundation and coma. Autonomic instability can lead to cardiac arrhythmias, fluctuating blood pressure, or persistent hypotension.

### *Management*

The first suspicion of MH should prompt immediate discontinuation of the offendmg anesthetic agent. Specific treatment for the muscle rigidity is avallable with dantrolene sodium, a muscle relaxant that blocks the release of calcium from the sarcoplasmic reticulum. When given early in the course of MH, dantrolene can reduce the mortality rate from 70% or higher (m untreated cases) to 10% or less (9,10). The dosing regimen for dantrolene in MH is as follows:

Dose regimen: 1to 2 mg/kg as lV bolus, and repeat every 15 minutes if needed to a total dose of 10 mg/kg. Follow the initial dosing

regimen with a dose of 1 mg/kg IV or 2 mg/kg orally four times daily for 3 days. Side effects: Muscle weakness, hepatocellular injury.

Treatment is extended to 3 days to prevent recurrences. The most common side effect of dantrolene is muscle weakness, particularly grip strength, which usually resolves in 2 to 4 days after the drug is discontinued (11). The most troublesome side effect of dantrolene is hepatocellular injury, which is *more* common when the daily dose exceeds 10 mg/ kg (9). Active hepatitis and cirrhosis are considered contra indications to dantrolent' therapy (11) but, considering the high mortality in MH if left untreated, these contraindications should not be absolute.

All patients who survive an episode of MH should be given a medical bracelet that identifies their susceptibility to MH. ln addition, because MH is a genetic disorder with a known inheritance pattern (autosomal dominant), immediate family members should be informed of their possible susceptibility to MH. A test is available to identify the responsible gene for MH in family members.

*Neuroleptic Malignant Syndrome*

The *neuroleptic malignant syndrome* (NMS) is strikingly similar to malignant hyperthermia in that it is a drug-induced disorder characterized by 4 clinical features: increased body temperature, muscle rigidity, altered mental status, and autonomic instability (12). As the name implies, NMS is caused by neuroleptic agents (an alternate term for antipsychotic medications). A list of offending drugs and drug regimens in NMS is shown in Table 38.2. Note that drugs other than neuroleptic agents can trigger NMS, so the name of this syndrome is misleading.

*Pathogenesis*

The one property shared by all the drugs in Table 38.2 is the ability to influence dopamine-mediated synaptic transmission in the central nervous system. A decrease in dopaminergic neurotransmission in the basal ganglia and hypothalamic-pituitary axis may be responsible for many of the clinical manifestations of NMS (12). As indicated in Table 38.2, there

TABLE 38.2 Drugs Implicated in the Neuroleptic Malignant Syndrome

| | |
|---|---|
| *I. Ongoing Drug Intake* | |
| Antipsychotic agents· | Butyrophenones (eg, haloperidol), phenothiazines, clozapine, olanzapine, respiradone |
| Antiemetic agents: | Metoclopramide, droperidol, prochlorperazine |
| CNS stimulants: | Amphetamines, cocaine |
| Other: | Lithium, overdose with tricyclic antidepressants |
| *II. Discontinued Drug Intake* | |
| Dopaminergic drugs: | Amantidine, bromocriptine, levodopa |

are two clinical situations that predispose to NMS: (1) therapy with drugs that inhibit dopaminergic transmission, or (2) discontinuing therapy with drugs that facilitate dopaminergic transmission. Most cases of NMS are triggered by drugs that inhibit dopaminergic neurotransmission, and the ones reported most frequently are haloperidol and fluphenazine (2). The incidence of NMS during therapy with neuroleptic agents is
reported at 0.2% to 1.9% (3).
There is no relationship between the intensity or duration of drug therapy and the risk of NMS (2), so NMS is an idiosyncratic drug reaction and not a manifestation of drug toxicity. There is some evidence of a familial tendency, but a genetic pattern of transmission has not been identified (4).

*Clinical Features*

Most cases of NMS begin to appear 24 to 72 hours after the onset of drug . therapy, and almost all cases are apparent in the first 2 weeks of drug therapy. The onset is usually gradual, and can take days to fully develop. In 80% of cases, the initial manifestation is muscle rigidity or altered mental status (2). The muscle rigidity has been described as *lead pipe rigidity* to distinguish it from the rigidity associated with tremulousness (cogwheel rigidity). The change in mental status can range from confusion and agitation to obtundation and coma. Hyperthermia (body temperature can exceed 41°C) is required for the diagnosis of NMS (12), but the increase in body temperature can be delayed for 8 to 10 hours after the appearance of muscle rigidity or change in mental status (15). Autonomic instability can produce cardiac arrhythmias, labile blood pressure, or persistent hypotension.

*Laboratory Studies*
**It** may be difficult to distinguish the extrapyramidal side effects of neuroleptic agents from the motor effects of NMS. The serum CK level can help in this regard because, although it can rise slightly in dystonic reactions, it should be higher than 1000 Units/L in NMS (3). The leukocyte count in blood can increase to 40,000/μL with a leftward shift in NMS (12), so the clinical presentation of NMS (fever, leukocytosis, altered mental status, hypotension) can be confused with sepsis. The serum CK level will distinguish NMS from sepsis.

*Management*
The single most important measure in the management of NMS is *immediate* removal of the offending drug. **If** NMS is caused by discontinuation of dopaminergic therapy, it should be restarted immediately with plans for a gradual reduction in dosage at a later time. General measures, including volume resuscitation and evaluation for multiorgan involvement (e.g., rhabdomyolysis), are the same as described for malignant hyperthermia.
Dantrolene sodium (the same muscle relaxant used in the treatment of MH) can be given intravenously for severe cases of muscle rigidity.

The optimal dose is not clearly defined, but one suggestion is to start with a single dose of 2-3 mglkg/day 02,16), and increase this every few hours if necessary to a total dose of 10 mg/kg/ day. Oral dantrolene has also been used successfully in NMS in doses of 50 to 200 mg daily (usually given in divided doses every 6 to 8 hours) (6). In cases of severe muscle rigidity (when the CPK is markedly elevated), the intravenous route seems a better choice, at least in the first few days of treatment. The risk of liver injury should be considered when using dantrolene in NMS because there are alternative treatments.

Bromocriptine mesylate is a dopamine agonist that has been successful in treating NMS when given orally in a dose of 2.5 to 10 mg three times daily (6). Some improvement in muscle rigidity can be seen within hours after the start of therapy, but the full response often takes days to develop. Hypotension is a troublesome side effect. There is no advantage with bromocriptine over dantrolene, except in patients with advanced liver disease (where dantrolene is not advised), Treatment of NMS should continue for about 10 days after clinical resolution because of delayed clearance of many neuroleptics (when depot preparations are implicated, therapy should continue for 2 to 3 weeks after clinical resolution) (2). There is a heightened risk of venous thromboembolism during NMS (2), so heparin prophylaxis is recommended (see Chapter 5). The mortality rate from NMS is about 20% (3), and (surprisingly) it is unclear if specific treatment with dantrolene or bromocriptine has a favorable effect on mortality 02,13).

**Serotonin Syndrome**

Overstimulation of serotonin receptors in the central nervous system produces a combination of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities that is known as the *serotonin syndrome* (SS) (7). The recent growth in popularity of seritonergic drugs such as selective serotonin reuptake inhibitors (SSRIs) has led to a marked increase in the prevalence of SS in recent years. The severity of illness can vary widely in cases of SS, and the most severe cases can be confused with any of the other hyperthermia syndromes.

*Pathogenesis*

Serotonin is a neurotransmitter in the central nervous system that participates in neuronal circuits involved in sleep-wakefulness cycles, mood, and thermoregulation. A variety of drugs can enhance serotonin neurotransmission in these circuits, and excessive doses of these *seritonergic* drugs can produce SS. A list of seritonergic drugs that are capable of producing SS is shown in Table 38.3. Many of these drugs work in combination to produce SS, although single-drug therapy can also result in SS. Many of the drugs involved in SS are mood enhancers, including illegal substances. Of particular note is methylenedioxy-methamphetamine or MDMA ("ecstasy"), which has become a favored street drug in recent years and is known for producing severe cases of SS (8). Note also that some of the drugs that can produce SS can also cause NMS (e.g., amphetamines).

TABLE 38.3 Drugs that Can Produce the Serotonin Syndrome·

| Mechanism of Action | Related Drugs |
|---|---|
| Increased serotonin synthesis | L-tryptophan |
| Decreased serotonin breakdown | MAOIs (including linezolide), ritonavir |
| Increased serotonin release | Amphetamines, MDMA ("ectasy"), cocaine, fenfluramine |
| Decreased serotonin reuptake | SSRIs, TCAs, dextromethorphan, meperidine, fentanyl, tramadol |
| Serotonin receptor agonists | Lithium, sumitriptan, buspirone, LSD |

'See Reference 17 for a comprehensive list of drugs and drug interactions that duce the serotonin syndrome. Abbreviations: *MAGis* = monoamine oxidase *MDMA* = methylenedioxy-methamphetamine, *SSRIs* = selective serotonin inhibitors, *TcAs* = tricvclic

*Clinical Manifestations*

The onset of SS is usually abrupt (in contrast to NMS, where the full syndrome can take days to develop), and over half of the cases are evident within 6 hours after ingestion of the responsible drug(s) (17). The clinical findings include mental status changes (e.g., confusion, delirium, coma), autonomic hyperactivity (e.g., mydriasis, tachycardia, hypertension, hyperthermia, diaphoresis) and neuromuscular abnormalities (e.g., hyperkinesis, hyperactive deep tendon reflexes, clonus, and muscle rigidity). The clinical presentation can vary markedly (7). Mild cases may include only hyperkinesis, hyperreflexia, tachycardia, diaphoresis, and mydriasis. Moderate cases often have additional findings of hyperthermia (temperature >38°C), clonus, and agitation. The clonus is most obvious in the patellar deep-tendon reflexes, and horizontal ocular clonus may also be present. Severe cases of SS often present with delirium, hyperpyrexia (temperature >40°C), widespread muscle rigidity, and spontaneous clonus. Life-threatening cases are marked by rhabdomyolysis, renal failure, metabolic acidosis, and hypotension.

A useful worksheet for the diagnosis of SS is shown in Table 38.4. The fist step in the diagnostic evaluation is to establish recent ingestion of one or more seritonergic drugs. Although the worksheet in Table 38.4 includes all drug ingestions in the past five weeks, most cases of SS follow within hours of drug ingestion (7). Hyperthermia and muscle rigidity can be absent in mild cases of the illness. The features that most distinguish 55 from other hyperthermia syndromes are hyperkinesis, hyperreflexia and clonus. However in severe cases of SS, muscle rigidity can mask these clinical findings. Severe cases of SS can be difficult to distinguish from MH and NMS, and the history of drug ingestion is important in these cases (although the same drugs can be implicated in NMS and SS).

*Management*

As is the case with all drug-induced hyperthermia syndromes, removal of the precipitating drugs is the single most important element in the management of SS. The remainder of the management includes measures to

TABLE 38.4 Diagnostic Worksheet for Serotonin Syndrome*

| Answer the following questions: | YES | NO |
|---|---|---|
| Has the patient received a seritonergic drug in the past 5 wks? | | |
| If the answer is YES, proceed to the questions below. | | |
| Does the patient have any of the following? | YES | NO |
| Tremor + hyperreflexia | | |
| Spontaneous clonus | | |
| Rigidity + Temp >38°C + ocular or inducible clonus | | |
| Ocular clonus + agitation or diaphoresis | | |
| Inducible clonus + agitation or diaphoresis | | |
| If the answer is YES to any of the above conditions, then the patient has | | |
| SEROTONIN SYNDROME | | |

'Adapted from Boyer EW, Shannon M. The serotonin syndrome. N Engl J 2005;352: 1112.

control agitation and hyperthermia, and the use of serotonin antagonists. Many cases of SS will resolve within 24 hours after initiation of therapy, but seritonergic drugs with long elimination half-lives can produce more prolonged symptomatology.

Benzodiazepines are considered essential for the control of agitation and hyperkinesis in SS. Physical restraints should be avoided because they encourage isometric muscle contractions and this can aggravate skeletal muscle injury and promote lactic acidosis (9).

Cyproheptadine is a serotonin antagonist that can be given in severe cases of SS (20). This drug is available for oral administration only, but tablets can be broken up and administered through a nasogastric tube. The recommended initial dose is 12 mg, followed by 2 mg every 2 hours for persistent symptoms. The maintenance dose is 8 mg every 6 hours. Cyprohepatidine can be sedating, but this should aid in the control of agitation in SS.

Neuromuscular paralysis may be required in severe cases of SS to control muscle rigidity and extreme elevations of body temperature (>41°C). Nondepolarizing agents (e.g., vecuronium) should be used for muscle paralysis because succinylcholine can aggravate the hyperkalemia that accompanies rhabdomyolysis. Dantrolene is not effective in reducing the muscle rigidity and hyperthermia in SS (7).

**HYPOTHERMIA SYNDROMES**

Hypothermia, or a decrease in body temperature below 35°C (95°F), can be the result of environmental forces (accidental hypothermia), a primary metabolic disorder (secondary hypothermia) or a therapeutic intervention (induced hypothermia), This section will focus primarily on environmental hypothermia.

*Adaptation to Cold*

Physiologically, the human body is much better equipped to survive in hot rather than cold environments. The physiological response to a decrease in body temperature includes cutaneous vasoconstriction (to reduce convective heat loss) and shivering (which can roughly double metabolic heat production). Unfortunately, these physiological adaptations to cold are protective only in conditions of mild hypothermia (see later), and they must be supplemented by behavioral responses to cold (e.g., wearing warm clothing and seeking shelter from the cold). Because of the importance of behavioral responses, hypothermia is particularly pronounced when behavioral responses are impaired (e.g., in the intoxicated or the elderly) or cannot be carried out (e.g., mountain climbers who are unable to gain shelter from the cold).

*Accidental Hypothermia*

Environmental hypothermia is most likely to occur in the following situations: 0) prolonged submersion in cold water (the transfer of heat to cold water occurs much more readily than the transfer of heat to cold air), (2) exposure to cold wind (wind promotes heat transfer by convection, as described earlier in the chapter), (3) when the physiological responses to cold are impaired (e.g., alcohol intoxication reduces cutaneous vasoconstriction and shivering in response to cold), and (4) when the behavioral responses to cold are impaired (as described in the last paragraph).

*Clinical Features*

Most standard thermometers record temperatures down to 34°C (94°F). When hypothermia is suspected, specialized electronic temperature probes that can be placed in the bladder, rectum, or esophagus and can record temperatures down to 25°C (77°F) should be used to record body temperature. The severity of hypothermia can then be classified as shown in Table 38.5.

The clinical manifestations of hypothermia can vary in individual patients, but they generally resemble the patterns shown in Table 38.5.

TABLE 38.5 Manifestations of Hypothermia

| Severity | Body Temperature | Clinical Manifestations |
|---|---|---|
| Mild | 32°C-35°C<br>90°F-95°F | Confusion, cold, pale skin, shivering, tachycardia |
| Moderate | 28°C-31.8°C<br>82°F-89°F | Lethargy, reduced or absent shivering, bradycardia, decreased respiratory rate |
| Severe | <28°C<br><82°F | Obtundation or coma, no shivering, edematous skin, dilated and fixed pupils, bradycardia, hypotension, |
| Life-threatening | <25°C<br><77°F | Apnea, asystole |

In mild hypothermia (32°C to 35°C or 90°F to 95°F), patients are usually confused and show signs of adaptation to cold, which include cold, pale skin (from cutaneous vasoconstriction) and brisk shivering. Shivering may be absent in patients with moderate hypothermia (28°C to 31.8°C or 82°F to 89°F), who instead present with lethargy, sluggish or absent pupillary light reflexes, a decreased heart rate, and hypoventilation. In severe hypothermia «28°C or <82°F), patients are usually obtunded or comatose with dilated, fixed pupils (which are not a sign of brain death in this situation). Additional findings include hypotension, severe bradycardia, oliguria, and generalized edema. Apnea and asystole are expected at body temperatures below 25°C (77°F).

*Laboratory Tests*

The laboratory tests of most interest in hypothermia are the arterial blood gases, serum electrolytes (particularly potassium), and tests of coagulation status and renal function. A generalized coagulopathy (with elevation of the INR and prolonged partial thromboplastin times) is common in hypothermia (21), but may not be evident if the coagulation profile is run at normal body temperatures. Arterial blood gases (which should be run at normal body temperatures) can reveal a respiratory acidosis or a metabolic acidosis (21). Serum electrolytes can reveal hyperkalemia, which is presumably due to potassium release by skeletal muscle from shivering or rhabdomyolysis. Serum creatinine levels can be elevated as a result of cold diuresis (which may be the result of diminished tubular responses to antidiuretic hormone), rhabdomyolysis, or acute renal failure.

*The Electrocardiogram*

About 80% of patients with hypothermia will have prominent J waves at the QRS-ST junction on the electrocardiogram (see Fig. 38.1). These waves, which are called *Osborn waves,* are not specific for hypothermia, and can also occur in association with hypercalcemia, subarachnoid hemorrhage, cerebral injuries, and myocardial ischemia (22). Despite the attention these waves have received, they are merely a curiosity, and have little or no diagnostic or prognostic value in hypothermia 03-21).

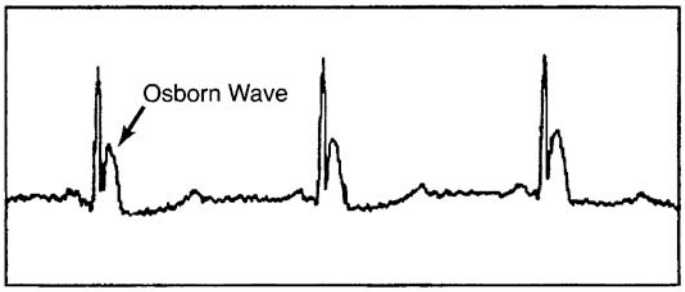


**FIGURE 38.1** The (overhyped) Osborn wave.

(Hypothermia should be evident by body temperature measurements before an electrocardiogram is obtained )
Almost any rhythm disturbance can occur in hypothermia, including first, second, and third-degree heart block, sinus; and junctional bradycardia, idioventricular rhythm, premature atrial and ventricular beats, and atrial and ventricular fibrillation (22)

*Rewarming*
External rewarming (removing wet clothes, (covering the patient in blankets, etc) can Increase body temperature at a rate of 1 degree to 2 degree per hour (21), and is adequate for most cases of hypothermia (23) There is a risk of a further decrease in body temperature during external rewarming (called afterdrop*),* which can trigger ventricular fibrillation (24). This phenomenon is attributed to central displacement of cold blood in cutaneous blood vessels. Fortunately, serious cardiac arrhythmias are not common, and do not contribute to mortality, during external rewarming for severe hypothermia (23,24)
There are several methods of internal rewarming. but they are invasive, time-consuming, and are needed onlv in the most severe cases of hypothermia. The easiest internal warming technique involves increasing the temperature of inhaled gases to 40°C to 45 C, which can raise the core temperature at a rate of *2.5 degree C* per hour in intubated patients (21). Other internal warming techniques include peritoneal lavage with heated fluids (21), extracorporeal blood rewarming (25), and heated intravenous fluids (26). Warmed gastric lavage is considered ineffective (21).

*Rewarming Shock*
Rewarming from moderate-to-severe hypothermia i.1 is often accompanied by hypotension *( rewarming shock )* that is attributed to a combination of factors, including hypovolemia *(from* cold diuresis). myocardial depression, and vasodilation (23,24) Volume infusion can help to alleviate this problem, but the intravenous fluids must be heated because infusion of fluids at room temperature (21°C or 7Q°F) can aggravate the hypothermia. Vasoactive drugs are required in about half of patients with severe hypothermia, and the need for vasoactive dmgs carries a poor prognosis (24).
Induced Hypothermia
External cooling to a body temperature of 32 degrees to 34°C (89 6°F to 93.2°F) has been shown to improve neurologic outcome in patients who remain comatose after certain types of cardiac arrest This topic is presented in Chapter 15.

**A FINAL WORD**
One of the most striking aspects of the disorders in this chapter is how uncommon they are. This is particularly true of the hyperthermia syndromes, and is also the case with heat-related illness.

The number of death from heat exposure is estimated at only 400 per year in the US (MorbIdIty and Mortality Weekly Report 2002;51:567-570) Considering that there are about 6,000 hospitals in the United States, you would have to work in about 15 hospitals per year before you would witness one death from heat exposureThis suggests a genetic predisposition to hyperthermIa, regardless of the cause.
Hypothermia is more prevalent than hyperthermia, but the numbers are still small In a 20 yr survey of a large urban hospItal In Paris, France (24), only 0.4% of admissions to the ICU were for severe hypothermia (body temperature <32 degree) Presumably. man's tendency to protect himself from the cold explains why hypothermia is kept in check.

**References**

**Chapter 39**

**FEVER IN THE ICU**

*Humanity has but three great enemies:*
*Fever,jamine and war.*
*Of these, by far the greatest,*
*By jar the most terrible,* is *fever.*
Sir *William Osler*

Despite Osler's harsh comments about fever, the appearance of fever in an ICU patient is not a sign of impending doom, but it is a sign that requires attention. This chapter describes the conditions that are most often associated with hospital-acquired (nosocomial) fever in the ICU (1,2). Additional considerations in immunocompromised patients are presented in Chapter 43. The final section of the chapter focuses on the practice of suppressing fever and why this practice should be abandoned, particularly in patients with infection.

**BODY TEMPERATURE**
Two scales (Celsius and Fahrenheit) are used to record body temperature, and the conversion from one scale to the other is shown in Table 39.1. Although readings on the Celsius scale are often called degrees "centi-grade," this unit is intended for the degrees on a compass, not for tem-peratures (3). The appropriate term for temperatures on the Celsius scale is *degrees Celsius.*

*Normal BodyTemperature*
Despite the fact that the body temperature is one of the most common measurements performed in clinical medicine, there is some disagreement about what the normal body temperature is in healthy adults. The following points illustrate some of the confusion regarding the normal body temperature.

TABLE 39.1 Temperature Conversions

| Corresponding Scales | | |
|---|---|---|
| (0C) | (OF) | Conversion Formulas |
| 100 | 212 | Conversions are based on the corresponding |
| 41 | 105.8 | temperatures at the freezing point of water: |
| 40 | 104 | 0 degree C = 32°F |
| 39 | 102.2 | and the temperture ranges (from freezing point to boiling point of water): |
| 38 | 100.4 | 100°C = 180°F or 5°C = 9°F |
| 37 | 98.6 | The above relationships are then combined |
| 36 | 96.8 | to derive the conversion formulas: |
| 35 | 95 | of = (9/5°C) + 32 |
| 34 | 93.2 | °C = 5/9 (OF - 32) |
| 33 | 91.4 | |
| 32 | 89.6 | |
| 31 | 87.8 | |
| 30 | 86 | |
| 0 | 32 | |

The traditional norm of 37°C (98.6°P) is a mean value derived from a study of axillary temperatures in 25,000 healthy adults, conducted in the late 19th century (4). However, axillary temperatures can vary by as much as 1.0°C (1.8°F) from core body temperatures (5) and, as a result, axillary temperatures are not recommended for recording body temperature in ICU patients (1).
Core body temperature can be 0.5°C (O.9°F) higher than oral temperatures (6), and 0.2°C to 0.3°C lower than rectal temperatures (1).
Elderly subjects have a mean body temperature that is approximately 0.5°C (O.9°F) lower than that of younger adults (4,7).
The normal body temperature has a diurnal variation, with the nadir in the early morning (between 4 and 8 a.m.) and the peak in the late afternoon (between 4 and 6 p.m.). The range of diurnal variation varies in individual subjects, with the highest reported range in an individual subject being 1.3°C (2.4°P) (8).
These observations indicate that the normal body temperature is not a single temperature, but rather is a range of temperatures that is influenced by age, time of day, and measurement site.

*Where to Measure Temperature*

The consensus view is that the temperatures in the pulmonary artery and the urinary bladder (measured with thermistor-equipped pulmonary artery catheters and bladder catheters, respectively), are the most accurate

representations of core body temperature (1). When these temperatures are not available (which is often), infrared probes placed in the external auditory canal to measure "ear canal temperature" (often mistaken as tympanic membrane temperature) can provide suitable measurements when used properly (9-11). Surprisingly, oral temperatures measured in intubated patients can be a close approximation of core body temperature when electronic probes (not mercury thermometers) are placed in the right or left sublingual pockets (10). Finally, rectal temperatures can also provide an accurate reflection of core body temperature (9), but rectal probes are not well tolerated by alert patients.

*Definition of Fever*

Fever is best defined as a temperature that exceeds the normal daily temperature range for an individual subject. However, this is not a practical definition because the body temperature is not monitored continuously in hospitalized patients, so it is not possible to determine the daily temperature variation for each patient. The Society of Critical Care Medicine, in their practice guideline (1), proposes that a body temperature above 38.3°C (101°F) represents a fever and deserves further evaluation to search for an infection. This is more useful as an operational definition that identifies when an elevated body temperature deserves further evaluation.

The Febrile Response

Fever is the result of inflammatory cytokines (called endogenous pyrogens) that act on the hypothalamus to elevate the body temperature. Unlike hyperthermia, which is the result of abnormal temperature regulation in the body (see Chapter 38), fever is a condition where the thermoregulatory system is intact but is operating at a higher set point (12). The elevated body temperatures in fever serve to enhance immune function and inhibit bacterial and viral replication. (The beneficial effects of fever are described in more detail later in the chapter.) Fever is therefore an adaptive response that aids the host in defending against infection and other bodily insults.

The following facts about fever deserve mention.

Fever is a sign of inflammation, not infection. Fever is not a specific response to infection, but rather is a response to any form of tissue injury that is sufficient enough to trigger an inflammatory response. This might explain why about 50% of ICU patients with fever have no apparent infection (13,14). The distinction between inflammation and infection is an important one, not only for the evaluation of fever, but also for curtailing the use of antibiotics to treat a fever.

The severity of the fever is not an indication of the presence or severity of infection. High fevers can be associated with noninfectious processes (e.g., drug fever), while fever can be mild or absent in patients with life-threatening infections (2).

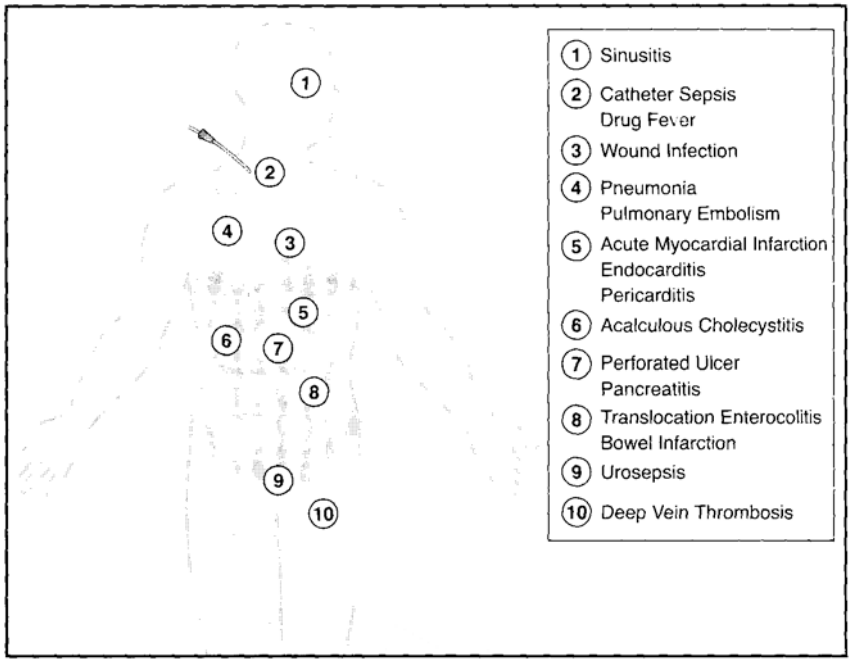


**FIGURE 39.1** Common causes of nosocomial fever in the ICU.

*Causes of Fever in the ICU*
Any condition ca pable of triggering an immune response is capable of causing a fever. The common conditions associated with hospital-acquired (nosocomial) fever in general medical-surgical ICUs are shown in Fig. 39.1. Most of these conditions are described briefly in this chapter.

*Noninfectious Causes of Fever*

*POSTOPERATIVE FEVER.* Surgery always involves some degree of tissue injury, and major surgery can involve considerable tissue injury. (In the words of Dr. John Millili, a surgeon and close friend, major surgery is akin to being *hit with a baseball bat!)* Because inflammation and fever are the normal response to tissue injury, fever is a likely consequence of major surgery. Fever in the first day following major surgery is reported in 15% to 40% of patients (15-17), and in most of these cases, there is no associated infection (15,16). These fevers are short-lived, and usually resolve within 24 to 48 hours.

*Atelectasis and Fever* There is a longstanding misconception that atelectasis is a common cause of fever in the early postoperative period. One possible source of this misconception is the high incidence of atelectasis in patients who develop a postoperative fever. This is demonstrated in Figure 39.2 (see the graph on the left), which is from a study involving patients who underwent open heart surgery (17). Close to 90% of the patients with a fever on the first postoperative day had radiographic

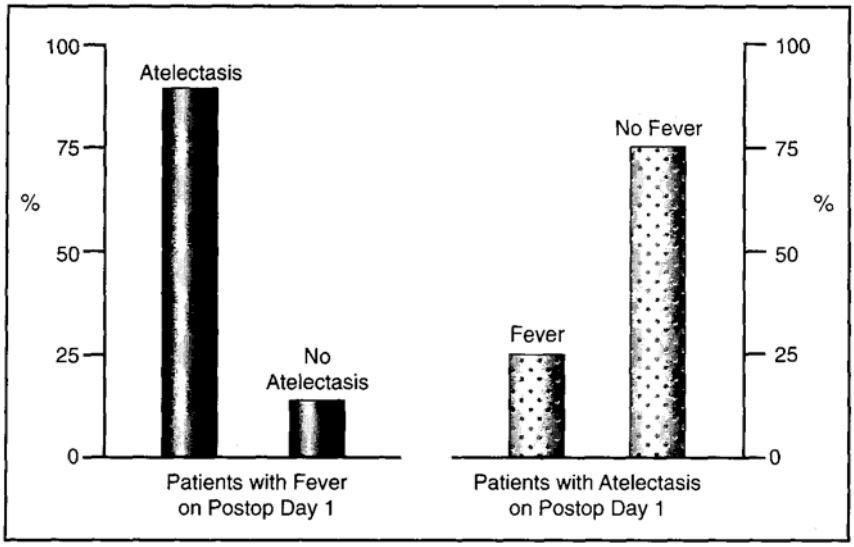


**FIGURE 39.2** The relationships between atelectasis and fever on the first postoperative day in 100 consecutive patients who had open heart surgery. (Data from Engoren M. Lack of association between atelectasis and fever. Chest 1995;167:81.)

evidence of atelectasis. This, however, is *not* evidence that the atelectasis is the source of fever. In fact, the graph on the right in Figure 39.2 shows that most (75%) of the patients with atelectasis did not have a fever. The inability of atelectasis to produce fever was demonstrated over 50 years ago in an animal study where lobar atelectasis produced by ligation of a mainstem bronchus was not accompanied by fever (18).

The high incidence of atelectasis in patients with po stop fever is explained by the fact that atelectasis is extremely common after major surgery. For example, upper abdominal surgery results in a 40% to 70% decrease in the functional residual capacity (FRC) of the lungs (the volume of air in the lungs at the end of expiration) for up to one week (19). Since atelectasis involves a decrease in FRC, virtually every patient who undergoes upper abdominal surgery is expected to have postop atelectasis. In fact, general anesthesia is accompanied by atelectasis in over 90% of cases (20), so atelectasis is almost a universal consequence of major surgery. Therefore, a high incidence of atelectasis is expected in any group of postop patients, not just those with fever.

Therefore, the available evidence indicates that atelectasis is very common after major surgery, but is not a common cause of postoperative fever. Most fevers that appear in the first 24 to 48 hours after surgery are most likely a result of the tissue injury sustained during the procedure.

### *Malignant Hyperthermia*

Another cause of elevated body temperatures in the immediate postoperative period is malignant hyperthermia, an inherited disorder characterized by intense muscle rigidity and hyperthermia in response to halogenated

inhalational anesthetics and depolarizing neuromuscular blockers (e.g., succinylcholine). This disorder is described in detail in Chapter 38.

### *Other Procedures Associated with Fever*

The following procedures or interventions can be accompanied by noninfectious fever.

#### *Hemodialysis*

Febrile reactions during hemodialysis are attributed to endotoxin contamination of the dialysis equipment, but bacteremia occurs on occasion (21). Blood cultures are recommended for all patients who develop fever during hemodialysis, but the dialysis does not have to be terminated unless the patient shows signs of sepsis (e.g., mental status changes or hypotension). Empiric antibiotics are recommended only for patients who appear septic. Vancomycin plus ceftazidime should suffice pending culture results. (One gram of each antibiotic given after dialysis will provide adequate serum levels pending culture results.)

#### *Bronchscopy*

Fiberoptic bronchosopy is followed by fever in 5% of cases (22). The fever usually appears 8 to 10 hours after the procedure, and it subsides spontaneously in 24 hours (22). The probable cause is release of endogenous pyrogens from the lung during the procedure. The fever is often associated with leukocytosis (22), but pneumonia and bacteremia are rare (23). There is no need for blood cultures or empiric antimicrobial therapy unless the fever does not subside or the patient shows signs of sepsis (e.g., mental status changes or hypotension).

#### *Blood Transfusions*

Febrile reactions occur in as many as 5% of patients receiving blood products. The fever is usually the result of antileukocyte antibodies, and appears during or shortly after the transfusion. For more information on febrile transfusion reactions, see Chapter 36.

## Venous Thromboembolism

Several groups of hospitalized patients are at risk for venous thromboembolism (see Table 5.1 and Figure 5.1), but the risk is highest in trauma victims and postoperative patients, particularly following orthopedic procedures involving the hip and knee. Most cases of hospital-acquired deep vein thrombosis are asymptomatic, but acute pulmonary embolism can produce a fever that lasts up to 1 week (24). The diagnostic approach to suspected venous thromboembolism is descnbed in Chapter 5.

### *Acalculous Cholecystitis*

Acalculous cholecystItis is an uncommon but serious disorder reported in up to 1.5% of critically **ill** patients (25). **It** is most common in

postoperative patients, trauma victims, and patients receiving parenteral nutrition. This condition is believed to be the result of ischemia and stasis within the gallbladder, eventually leading to edema of the cystic duct that blocks drainage of the gallbladder. The resulting clinical syndrome includes fever (70 to 95% of cases) and right upper quadrant tenderness (60 to 100% of cases) (25). Diagnosis is often possible with right upper quadrant ultrasound. Perforation of the gallbladder can occur within 48 hours after onset. The treatment of choice is cholecystectomy, or percutaneous cholecystostomy in patients who are too **ill** for surgery. (For more information on this disorder, see Chapter 42.)

### Pharmaceutical Agents

*Drug Fever*

Drug-induced fever can be the result of a hypersensitivity reaction, an idiosyncratic reaction, or an infusion-related phlebitis. *Drug fever* is a recognized entity in the ICU, but the significance and prevalence of this entity in the ICU is not known. The therapeutic agents most often implicated in drug fever are listed in Table 39.2.

Drug fever is poorly understood. The onset of the fever varies from a few hours to a few weeks after the onset of drug therapy (2). The fever can appear as an isolated finding or can be accompanied by the other manifestations listed in Table 39.2 (26). Note that about half of patients have rigors, and about 20% develop hypotension, indicating that patients with a drug fever can appear to be seriously ill. Evidence of a hypersensitivity reaction (i.e., eosinophilia and rash) is absent in most cases of drug fever.

Suspicion of drug fever usually occurs when there are no other probable sources of fever. In this situation, it is best to discontinue possible offenders. The fever should disappear in 2 to 3 days, but it can take up to 7 days to disappear (27).

*Drug-Induced Hyperthermia Syndromes*

The drug-induced hyperthermia syndromes include malignant hyperthermia (mentioned earlier), neuroleptic malignant syndrome, and

TABLE 39.2 Drug-Associated Fever in the ICU

| Common Offenders | Occasional Offenders | Clinical Findings· |
|---|---|---|
| Amphotericin | Cimetidine | Rigors (53%) |
| Cephalosporins | Carbamazepine | Myalgias (25%) |
| Penicillins | Hydralazine | leukocytosis (22%) |
| Phenytoin | Rifampin | Eosiniphillia (22%) |
| Procainamide | Streptokinase | Rash (18%) |
| Quinidine | Vancomycin | Hypotension (18%) |

'From Mackowiak and LeMaistre (26).

serotonin syndrome. These disorders are described in detail in Chapter 38. The neuroleptic malignant syndrome may be an important concern in ICUs where haloperidol is used for sedation.

### Endocrine Disorders

The endocrine disorders known to produce fever are thyrotoxicosis and adrenal crisis. Thyrotoxicosis is unlikely to appear *de novo* in the ICU, but adrenal crisis due to spontaneous adrenal hemorrhage is a recognized complication of anticoagulant therapy and disseminated intravascular coagulation (DIC). These endocrine disorders are described in Chapter 48.

#### Infarctions

Ischemic injury in any organ will trigger a local inflammatory response and this can produce a fever. Myocardial and cerebrovascular infarctions are usually heralded by other symptoms, but bowel infarction can be clinically silent in elderly, debilitated patients or patients with depressed consciousness. The only sign of a bowel infarction may be an unexplained fever or metabolic (lactic) acidosis. Unfortunately, there are no reliable diagnostic tests for bowel infarction, and the diagnosis is usually made at laparotomy.

### Systemic Inflammatory Response Syndrome

The clinical entity known as *systemic inflammatory response syndrome* (SIRS) is characterized by signs of systemic inflammation (e.g., fever, Leukocytosis) without evidence of infection. Possible sources of SIRS include tissue injury from trauma, ischemia, or toxic insults, and translocation of endotoxin and bacterial antigens from the lumen of the gastrointestinal tract. SIRS is often accompanied by inflammatory injury in one or more vital organs (e.g., acute respiratory distress syndrome) (28), and it can progress relentlessly to multiorgan failure and death. This condition is described in more detail in Chapter 40.

#### *Other Causes*

Other noninfectious causes of fever in the ICU include toxin-induced organ injury (e.g., alcohol-induced pancreatitis and hepatitis), delirium tremens, and thrombotic thrombocytopenia purpura. In each of these conditions, fever is accompanied by a constellation of clinical findings that, taken together, arouses suspicion of the disorder.

#### *Iatrogenic Fever*

Faulty thermal regulators in water mattresses and aerosol humidifiers can cause fever by transference (29). It takes only a minute to check the temperature settings on heated mattresses and ventilators, but it can take far longer to explain why such a simple cause of fever was overlooked.

TABLE 39.3 Nosocomial Infections in Medical and Surgical ICU Patients in the United States*

| Nosocomial Infection | % Total Infections | |
|---|---|---|
| | Medical Patients | Surgical Patients |
| Pneumonia | 30% | 33% |
| Urinary Tract Infection | 30% | 18% |
| Bloodstream Infection | 16% | 13% |
| Surgical Site Infection | – | 14% |
| Cardiovascular Infection | 5% | 4% |
| GI Tract Infection | 5% | 4% |
| Ear, Nose & Throat Infection | 4% | 4% |
| Skin & Soft Tissue Infection | 3% | 3% |
| Others | 7% | 7% |

*From Richards MJ et a!. & the National Nosocomial Infections Surveillance Nosocomial infections in combined medical-surgical intensive care units in the States. Infect Control Hosp Epidemio!. 2000:21 :510-515.

**Common Nosocomial Infections**

The National Nosocomial Infections Surveillance System is a government-sponsored program that monitors nosocomial infections in 99 hospitals in the United States, and the results of this survey for medical and surgical ICU patients (over the years 1992 through 1997) is shown in Table 39.3 (30). Four infections account for over three-quarters of the nosocomial infections in these patients: pneumonia, urinary tract infections, bloodstream infections, and surgical site infections. Three of these infections are primarily related to indwelling devices (i.e., 83% of pneumonias occur in intubated patients, 97% of urinary tract infections occur in catheterized patients, and 87% of bloodstream infections originate from intravascular catheters) (30).

The pathogenic organisms isolated in three of the common nosocomial infections are shown in Table 39.4. (31) *Staphylococcus allrells* and *Pseudomonas aerllginosa* are the two most common isolates in pneumonia, *Candida albicans* is the most common isolate in urinary tract infections, and staphylococci are responsible for about half of the bloodstream infections that originate from intravascular catheters. The microbial spectrum of these infections provides a valuable guide for selecting empiric antibiotic regimens.

**Pneumonia**

Nosocomial pneumonia in the ICU is primarily a disease of ventilator-dependent patients. Pneumonia should be suspected when there is a new infiltrate on chest x-ray and two of the following conditions are present: fever, Leukocytosis, and purulent tracheal secretions (32). The diagnosis of pneumonia requires isolation of one or more organisms

TABLE 39.4 Pathogens Involved in Nosocomial Infections·

| | % of Infections | | |
|---|---|---|---|
| Pathogen | Pneumonia | UTI | Bloodstream Infection |
| *Staphylococcus aureus* | 20 | 2 | 13 |
| *Staphylococcus epidermidis* | 1 | 2 | 36 |
| Enterococci | 2 | 14 | 16 |
| *Pseudomonas aeruginosa* | 21 | 10 | 3 |
| *Klebsiella pneumoniae* | 8 | 6 | 4 |
| Enterobacter | 9 | 5 | 3 |
| *Escherichia coli* | 4 | 14 | 3 |
| *Candida albicans* | 5 | 23 | 6 |

'From Richards MJ, et al. Nosocomial infections in medical intensive care units United States. Crit Care Med 1999;27:887-892.
UTI = urinary tract infection

from the lower respiratory tract. There are a variety of methods for obtaining and culturing respiratory secretions, and these are described in Chapter 41. (For an excellent and up-to-date practice guideline on nosocomial pneumonia, see reference 32.)

**Urinary Tract Infections**

Urinary tract infection should be suspected as a cause of nosocomial fever in any patient with an indwelling bladder catheter for more than a few days. The diagnosis of urinary tract infection is difficult in chronically catheterized patients because the urine in these patients often contains large numbers of bacteria. Therefore, a positive urine culture is not always evidence of infection in a chronically instrumented patient. The demonstration of pyuria by gram stain or ICUkocyte esterase dipstick test (for detection of granulocytes in the urine) can help to identify patients with significant bacteriuria. The approach to urinary tract infections in catheterized patients is described in more detail in Chapter 42.

*Catheter Sepsis*

Infections caused by indwelling vascular catheters should be suspected in any case of unexplained fever when a catheter has been in place for more than 48 hours, or when purulence is found at the catheter insertion site. If the patient appears toxic, or there is purulence at the catheter insertion site, the catheter should be removed and a distal segment of catheter should be sent for *semiquantitative* cultures (see Table 7.4 for the semiquantitative culture technique). This must be combined with a blood culture obtained from a distant venipuncture site. If the patient is not seriously ill and there is no purulence at the catheter insertion site, the

catheter can be left in place. In this situation, one blood sample should be withdrawn through the catheter and a second blood sample should be obtained from a distant venipuncture site: both samples should then be submitted for *quantitative* blood cultures (see Table 7.3 for a description of the quantitative culture technique).
Except for the presence of purulent drainage at the catheter insertion site, it is not possible to determine if an intravascular catheter is the source of nosocomial fever without the appropriate culture results. Therefore, the decision to initiate empiric antibiotic therapy will be determined by the clinical condition of the patient. If there are no signs of severe sepsis (e.g., mental status changes or hemodynamic instability) antibiotics can be withheld. If empiric antibiotic therapy is needed, coverage for staphylococci (with vancomycin or a carbepenem) is mandatory. For more information on the diagnosis and treatment of catheter-related sepsis, see Chapter 7.

*Wound Infections*
Surgical wounds are classified as clean (abdomen and chest unopened), contaminated (abdomen or chest opened), or dirty (direct contact with pus or bowel contents) (33). Wound infections typically appear at 5 to 7 days after surgery. Most infections do not extend beyond the skin and subcutaneous tissues, and can be managed with debridement only. Antimicrobial therapy (to cover streptococcus, staphylococcus, and anaerobes) should be reserved for cases of persistent erythema or for evidence of deep tissue involvement (15). In fever that follows median sternotomy, sternal wound infection with spread to the mediastinum is a prominent concern (34). In this situation, sternal instability can be an early sign of infection.
Necrotizing wound infections are produced by Clostridia or beta-hemolytic streptococci. Unlike other wound infections, which appear 5 to 7 days after surgery, necrotizing infections are evident in the first few postoperative days. There is often marked edema around the incision, and the skin may have crepitance and fluid-filled bullae. Spread to deeper structures is rapid and produces progressive rhabdomyolysis and myoglobinuric renal failure. Treatment involves extensive debridement and intravenous penicillin. The mortality is high (above 60%) when treatment is delayed.

**LESS COMMON INFECTIONS**

*Paranasal Sinusitis*
Indwelling nasogastric and nasotracheal tubes can block the ostia that drain the paranasal sinuses, leading to accumulation of infected secretions in the sinuses (35,36). The maxillary sinuses are almost always involved, and the resulting acute sinusitis can be an occult source of fever. This complication is reported in 15 to 20% of patients with nasal tubes (35,36) although its significance in many patients is unclear (see later).

*Diagnosis*

Purulent drainage from the nares may be absent, and the diagnosis is suggested by radiographic features of sinusitis (i.e., opacification or airfluid levels in the involved sinuses). Although CT scans are recommended for the diagnosis of nosocomial sinusitis (35,36), portable sinus films obtained at the bedside can also be revealing, as shown in Figure 39.3. The maxillary sinuses can be viewed with a single "occipitomental view," also called a "Waters view," which can be obtained at the bedside (37). Because CT scans require patient transport out of the ICU, it is convenient to attempt visualization of the maxillary sinuses with portable sinus films. CT scans are then reserved only for cases where the portable sinus films are of poor quality. **It** is important to emphasize that 30 to 40% of patients with radiographic evidence of sinusitis do not have an infection documented by culture of aspirated material from the involved sinus (35,36). Therefore, radiographic evidence of sinusitis is not sufficient for the diagnosis of purulent sinusitis. The diagnosis must be confirmed by sinus puncture and isolation of pathogens by quantitative culture ($2{:}10^3$ colony forming units per milliliter) (35,36).

*Treatment*
Responsible pathogens include gram-negative bacteria (especially *Pseudomonas aeruginosa)* in 60% of cases, gram-positive bacteria (particularly *Staphylococcus aureus)* in 30% of cases, and yeasts (particularly *Candida albicans)* in 10% of cases (1). Local irrigation of the sinuses with antimicrobial solutions can be effective (36), but a brief course of systemic antibiotics seems wise because invasion of the bloodstream is a recognized risk with nosocomial sinusitis (unlike outpatient sinusitis, where septicemia is rare). When a sinus aspirate is purulent or shows organisms on Gram stain, empiric antimicrobial therapy can be guided by the predominant organism(s) on Gramstain. Nasal tubes should also be removed.

*Significance*
Despite the recognized potential for harm, nosocomial sinusitis is unproven as an entity that deserves attention in the evaluation of nosocomial fever. The problem is that nosocomial sinusitis occurs in about one-quarter of patients with indwelling nasal tubes, yet sinusitis is often overlooked in the evaluation of nosocomial fever without apparent harm. This issue needs to be resolved before nosocomial sinusitis can gain the respect given to other nosocomial infections.

**Pseudomembranous Enterocolitis**
Enterocolitis from *Clostridium difficile* should be suspected for cases of nosocomial fever accompanied by diarrhea in patients who have received antibiotics or chemotherapy within 2 weeks prior to the onset of the fever 0). The diagnosis-requires documentation of C. *difficile* toxin in stool samples or evidence of pseudomembranes on proctosigmoidscopy (38). In severe cases of diarrhea, proctosigmoidscopy is preferred because it allows an immediate diagnosis. Otherwise, a stool sample should be submitted for C. *difficile* toxin assay. If this is negative, a second stool sample should be submitted (1). Empiric antibiotics should not be necessary unless the diarrhea is severe or the patient appears toxic. Therapy can include oral or intravenous metronidazole (500 mg every 6 hours) or oral vancomycin (500 mg orally every 6 hours). This disorder is described in more detail in Chapter 42.

**Abdominal Abscess**
Abdominal abscesses typically become symptomatic at one to two weeks after laparotomy. Septicemia occurs in approximately 50% of cases (39). Computed tomography of the abdomen will reveal the localized collection in more than 95% of cases (39). Initial antimicrobial therapy should be directed at gram-negative enteric pathogens, including anaerobes (e.g., *Bacteroides fragilis),* but definitive treatment requires surgical or percutaneous drainage.

### Other Infections

Other infections that should be considered in selected patient populations are endocarditis (in patients with prosthetic valves), meningitis (in neurosurgical patients and those with human immunodeficiency virus infection), and spontaneous bacterial peritonitis (in patients with cirrhosis and ascites).

## EARLY MANAGEMENT DECISIONS

*Blood Cultures*

Blood cultures should be obtained whenever an infection is suspected as a cause of nosocomial fever. No more than one set of blood cultures should be obtained from each venipuncture site (40). The appropriate number of venipuncture sites is determined by the likelihood of blood-stream infection. The following scheme is recommended (40).

If the likelihood of septicemia is low (e.g., when pneumonia or urinary tract infection is suspected) no more than two venipuncture sites are required for blood cultures.

If the probability of septicemia is high (e.g., when catheterrelated sepsis or endocarditis is suspected), at least three venipuncture sites are recommended for blood cultures. If the patient has received antimicrobial agents within the past few weeks, at least four venipuncture sites are recommended.

*Volume of Blood*

One of the lesser known features of blood cultures is the influence of blood volume on the culture results. In cases of low-level bacteremia, increasing the volume of blood that is cultured will increase the chances of showing growth of the microorganism. Therefore, to achieve optimal results with blood cultures, a volume of 20 to 30 mL of blood should be withdrawn from each venipuncture site (40). The volume of blood added to each culture bottle should be kept at the usual 1:5 ratio (blood volume: broth volume).

### Empiric Antimicrobial Therapy

Empiric antibiotic therapy is indicated in the following situations:

When the likelihood of infection is high.

When there is evidence of severe sepsis or severe organ dysfunction (e.g., depressed consciousness, progressive hypoxemia, hypotension, metabolic acidosis, or decreasing urine output).

When the patient is immunocompromised (e.g. neutropenia).

Empiric antibiotic therapy should be selected on the basis of antibiotic susceptibility patterns in each ICU. For ICUs with multidrug resistant

pathogens (e.g., methicillin-resistant Staphylococcus aureus), empiric coverage for gram-positive infections should include vancomycin or linezolid (the latter agent can be used when vancomycin-resistant enterococci have been encountered in the ICU) and empiric coverage for gramnegative infections can include either a carbepenem (imipenem cilastatin or meropenem), an antipseudomonal cephalosporin (ceftazidime or cefipime) or an antipseudomonal penicillin (ticarcillin clavulnate or pipericillin tazobactam), In immunocompromised patients, an aminoglycoside can be added for gram-negative (particularly pseudomonal) coverage (41), although there is no evidence that this improves outcome.

*Antipyretic Therapy*

The public perception of fever as a malady that needs to be treated is very much at odds with the emerging concept of fever as an adaptive response that enhances our ability to eradicate infection. The following is a brief description of the benefits derived from fever and the reasons to avoid the urge to suppress fever.

*Fever* as *a Host Defense Mechanism*

An increase in body temperature can enhance immune function by increasing the production of antibodies and cytokines, activating T-lymphocytes, facilitating neutrophil chemotaxis, and enhancing phagocytosis by neutrophils and macrophages (2,42,43). In addition, high temperatures inhibit bacterial and viral replication. The effect of body temperature on the growth of bacteria in blood cultures is demonstrated in Figure 39.4.

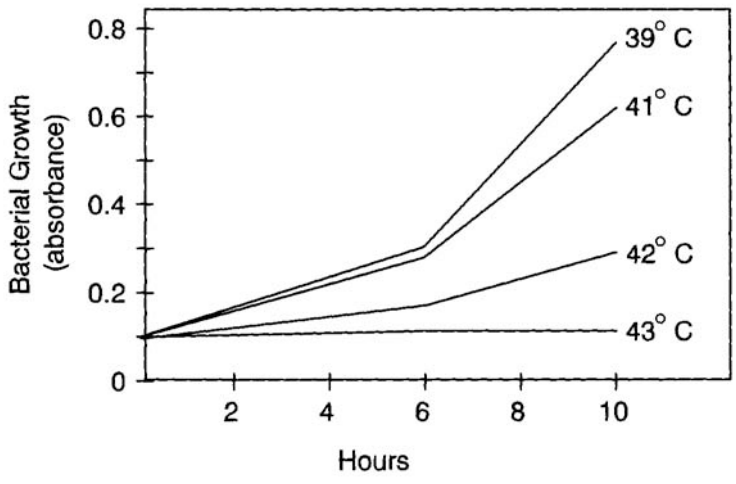


**FIGURE 39.4** The influence of body temperature on the growth of *Pasteurella multocida* in the blood of infected laboratory animals. The range of temperatures in the figure is the usual range of febrile temperatures for the study animal (rabbits). (Data from Kluger M, Rothenburg BA. Fever and reduced iron: their interaction as a host defense response to bacterial infection. Science 1979;203:374–376.)

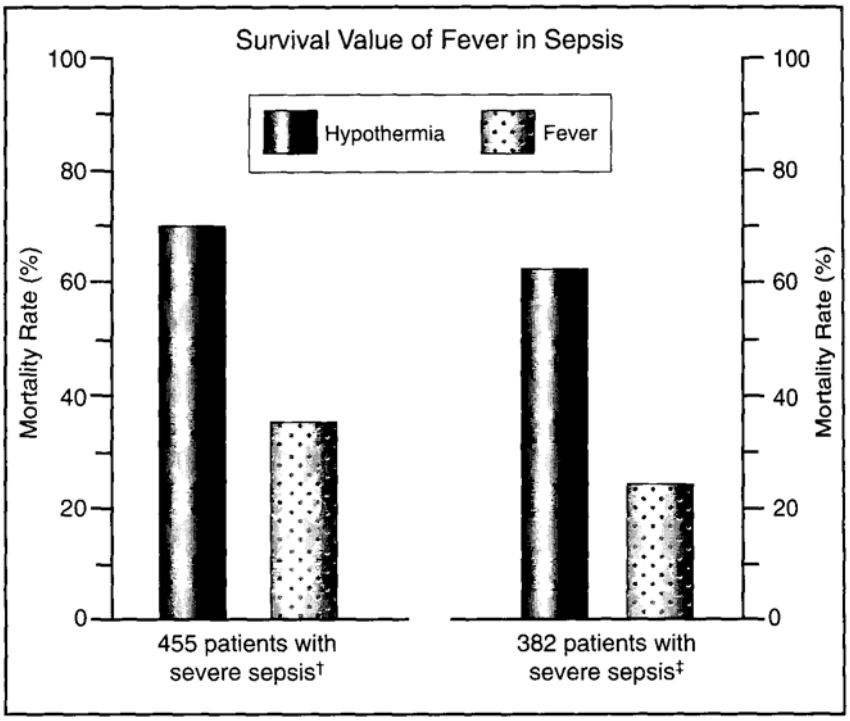


**FIGURE 39.5** The influence of body temperature on survival in two cohorts of patients with severe sepsis. †The Ibuprofen in Sepsis Study Group (from Reference 46). ‡The Methylprednisolone Severe Sepsis Study Group (from Reference 45).

Note that an increase in body temperature of 4°C completely suppresses the growth of microorganisms in the blood. This change in body temperature would correspond to an increase in our body temperature from 37°C (98.6°F) to 41°C 005.8°F), thereby showing that increases in body temperature in the same range experienced clinically can halt the growth of microorganisms in blood. A similar ability of increased body temperature to inhibit bacterial growth has been demonstrated in an animal model of pneumococcal meningitis (44).

The beneficial effects of fever on immune function and microbial growth in animal studies is also evident in human studies showing that septic patients who develop hypothermia have at least twice the mortality rate of septic patients who are capable of developing fever (45,46). The results of these studies are shown in Figure 39.5. The apparent survival value of fever in these studies is reason to avoid fever suppression in patients with nosocomial infections. In fact, considering that sepsis is the leading cause of death in most ICUs, fever suppression should be contraindicated in patients with severe or life-threatening infections.

*Fever and Tachycardia*

Tachycardia is considered a consequence of fever, and this is the basis for the claim that fever suppression is necessary to reduce tachycardia

in patients with coronary artery disease. Two considerations are relevant to this issue. The first consideration is whether fever is directly responsible for tachycardia, or whether the process producing the fever (e.g., sepsis or inflammation) is responsible for the tachycardia. The association between fever and tachycardia was established in animal models of sepsis, and it is likely that the inflammatory response to sepsis (which is known to include tachycardia) is the real culprit in the apparent association between fever and tachycardia. The second consideration is the pathophysiology of myocardial infarction. The concern that feverinduced tachycardia can trigger a myocardial infarction neglects the fact that acute myocardial infarction is the result of an occlusive blood clot that forms in a coronary artery, and it is unlikely that a fever or a tachycardia will produce such a clot.
The only clinical situation where reduction of a fever is justified is in the early period following ischemic brain injury, which is described next.

*Fever and Ischemic Brain Injury*
Experimental studies in animals show that increased body temperature following an episode of cerebral ischemia results in more extensive tissue injury (47), and clinical studies in patients with ischemic stroke show that the patients who develop a post-stroke fever have more extensive neurologic deficits and a higher mortality (48). The ability of fever to aggravate ischemic brain injury is presumably related to the increase in cerebral oxygen consumption that accompanies fever. Another possible mechanism is enhanced production of toxic oxygen metabolites, which can be particularly damaging to the brain. Regardless of the mechanism, the consensus of stroke experts is that antipyretic therapy is mandatory for fever associated with ischemic stroke. This is similar in principal to the use of therapeutic hypothermia to improve neurologic recovery after cardiac arrest, which is described in Chapter 15.

*Antipyretic Drugs*
Prostaglandin E is believed to mediate the febrile response to endogenous pyrogens, and drugs that interfere with prostaglandin E synthesis are effective in reducing fever (49). These drugs include aspirin, acetaminophen, and the nonsteroidal anti-inflammatory agents (NSAIDS). Acetaminophen is favored over aspirin and the NSAIDS because of a favorable side effects profile. However, acetaminophen is by no means a benign drug, and life-threatening hepatotoxicity has been reported with doses as low as 4 grams daily (see Chapter 53 for information on acetaminophen toxicity. The usual dose for fever suppression is 325 to 650 mg every 4 to 6 hours, and the total daily dose should not exceed 4 grams. Acetaminophen is given orally or by rectal suppository, but there is no intravenous preparation of the drug.
Ibuprofen is a popular over-the-counter NSAID that has been given intravenously (in a dose of 10 mg/kg up to 800 mg every 6 hours for 8 doses) to ICU patients with sepsis, and has proven both safe and effective as an antipyretic agent in this patient population (50). Its value as an antipyretic agent in ischemic stroke is unknown. Because ibuprofen

(like all NSAIDS), produces a reversible inhibition of platelet adherence, it could pose a risk for the transformation of an ischemic stroke into hemorrhagic stroke.

*Cooling Blankets*

The use of cooling blankets to reduce fever is inappropriate, and shows a lack of knowledge about the physiology of the febrile response. The febrile response raises the body temperature by promoting cutaneous vasoconstriction and producing a generalized increase in muscle tone. This is what the body normally does in response to a cold environment, so the febrile response mimics the physiological response to cold. Stated another way, the febrile response makes the body behave like **i**t is wrapped in a cooling blanket. Adding a cooling blanket will only add to the cold (febrile) response by producing more cutaneous vasoconstriction and a further increases in muscle tone (to the point of shivering). This would explain why cooling blankets are notoriously ineffective in reducing fever.

Cooling blankets are more appropriate for patients with hyperthermia, where the body is trying to give up heat to the environment. However, the tendency for cooling blankets to promote shivering limits their value in hyperthermia syndromes associated with muscle rigidity (e.g., neuroleptic malignant syndrome).

**A FINAL WORD**

There's a wrong way and a right way to evaluate nosocomial fever. The wrong way is to culture everything in sight, order a barrage of laboratory studies and x-rays, and start antibiotics without hesitation. The right way is to develop a stepwise approach that begins by examining the patient to assess the severity of the condition. Next, consider if anything has been done to the patient in the past 24 to 48 hours (e.g., a procedure or a change in drug therapy). **I**f this is unrevealing, then use the patient's clinical condition to identify possible sources of the fever. (For example, if the patient is on a ventilator, then pneumonia is a consideration.) Remember that you have a 50-50 chance of finding an infection (because infections are present in about 50% of patients with nosocomial fever), so don't start antibiotics unless an infection is apparent or highly suspected, or the patient is immunocompromised. And *please* don't use a cooling blanket!

**REFERENCES**