Adverse drug reactions resulting in hyperthermia in the intensive care unit

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Hyperthermia is frequently seen in the intensive care setting and is associated with significant morbidity and mortality. It is often initially misdiagnosed as fever associated with infection. Atypical presentations of classic syndromes are common. Clinical suspicion is the key to diagnosis. Adverse drug reactions are a frequent culprit. Syndromes include adrenergic "fever," anticholinergic "fever," antidopaminergic "fever," serotonin syndrome, malignant hyperthermia, uncoupling of oxidative phosphorylation, and withdrawal from baclofen. This review describes the pathophysiology of hyperthermia, as distinct from fever, and the physiology, diagnosis, and treatment of serotonin syndrome, neuroleptic malignant syndrome, malignant hyperthermia, and baclofen withdrawal. Much of the available evidence regarding the treatment of these disorders is based on single case reports, case series, or animal models. Therapeutic modalities consist of identification/withdrawal of possible offending agent(s), support directed at lowering temperature and preventing/treating complications, as well as targeted pharmacologic therapy directed at the specific cause. Early recognition and treatment using a multidisciplinary approach are essential to achieve the best possible outcome. (Crit Care Med 2010; 38[Suppl.]:S244–S252)

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Core temperature is one of the most tightly regulated variables of human physiology. As with many other physiologic systems, thermoregulation utilizes negative feedback with a high gain to minimize perturbations from a preset normal temperature (1). The "set point" is much closer to dangerous hyperthermia than hypothermia, concordant with the known dominance of warm-sensitive neurons over cold-sensitive neurons (2). Experimental evidence (3) suggested that the preoptic/anterior hypothalamic area, dorsomedial nucleus of the hypothalamus, periaqueductal area of the midbrain, and the nucleus raphe pallidus in the medulla have a critical role in thermoregulation. Redundant afferent signals arrive in the central nervous system from nearly every tissue, dominated by the preoptic/anterior hypothalamic area centrally and the skin peripherally. The preoptic/anterior hypothalamic area warm-sensitive neuron activity is determined by its own temperature and incoming information from skin and visceral thermoreceptors. The level of activity of warm-sensitive neurons triggers heat-loss or heat-gain responses; increased activity triggers sympathetic mediated heat loss through vasodilation and sweating, whereas decreased activity results in cold-defense mediated via skin vasoconstriction and shivering. Precision of sensing is similar in men and women but is decreased at the extremes of age. The exact mechanism, which determines threshold temperatures for these actions, is incompletely understood, but is known to involve activity of norepinephrine, dopamine, serotonin, acetylcholine, prostaglandin, and neuropeptides. Heat stress responses to elevated core body temperature result in active dilation of cutaneous vessels to increase skin blood flow, engendered by an increase in cardiac output and a shift of flow away from renal/splanchnic beds (4). Sweat gland activity is mediated through postganglionic parasympathetic stimulation. The combination of increased skin flow and sweating results in heat loss through convection and evaporation.

Abnormalities resulting in increased core temperature are best classified as fever or hyperthermia. Fever is associated with an increased hypothalamic set point, related to infection/inflammation or rare instances of hypothalamic damage. The Society of Critical Care Medicine practice parameters define fever in the intensive care unit (ICU) as a temperature of ≥38.3°C (101°F) (5). Alternatively, hyperthermia results from an imbalance of heat generation and heat dissipation. Heat-generating processes that outstrip normal heat-losing processes include increased basal metabolic rate, increased muscle activity from hypertonia, shivering or seizure, increased effect of thyroid hormone, or increased sympathetic activity. Conversely, hyperthermia may also result from primary impairment of heat-dissipating mechanisms and may be exaggerated in the setting of elevated ambient temperature, loss of important behavioral responses to heat stress, extremes of age, or decreased cardiac output. A classic dilemma of extreme importance and difficulty is making the distinction between fever and hyperthermia. As with many drug-mediated effects, drug-induced hyperthermia may be predictable or idiosyncratic. Mechanisms are often multifactorial, and syndromes often have overlapping phenotypes. Patients may present with formes frustes or atypical manifestations more commonly than in a classic pattern. There is no pathognomonic symptom, sign, or test, but clues to drug-induced hyperthermia may be gained from evaluation of recent drug intake, including prescribed, over-the-counter, herbal, and illicit drugs. Classic

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Table 1. Common features of hyperthermia syndromes

	Adrenergic Fever	Anticholinergic Fever	Antidopaminergic Fever (NMS)	Serotonin Syndrome	Malignant Hyperthermia	Uncoupling of Oxidative Phosphorylation	Baclofen Withdrawal
Receptor involvement	α, β, sometimes serotonin	Cholinergic	Dopamine	Serotonin	Ryanodine 1	Direct mitochondrial toxicity	GABA α, serotonin
Onset	Variable	Variable	Variable-commonly days after exposure	Variable, typically minutes to hours after exposure(s)	Immediate to hours after initiation of anesthesia	Variable	1–3 days after discontinuation of baclofen
Hyperthermia	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mental status changes	Variable	Yes	Yes	Yes	N/A, usually occurs while patient is anesthetized	Yes	Yes
Muscular	Agitation	Tremor, agitation	Progressive generalized rigidity	Akathisia, clonus, rigidity > lower extremities, hyperreflexia	Fulminant muscle rigidity	Agitation	Spasm
Autonomic instability	Yes	Tachycardia	Yes	Yes	Tachycardia	Tachycardia	Yes
Common offending agents	Amphetamines, MDMA, cocaine, MAOIs, theophylline, thyroxine	Neuroleptics, antispamodics, antihistamines, anti-parkinsonsian drugs, atropine, scopolamine, herbals containing belladonna alkaloids, mushrooms	Withdrawal of dopamine agonists, initiation of antipsychotic medications, including atypicals, metoclopramide, droperidol	SSRI, medications with serotonin activity	Succinylcholine, inhaled anesthetic agents	Salicylate preparation, PCP, MH agents	Discontinuation of intrathecal baclofen
Duration of pharmacologic treatment	Variable	Variable	Variable	Unknown	48–72 hrs after symptoms resolve	Variable	Until symptoms resolve
Pharmacotherapy	Sympatholytics, including benzodiazepines	Sedatives, physostigmine (controversial)	Possibly effective-bromocriptine, dantrolene	Benzodiazepines, cyproheptadine > chlorpromazine	Dantrolene	Alkalinization-salicylates	Intrathecal baclofen > oral baclofen, GABA α agonists, cyproheptadine
Rechallenge	Variable	Variable	Cautiously	Not recommended	Not recommended	Variable	N/A

NMS, neuroleptic malignant syndrome; MH, malignant hyperthermia; MDMA, methylenedoxymethamphetamine or Ecstasy; MAOIs, monoamine oxidase inhibitors; SSRI, selective serotonin reuptake inhibitor; PCP, phencyclidine; GABA, γ-aminobutyric acid; N/A, not applicable.

toxidromes must be recognized. Rising body temperature without evidence of extreme ambient heat exposure may indicate drug-induced hyperthermia, rather than fever, when the temperature is not preceded by vasoconstriction or followed by sweating, when high temperatures are accompanied by hypertonia or dysautonomia or are not responsive to antipyretics. The height and pattern of temperature elevation are nonspecific, as are the temperature-related complications, such as encephalopathy, disseminated intravascular coagulation (DIC), rhabdomyolysis, and liver dysfunction, among others.

Drug-induced hyperthermic syndromes fall into seven major categories (Table 1): 1) adrenergic fever, such as with exposure/overdose of cocaine, 3,4-methylenedioxymethamphetamine (Ecstasy), thyroxine, or abrupt withdrawal from sedative-hypnotics; 2) anticholinergic fever, such as from atropine, scopolamine, or the anticholinergic properties of many psychotropic medications, antihistamines, antispasmodics; 3) antidopaminergic fever (neuroleptic malignant syndrome [NMS] related to neuroleptics or withdrawal of anti-parkinsonian medication); 4) serotonin syndrome from drugs or drug combinations that increase central nervous system serotonin concentration; 5) malignant hyperthermia (MH) from volatile anesthetics and depolarizing muscle relaxants; 6) uncoupling of oxidative-phosphorylation, such as with phencyclidine or salicylate overdose; 7) baclofen withdrawal syndrome from the abrupt discontinuation of intrathecal baclofen (6).

Hyperthermia secondary to drugs, prescribed or illicit, can be life threatening if not recognized and treated emergently. The adverse drug reaction may be the reason for admission to the ICU or occur in the ICU as a result of treating other conditions, drug interactions, or not restarting medications that patients were taking before admission. This text will focus on serotonin syndrome, NMS, MH, and baclofen withdrawal. Much of what we know about these disorders has been gleaned from animal models and case reports.

Serotonin syndrome

A significant adverse drug reaction causing hyperthermia is the serotonin syndrome, also referred to as *serotonin toxicity*, *serotonin behavioral syndrome*, or *serotonin hyperactivity syndrome*. It is a toxicity resulting from an adverse drug reaction, drug interaction, or overdose of serotonergic medications. Earlier reports indicated that serotonin syndrome resulted from overstimulation of

the 3-(β-aminoethyl)-5-hydroxyindole (5HT)1a receptors. More recently, the 5HT-2a receptors have been given a significant role in the development of serotonin syndrome (7). Excess serotonin effect may result from medications or drug interactions that: 1) inhibit serotonin metabolism; 2) potentiate serotonin activity; 3) activate serotonin receptors; 4) inhibit serotonin synaptic uptake; or 5) increase substrate supply (8).

The true prevalence of serotonin syndrome is unknown. Serotonin syndrome occurs in as many as 14% of patients who overdose with selective serotonin reuptake inhibitors (SSRIs) alone (9). When overdose with multiple serotonergic agents has occurred, the incidence of developing serotonin syndrome should be much higher. Serotonin syndrome also may occur in the case of therapeutic dosing of medications. The total number of prescriptions written for serotonergic medications continues to increase, and the indications for these medications are expanding. In 2008, escitalopram was the ninth most commonly dispensed medication in the United States (10). The Toxic Exposure Surveillance System (11) reported in 2002 that there were 26,733 exposures to SSRIs, resulting in 7349 significant adverse effects and 93 deaths. The symptoms consistent with serotonin syndrome were initially reported in the early 1950s and 1960s with monoamine oxidase inhibitors (12). The number of case reports and case series in the literature continues to expand (13). Table 2 contains a partial list of medications that increase serotonergic activity.

Serotonin is produced by decarboxylation and hydroxylation of the substrate L-tryptophan. It is degraded by monoamine oxidase and is actively absorbed by platelets in the peripheral circulation. Peripherally, serotonin is involved in the regulation of gastrointestinal motility, blood pressure, and coagulation. Centrally, serotonergic neurons are found primarily in the midline raphe nuclei. These neurons are responsible for the regulation of behavior, hunger, thermoregulation, nociception, and motor tone. It is unknown whether serotonin syndrome is caused by excess serotonin at one receptor type or whether multiple receptors are involved. It is likely that both the 5HT1a and 5HT2a receptors contribute; γ-aminobutyric acid (GABA) and N-methyl-D-aspartic acid receptor antagonism may contribute as well. It is unlikely that dopamine plays a role in the development of serotonin syndrome (14).

Table 2. Common medications with serotonergic activity

Selective serotonin reuptake inhibitors	Miscellaneous Antidepressants
Citalopram	Buspirone
Escitalopram	Nefazodone
Fluoxetine	Trazodone
Paroxetine	Antibiotic/Antiviral Medications
Sertraline	Linezolid
Serotonin and norepinephrine reuptake inhibitors	Ritonavir
Duloxetine	Herbal Medications
Venlafaxine	St. John's wort
Monoamine oxidase inhibitors	Additional Medications
Isocarboxazid	Cyclobenzaprine
Phenylzine	Dextromethorphan
Tranylcypromine	Fentanyl
Selegiline	Granisetron
Tricyclic antidepressants	Meperidine
Amitriptiline	Metoclopramide
Desiprimine	Ondansetron
Doxepin	Pentazocine
Imipramine	Tramadol
Lofepramine	
Nortriptyline	

This is not an all-inclusive list.

Serotonin syndrome is described as a triad of symptoms, which includes mental status changes, autonomic hyperactivity, and neuromuscular abnormalities. The mental status changes range from mild agitation and slightly pressured speech to agitated delirium, seizures, or coma. The autonomic derangements include tachycardia, hypertension, or hypotension and hyperthermia, increasing >41.1°C in severe cases. The most sensitive physical examination finding is the presence of clonus. Other neuromuscular manifestations include muscle rigidity and hyperreflexia, usually greater in the lower extremities than the upper extremities. If left untreated, rhabdomyolysis, metabolic acidosis, renal failure, or DIC may result. The clinical manifestations and toxicity associated with serotonin syndrome seem to be dose-related, reflecting serotonin concentration at the synaptic cleft (15). The hyperthermia associated with serotonin syndrome is related to the neuromuscular manifestations of serotonin syndrome and, to a lesser extent, disruption of homeostasis in the hypothalamus.

Differentiating the diagnosis of serotonin syndrome from other adverse reactions or syndromes can be difficult (Table 1). Standards have been developed to help determine whether the diagnosis of serotonin syndrome should be made. The Sternbach criteria (16) require the patient to exhibit at least three of the following symptoms: mental status changes, agitation, hyperreflexia, myoclonus, diaphoresis, shivering, tremor, diarrhea, incoordination, or elevated temperature. This has been criticized due to a heavy reliance on mental status for the diagnosis. Patients with symptoms, such as delirium from anticholinergic medications, may be diagnosed with serotonin syndrome based on the Sternbach criteria (17). Radomski and colleagues differentiated a mild state of serotonin-related symptoms vs. the "full-blown" form of serotonin syndrome (18). Symptoms associated with the mild state included restlessness, insomnia, incoordination, dilated pupils, akathisia, tachycardia, tachypnea/dyspnea, diarrhea, and autonomic instability. The severe form included impairment in the level of consciousness, elevated mood, coma, myoclonus, tremor, shivering, rigidity, hyperreflexia, hyperthermia, and sweating. Dunkley and colleagues (17) developed the Hunter serotonin toxicity criteria, which include clonus, agitation, diaphoresis, tremor, hyperreflexia, hypertonia, and hyperthermia. The authors found that spontaneous clonus, inducible clonus, ocular clonus, agitation, diaphoresis, tremor, and hyperreflexia were required for accurately predicting serotonin toxicity, clonus being the most important variable. The major differential diagnoses that should be ruled out are infection, heat stroke, NMS, and other intoxication syndromes, such as adrenergic or anticholinergic fever. Unfortunately, there is no laboratory test to diagnose serotonin syndrome. Serotonin

serum levels are not useful, as the concentration at the synaptic cleft correlates with toxicity.

The classes of medications that are most commonly associated with serotonin syndrome are the SSRIs and tricyclic antidepressants. Selective serotonin reuptake inhibitors increase serotonin in the synapse by inhibiting presynaptic reuptake of serotonin. The SSRIs can be both substrates as well as inhibitors of the P-450 enzyme system. For example, fluoxetine is a substrate for both the P-450 2C9 and 2D6 isoenzymes as well as an inhibitor of the 2D6 isoenzyme. Therefore, these agents can interfere with the metabolism of other medications, and other medications may inhibit the metabolism of the SSRIs. Monoamine oxidase inhibitors decrease the ability to break down serotonin, increasing the risk of serotonin syndrome, when other medications with serotonergic activity are given in combination. Tricyclic antidepressants inhibit the reuptake of serotonin by inhibiting the synaptic serotonin transporter, therefore increasing the extracellular serotonin concentration. Tricyclic antidepressants and monoamine oxidase inhibitors can also be affected by the cytochrome P-450 isoenzyme system. Therefore, it is important to be aware of the pharmacokinetics and the cytochrome P-450 drug interactions of the different agents. This is important when changing from one antidepressant to another, adding medications with slight serotonergic activity to a medication regimen that already contains a serotonergic agent, as well as determining the duration of treatment in patients who are being treated for serotonin syndrome.

More recently, linezolid, an antibiotic commonly used in critically ill patients, has been implicated in multiple cases of serotonin syndrome. Linezolid is a weak inhibitor of monoamine oxidase and, when combined with agents with serotonergic activity, it can precipitate the syndrome (19). Other agents implicated include lithium, bromocriptine, carbamazepime, trazodone, cocaine, and meperidine. Intrathecal baclofen withdrawal, usually due to pump malfunction or delivery system disruption, has many similarities to serotonin syndrome and may be mediated, in part, by excess central nervous system serotonergic activity (20).

Treatment of serotonin syndrome has not been critically evaluated in the literature. Most patients who develop serotonin syndrome will have improvement or resolution of symptoms within 24 hrs after discontinuation of the offending agent(s) and initiation of supportive therapy. Supportive therapy primarily aimed at reducing muscle rigidity, thought to be the major contributor to hyperthermia and death, consists of intravenous hydration, core or rapid external cooling, liberal use of benzodiazepines to produce muscle relaxation and limit anxiety, and avoidance of physical restraints (3, 21). Although described in the setting of rapid induction of therapeutic hypothermia in comatose survivors after cardiac arrest, one author (D.R.S.) has had much success in treating fulminant drug-induced hyperthermia with the rapid infusion of 30 mL/kg of iced (4°C) saline (22). Symptoms may persist in the patient who has taken medications with prolonged elimination half-life, such as fluoxetine. Boyer and Shannon (14) recommended intubation, sedation, and chemical paralysis for patients who develop hyperthermia with a temperature of >41.1°C.

Hypertension should be treated with short-acting, easily titratable, intravenous agents. Hypotension in patients who have a monoamine oxidase inhibitor implicated in serotonin syndrome should be treated with direct catecholamines, such as phenylephrine, norepinephrine, or epinephrine. Indirect agents, such as dopamine, are metabolized by monoamine oxidase to epinephrine and norepinephrine. When monoamine oxidase is inhibited, the amount of norepinephrine or epinephrine produced is uncontrolled, and an exaggerated response may occur.

Several medications have been utilized successfully to alleviate the symptoms associated with serotonin syndrome. Cyproheptadine and chlorpromazine (felt to be a second choice due to worse side-effect profile) are serotonin receptor antagonists that have been used successfully, although neither agent has been evaluated in a randomized trial. Cyproheptadine is a histamine-1 receptor antagonist, which also has prominent 5HT2a receptor antagonism. Doses of 12–32 mg are estimated to bind 85% to 95% of serotonin receptors. No standardized dosage regimen has been proposed, but regimens that have been successfully utilized are 4 mg orally every 2–4 hrs or 12 mg orally once, followed by 2 mg every 2 hrs as symptoms continue, then 8 mg orally every 6 hrs. The side effects of cyproheptadine are mild, drowsiness being the most common. Cyproheptadine is not available as an injectable formulation, but the oral form may be crushed and administered through a nasogastric or other feeding tube. In situations where enteral administration of the medication is not feasible, chlorpromazine has been used in doses of 50 mg intramuscularly, which can be repeated if symptoms recur. Chlorpromazine is utilized for the treatment of psychosis. It is a dopamine antagonist with nonspecific serotonin antagonist activity at the site of the 5HT1a and 5HT2a receptors. Chlorpromazine can cause hypotension and should be avoided in the setting of cardiovascular instability. Chlorpromazine has been useful in treating hyperthermia in case reports (23).

Agents that will require more research to determine usefulness are olanzapine and dantrolene. Olanzapine is a medication used for psychosis/delirium, which has serotonin receptor antagonism. At this point, there are no reports of its use for the treatment of serotonin syndrome, and it should be avoided. Dantrolene inhibits skeletal muscle contraction by inhibiting calcium influx from the sarcoplasmic reticulum. Although it is recommended for the treatment of muscle rigidity in NMS, it is unknown whether it would be useful in serotonin syndrome. There are two cases where it was used successfully for serotonin syndrome at low doses (24, 25). Conversely, it is suggested that it may increase availability of serotonin by interfering with serotonin metabolism (26). Because the hyperthermia associated with serotonin syndrome is not due to alterations in temperature "set point" in the hypothalamus, antipyretics like acetaminophen or ibuprofen are not useful.

NMS

NMS is commonly caused by the typical antipsychotic medications, but it can also occur with the newer atypical agents, such as quetiapine or olanzapine and drugs of abuse. As delirium becomes more frequently recognized in the ICU and is associated with increased morbidity and mortality, the use of antipsychotic medications may become more prevalent (27). NMS has been reported to have an incidence of 0.2% to 12% in retrospective evaluations and 0.7% to 1.8% and 0.02% to 2.44% in two prospective evaluations (28, 29). It has been suggested that the frequency of NMS may be decreasing due to an increased reliance on atypical antipsychotic medications. In 1989, it was reported that mortality from NMS was 11.9%, a reduction from 18.8% in the years before 1984 (30). Unfortunately,

there has not been any suggestion in the literature as to the incidence, prevalence, or mortality in critically ill patients.

Although the exact mechanism is unknown, the development of NMS is thought to occur from a reduction in central nervous system dopamine neurotransmission. Acute reduction in dopamine activity along nigrostriatal and hypothalamic pathways is believed to result in the clinical manifestations. Potential mechanisms include: 1) the introduction of agents that block dopamine transmission, including neuroleptic medications and the antiemetic medications prochlorperazine, promethazine, droperidol, and metoclopramide; 2) changing from one antipsychotic medication to another; 3) new prescription of medications that may alter other neurotransmitters, such as serotonin or epinephrine; or 4) a withdrawal of L-dopa or dopamine agonist treatment. Patients who are treated with L-dopa, amantidine, bromocriptine, pergolide, ropinirole, or pramipexole and suddenly stop treatment are at risk of a subtype of NMS, the parkinsonism-hyperpyrexia syndrome (31). This can also occur from decreased systemic absorption or altered metabolism of these medications. Peripheral effects of NMS may include muscle damage as a result of changes in muscle mitochondrial function and altered cellular metabolism. It is unclear whether these changes are due solely to peripheral effects of neuroleptic medications on skeletal muscle or are exaggerated by inherited defects (32). The exact mechanism of hyperthermia is not understood; one hypothesis suggests that central dopamine blockade can produce muscle rigidity and fever through effects on central thermoregulation and neuromuscular control (33).

Typical antipsychotic medications are antagonists at the D_2 dopamine receptor, and atypical antipsychotic medications are thought to have a greater affinity at the D_3 and D_4 receptor. Both types may interfere with the release of dopamine or block postsynaptic dopamine receptors. The most commonly associated medications implicated in NMS are the potent antipsychotic medications haloperidol and depot fluphenzaine, although it should be noted that these medications have been prescribed most frequently. More recent reports implicate the atypical antipsychotic medications, such as olanzapine, risperidone, ziprasidone, aripiprazole, and quetiapine. A review of NMS indicates that the clinical presentation is similar with both types of antipsychotic medications. Clozapine seemed to present with less rigidity and tremor. Fever of $>40°C$ was present in only 5% of the cases implicating risperidone (34).

In addition to antipsychotic medications, case reports link NMS to antidepressants. Twenty-three cases have been reported, mostly involving the use of tricyclic antidepressants. Although these reports presumably describe NMS, it is difficult to determine whether the patients were instead experiencing serotonin syndrome or another disorder (35). Lithium has also been reported to cause NMS as well as increase the risk of developing the syndrome when combined with dopamine antagonist medications. Cocaine can cause a variant of NMS. These patients can present with hyperthermia and agitated delirium and low cocaine levels but without rigidity. It is thought that cocaine alters dopamine reuptake at the nerve terminal; thus, when cocaine concentration is reduced, dopamine transmission is also reduced (36).

NMS can occur in children, adolescents, or adults. It has been reported to occur more often in younger adults, which may be due to an increase in use of neuroleptic medications in this age group. Many patients who are prescribed neuroleptic medications have schizophrenia, commonly diagnosed in young adulthood. The tetrad of symptoms associated with the development of NMS includes mental status changes, rigidity, hyperthermia, and autonomic dysfunction. Mental status changes include confusion, delirium, stupor, and coma. In the intensive care setting where confusion and delirium may be attributed to alternate causes, late onset of stupor and coma may be more common, although there is insufficient literature available in this setting. It has been noted that mental status changes precede systemic symptoms in $>80\%$ of cases of NMS (37). Symptoms associated with motor dysfunction include increased tone with resistance to passive movement, dystonia, and parkinson-like symptoms, such as akinesia or bradykinesia. Temperature of $>38°C$ is commonly seen, many times exceeding 41°C. There are cases that have been reported where hyperthermia was not present (38).

NMS usually evolves over 24–72 hrs, although much slower onset has reported to occur. NMS may occur at any time during treatment. This is in contradistinction to serotonin syndrome, which characteristically develops in minutes to hours of exposure to the offending agent(s). NMS usually lasts for 7–10 days, longer with depot injections of neuroleptic agents due to slower clearance. The most consistently reported risk factors in patients with NMS include psychomotor agitation, high doses of neuroleptic medications, quick up-titration of the dose, parenteral administration and use of multiple agents that reduce dopamine transmission. One case-control trial evaluated the clinical and pharmacologic risk factors for developing NMS in 12 patients diagnosed with NMS compared with 24 patients who received neuroleptic medications who did not meet the criteria for the diagnosis of NMS. Patients had more preceding psychiatric symptoms, such as agitation, confusion, disorganization, and catatonia. Medication risk factors included higher maximum, mean and total neuroleptic dose, higher number of parenteral injections over 5 days, and greater neuroleptic dose increase compared with initial dose (39). Care must be exerted when evaluating these risk factors due to the low number of patients studied, although the results are consistent with other published reports of NMS (40).

NMS remains a diagnosis that involves high clinical suspicion; in many cases, it is a diagnosis of exclusion. The *Diagnostic and Statistical Manual of Mental Disorders* includes diagnostic criteria to help clinicians with the diagnosis of NMS (Table 3) (41). The criteria require that the symptoms are associated with the use of an antipsychotic medication, although NMS can be induced by abrupt withdrawal of a dopaminergic agent. Levenson (42) proposed new criteria in which high probability patients are required to have all three major criteria (hyperthermia, rigidity, and elevated creatine phosphokinase) and four of five minor criteria (tachycardia, abnormal blood pressure, altered consciousness, diaphoresis, and leukocytosis). Additional diagnoses in critically ill patients who should be considered when "ruling-in" NMS include infections, such as meningitis or encephalitis; neurologic illness, such as nonconvulsive status epilepticus and delirium; endocrine abnormalities, including thyrotoxicosis and pheochromocytoma; heatstroke; as well as the other drug-induced hyperthermias (Table 1) (43).

Although there is no definitive laboratory value or diagnostic test to diagnose NMS, laboratory abnormalities have been commonly observed. Many patients will present with a leukocytosis in the range

Table 3. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*—Criteria for diagnosis of neuroleptic malignant syndrome

A.	Development of severe muscle rigidity and elevated temperature associated with the use of neuroleptic medication (41)
B.	Two or more of the following:
	Diaphoresis
	Dysphagia
	Tremor
	Incontinence
	Changes in level of consciousness ranging from confusion to coma
	Mutism
	Tachycardia
	Elevated or labile blood pressure
	Leukocytosis
	Laboratory evidence of muscle injury (i.e., elevated creatine phosphokinase)
C.	The symptoms in criteria A and B are not due to another substance (e.g., phencyclidine) or a neurologic or other general medical condition (e.g., viral encephalitis)
D.	The symptoms in criteria A and B are not better accounted for by a mental disorder (e.g., mood disorder with catatonic features

of 10,000–40,000 white blood cells/μL (44), low serum magnesium, calcium and iron, metabolic alkalosis, as well as elevated liver enzymes lactate dehydrogenase, aspartate transaminase, alanine aminotransferase, and alkaline phosphatase (23). In addition to symptoms directly associated with NMS, the patient may have associated complications. NMS may account for significant morbidity, with secondary central nervous system damage. Four case reports (45) described cerebellar injury after this syndrome. Recently, a review of patients who developed NMS with traumatic brain injury was reported. The authors identified nine patients who developed NMS and were receiving haloperidol. Treatment was successful in all patients, but all were noted subsequently to have reduced neurologic function. It was concluded that patients with traumatic brain injury should be monitored closely, especially if they are receiving haloperidol parenterally at high doses. It is important to note that haloperidol may have negative effects on cognition and function, making it an unattractive medication in this patient population (46). The development of heme pigment-associated renal failure from rhabdomyolysis is an important risk factor for mortality (30). Patients also are at extremely high risk for venous thromboembolism, with pulmonary embolism reported to be the cause of death in 23% of patients who develop NMS (32).

Patients who develop NMS should be cared for in the ICU. The most important factor in treating a patient with NMS is to remove the agent suspected to cause the episode. Additional supportive measures include adequate intravenous hydration, nutrition, aggressive cooling measures, and use of adjunctive benzodiazepine for muscle relaxation.

It is unclear if direct pharmacologic treatment is more effective than supportive measures alone. There are contradictory reports in the literature regarding the comparison. One trial (47) indicated a more rapid response and reduction in duration of symptoms by utilizing the combination. A second trial (48) noted that those treated with targeted medications have a more prolonged course and a greater potential for complications than those treated with supportive care alone. Dantrolene and bromocriptine are the most commonly utilized medications for treatment of NMS. There are case reports describing other potentially effective medications, such as parenteral clonidine, carbamazepine, amantadine, parenteral levodopa, and anticholinergic medications. If treatment with pharmacologic agents is instituted, it should continue for at least 10 days after resolution of the episode, then tapered slowly. If the episode was attributed to a depot antipsychotic medication, the pharmacologic treatment should continue for 2–3 wks.

Dantrolene relaxes skeletal muscles due to depression of excitation-contraction coupling, interfering with the ability to transform a chemical signal at the neuromuscular junction into a muscle contraction. It is unclear whether the use of dantrolene will shorten the duration of the episode, reduce morbidity, or reduce mortality. It may be useful in cases that involve extreme temperature elevations, rigidity, and true hypermetabolism (43).

Bromocriptine is a dopaminergic agonist that may be useful in patients who develop parkinsonism symptoms due to abrupt discontinuation of dopamine-stimulating medications. Bromocriptine can exacerbate hypotension and psychosis and should be avoided in patients who are agitated or in shock. The usual dose of bromocriptine is 2.5 mg twice daily or three times daily and can be titrated to doses as high as 45 mg, if indicated. It is not available in a parenteral formulation.

Electroconvulsive therapy has been reported to improve some of the components of NMS, including fever, sweating, and loss of consciousness. It may be instituted in: 1) cases of severe NMS refractory to medical treatment; 2) if it is not possible to differentiate a diagnosis of neuroleptic malignant syndrome from acute lethal catatonia; 3) treatment of residual catatonia or psychosis in the immediate time period after neuroleptic malignant syndrome; or 4) when the underlying psychiatric diagnosis is psychotic depression or catatonia. It is important to ensure the patient is well hydrated to prevent additional injury to the kidney.

After an episode of NMS, reintroduction of dopamine antagonist medications will result in recurrence in approximately 30% to 50% of patients (43). Factors associated with recurrence include the use of high-potency neuroleptics, short time interval between the episode and reintroduction of the neuroleptic medication, higher initial dose, and concurrent use of lithium. Therefore, it is suggested to use extreme caution when reintroducing neuroleptic medications in a patient who previously has experienced NMS. In cases where neuroleptics are felt essential, it is important to initiate the rechallenge with a low dose of the medication and to titrate the agent slowly.

MH

MH is a genetically based, life-threatening complication that can occur after the administration of depolarizing neuromuscular blocking agents, such as succinylcholine, and potent inhalation gases such as halothane, sevoflurane, isoflurane or desflurane, and less commonly with these agents alone. Rarely, stress, such as vigorous exercise or extreme heat, may precipitate this disorder, referred to as "awake MH." The majority of patients will exhibit symptoms immediately after the offending agents are given, whereas others may have initiation of symptoms several hours after administration. Therefore, it is important that the critical care team is able to recognize and promptly treat MH as well as provide supportive care for the complications that may arise during and after the episode.

It is estimated that MH occurs in 1 of 5000 to 1 of 10,000 children and 1 of 50–100,000 adults receiving anesthesia. Although an episode may occur after the initial exposure to the agent, on average, patients require three exposures before an episode of MH is triggered. It is more common in males than females. MH can

occur in patients of all ages, with a mean age of 18 yrs, although more than half of all cases have occurred in patients <15 yrs of age (49). There does not seem to be cross reactivity between NMS and MH, but animal models have indicated that serotonin agonists may induce an episode of MH in a susceptible animal.

The ryanodine receptor gene 1 encodes for calcium release in skeletal muscle during excitation-contraction coupling. The ryanodine receptor gene 1 also has binding sites for adenosine triphosphate, magnesium, volatile anesthetics, and dantrolene. Mutations in this gene account for at least half of the patients susceptible to developing an episode of MH. The mutations are responsible for inducing an elevation of cytoplasmic calcium-inducing skeletal muscle contraction. Cell metabolism is accelerated—causing excessive heat and lactate production that result in hyperthermia and acidemia. Rhabdomyolysis often occurs. Skeletal muscle adenosine triphosphate is rapidly depleted during MH, causing myonecrosis.

The most sensitive indicator of a patient potentially experiencing an episode of MH is an unexplained rapid rise in end-tidal CO_2, indicating muscle hypermetabolism. Additional early symptoms include an unexplained tachycardia and masseter muscle spasm, usually after the increase in exhaled CO_2. Tachycardia occurs in almost all patients, likely due to release of catecholamines. Hyperthermia is a later sign and will usually progress to temperature of ≥41°C. It is important to recognize that some patients do not experience temperature elevation, so the absence of hyperthermia should not rule out a potential diagnosis of MH. Generalized muscle rigidity occurs in approximately one third of patients and may be indicative of a more severe case of MH. Untreated patients may progress to DIC and eventually cardiac arrest.

The "gold standard" for diagnosis is the *in vitro* contracture test of which there are two methods: one developed by the European Malignant Hyperthermia Group and the other by the North American Malignant Hyperthermia Group. Each test evaluates contracture of muscle fibers in the presence of halothane and caffeine. The North American Malignant Hyperthermia Group protocol states that a diagnosis of malignant hyperthermia susceptible when either halothane or caffeine test is positive. The European Malignant Hyperthermia Group protocol requires both tests to be positive to indicate a susceptible individual. The *in vitro* contracture test is expensive, requires a surgical procedure, and is not widely available, although both protocols are sensitive and specific. Deoxyribonucleic acid analysis is also available, but mutations may occur in all regions of the gene, and the sensitivity and predictive value varies within populations. The European Malignant Hyperthermia Group (50, 51) recommends that if deoxyribonucleic acid analysis is performed, it should be in conjunction with the *in vitro* contracture test.

In addition to NMS and serotonin syndrome (Table 1), there are many diagnoses that should be considered when making a diagnosis of MH. Some disorders that may have similar symptoms include thyroid storm, pheochromocytoma, sepsis, illicit drug overdose, such as with cocaine or 3,4-methylenedioxymethamphetamine (Ecstasy), faulty equipment for measuring temperature, warming machine valve malfunction, as well as accidental intrathecal injection of contrast agents (52).

The most important treatment is to immediately discontinue the offending agent. If there are multiple agents that have the potential to cause MH, all possible agents should be discontinued. The patient should immediately be administered 100% oxygen, because oxygen is rapidly depleted during an acute episode of MH due to the profound systemic oxygen consumption. In addition, ventilation should be instituted at a rate of two to three times the predicted minute ventilation. Sedation should be maintained with the use of intravenous sedatives, and if medication-induced paralysis is needed, nondepolarizing neuromuscular blocking agents should be utilized. Dantrolene sodium should be immediately administered at a dose of 2.5 mg/kg intravenously, with repeated doses as needed until symptoms of hyperthermia and tachycardia resolve. Doses of 10 mg/kg are usually sufficient, but some patients may require higher cumulative doses. A diagnosis of MH should be reconsidered if the patient has not responded after 20 mg/kg has been administered. Dantrolene and evaluation and treatment for rhabdomyolysis and DIC should be continued for a minimum of 48 hrs, as rare recurrence of MH has been reported within 48 hrs after initial treatment.

Patients should be monitored in the intensive care setting, and complications associated with the MH episode should be treated with usual measures. Early in the MH episode, potassium may increase and needs to be treated promptly to avoid cardiac conduction block. It is important to avoid calcium-channel blockers if treating tachyarrhythmias. Calcium-channel blockers interact with dantrolene, and the combination may considerably worsen hyperkalemia, resulting in cardiac arrest. Agents that are safe to use for anesthesia or to facilitate intubation in patients who are at risk for MH or have had a prior episode of MH include all nondepolarizing neuromuscular blocking agents, such as rocuronium or vecuronium, nitrous oxide, intravenous anesthetic agents, such as ketamine, propofol, etomidate, benzodiazepines, barbiturates, and thiopental, as well as local anesthetic agents and opiates.

Baclofen withdrawal

Baclofen is a medication that is used to treat severe muscle spasm in patients with spinal cord injury, cerebral palsy, traumatic brain injury, multiple sclerosis, and many other disorders. It can be given orally or intrathecally via a continuous pump to allow for higher local spinal cord doses, resulting in less sedation. Baclofen is a GABA β agonist that acts by binding to presynaptic GABA β receptors in the brain stem, resulting in an inhibitory effect on the spinal cord and brain. Abrupt discontinuation of intrathecal baclofen can cause a life-threatening syndrome consisting of hyperthermia, autonomic dysfunction, increased spasticity, and altered mental status. Rhabdomyolysis, seizures, DIC, and death may occur. Long-term use of baclofen may cause a reduction in sensitivity of the receptors, and discontinuation of the medication may cause disinhibition of GABA β modulated pathways.

Although the symptoms of baclofen withdrawal may be similar to NMS, serotonin syndrome, and malignant hyperthermia, it can usually be easily distinguished by patient history (Table 1). If one of the above-mentioned syndromes is suspected, any potential offending medication should be discontinued. Baclofen withdrawal may occur due to malfunction of pump, catheter dislodgment, catheter kink, the need to refill the pump, or purposeful removal of the baclofen pump, such as the case of infection (20).

Baclofen withdrawal usually evolves over 1–3 days after the cessation of intrathecal baclofen; it may not respond to

high-dose oral or intrathecal doses of baclofen and may last for weeks (20). There is no specific treatment proven to be clearly superior once the syndrome is underway, although early reinstitution of intrathecal baclofen is felt by one author (D.R.S.) to be the most effective, if at all possible. Many of the available treatments have not been evaluated in the literature and are reported only in single cases or small series. Oral baclofen, benzodiazepines, and dantrolene have been used, as well as propofol and cyproheptadine, a serotonin antagonist. Baclofen may reduce the release of serotonin during long-term therapy; on cessation of baclofen, there seems to be an excess release of serotonin, causing a form of serotonin syndrome. Several case reports (53) have reported success with cyproheptadine in combination with enteral baclofen, benzodiazepines, and supportive care. Although the exact mechanism of action of propofol is unknown, it is a potent GABA α agonist that has been reported as a successful treatment in two patients (54, 55). Overall, there is no algorithm for the treatment of baclofen withdrawal, and the syndrome may present a significant challenge to the practitioner.

Conclusion

Cases of drug-induced hyperthermia are likely underdiagnosed. Delay in diagnosis or misdiagnosis as sepsis-associated fever may result in increased morbidity and mortality associated with the primary syndrome or the adverse effects of unnecessary diagnostic/therapeutic tests or procedures or adverse reactions to antibiotics. A thorough history, most importantly related to previous or active drug/medication exposure, is the key to diagnosis in most cases, and immediate withdrawal or reinstitution of possible offending agents is potentially lifesaving. For severe cases, aggressive supportive care in the ICU setting is clearly warranted. A multidisciplinary approach, often involving intensive care, toxicology, pharmacology, neurology, and psychiatry should be utilized in the diagnosis/management of these complex and life-threatening disorders.

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