DESCRIPTION OF THE NEPHROLOGY TRAINING PROGRAM AT VANDERBILT UNIVERSITY SCHOOL OF MEDICINE

The Nephrology Training Program at Vanderbilt University, under the direction of Dr. Harry Jacobson, includes 20 full-time faculty members with diverse interests in basic and clinical research. The program provides extensive experience in consultative nephrology, acute and chronic hemodialysis, peritoneal dialysis, renal transplantation, hypertension management, and evaluation and management of nephrolithiasis.

Fellowship opportunities are available for either 2 or 3 yr and encompass clinical and research training. During the clinical experience, fellows rotate among clinical services at four different hospitals: Vanderbilt University Medical Center, Nashville Veteran's Administration Hospital, St. Thomas Hospital, and the Metropolitan Nashville General Hospital. As such, they engage in a tremendous range of inpatient and outpatient activities.

Throughout the academic year, faculty, fellows, housestaff, and students attend a number of stimulating conferences. These include weekly renal grand rounds, weekly renal research conference, a renal physiology lecture series, clinical case presentations, and a weekly transplant conference. Additionally, clinical journal club is offered biweekly alternating with research journal club, and a renal biopsy conference is presented monthly in cooperation with the renal pathologists. By participating in this forum, fellows are exposed to the pathology and physiology of the kidney. They also encounter issues in renal transplantation, transplant immunology, and basic concepts of nephrologic radiology, urology, and other essential aspects of clinical nephrology. The research conferences and renal grand rounds review current scientific work within the division and highlight many invited lecturers who present pertinent issues relevant to contemporary nephrology.

Research activities in the Vanderbilt Renal Division cover a broad scope of basic and clinical interests. Ongoing basic research focuses on biochemical signaling pathways in epithelial cells; physiology, pharmacology, biochemistry, and molecular biology of biologically active eicosanoids; the molecular mechanisms of endothelial cell differentiation; the regulation of membrane transport proteins in renal epithelial cell models; molecular mechanisms of renal cell injury and scarring; and basic mechanisms responsible for salt-sensitive hypertension. Basic research in transplantation is directed at the molecular characterization of lymphocyte activation.

Clinical research activities include interventional trials examining the effects of diet and pharmacologic therapy on the progression of renal disease; studies in blood-membrane interactions; investigation of nutrition and adequacy of dialysis; studies on the mechanism of β2-microglobulin amyloid development and prevention; examination of the effects of growth hormone in dialysis patients; and studies in the use of therapeutic apheresis in various renal and nonrenal diseases. The Vanderbilt Nephrology Division is also involved in several prospective clinical trials examining important issues in clinical nephrology, hypertension, and dialysis.

The Vanderbilt nephrology fellowship provides a well-rounded clinical experience. Fellows also have great opportunity to develop skills in research ranging from molecular and cellular biology to the study of important problems in clinical nephrology. As a result, fellows can be well prepared for either a career in the clinical practice of nephrology or a career in academic nephrology.
Rhabdomyolysis is a potentially lethal disorder arising as a consequence of traumatic or nontraumatic muscle injury. Many factors have been implicated as potential causes for rhabdomyolysis including muscle trauma or injury, muscle ischemia, toxin or drug ingestion, extreme physical activity, metabolic disorders, and infectious processes. Massive rhabdomyolysis can produce a variety of manifestations as a result of the release of myocyte contents into plasma. These complications include electrolyte abnormalities, disseminated intravascular coagulation, acute cardiomyopathy, and acute renal failure.

Myoglobinuric renal failure was first recognized in individuals suffering crush injuries during the "blitz" in London in World War II. Since that era, acute renal failure has been observed with greater frequency in the setting of nontraumatic rhabdomyolysis. Often, drugs have been the causal factor underlying the development of nontraumatic rhabdomyolysis and, hence, the renal failure associated with this syndrome. Many patients present with asymptomatic rhabdomyolysis demonstrable only by elevations in serum creatine phosphokinase (CPK). Others come to medical attention only after developing a fulminant syndrome of muscle damage. They may suffer from life-threatening hyperkalemia, hypocalcemia, metabolic acidosis, and the adult respiratory distress syndrome. In this article, we review a case of drug-induced rhabdomyolysis with renal failure in a patient with the neuroleptic malignant syndrome (NMS). This case provides a forum for examining the spectrum of differential diagnoses the clinician must consider when encountering such a patient. We address the significant clinical features of NMS and its pathophysiology. We also discuss the association between NMS and renal failure and address various therapies for this severe and potentially fatal drug reaction.

CASE REPORT

A 55-year-old woman was arrested for assault. Because of persistent combativeness, she was taken to a local emergency room where she received 10 mg of haloperidol IM. She was incarcerated overnight. The next morning, she remained combative and was taken to a different emergency department. There, she was noted to be febrile (39.1°C), tachycardic (heart rate, 132 beats/min), hypertensive (220/88
mm Hg), and diaphoretic. A urine drug screen documented tricyclic compounds. Laboratory studies included an arterial blood gas: pH 7.32; Pco2, 14 mm Hg; Po2, 110 mm Hg; serum Na, 142 mEq/L; K, 4.2 mEq/L; HCO3-, 12.5 mEq/L; and creatinine, 2.1 mg/dL. The patient was given haloperidol (15 mg im), pentobarbital (50 mg im), and clonidine (0.1 mg po). She was discharged to a psychiatric facility.

Twelve hours later, she returned to the emergency department more diaphoretic. Her temperature had increased to 41.5°C, her heart rate was 120 beats/min, and her blood pressure was 170/90 mm Hg. A physical examination revealed an agitated obese woman in moderate distress. Ecchymoses were present on the patient's right flank, right hand, and both lower extremities. A funduscopic examination was unremarkable. The mucous membranes were dry. Chest auscultation documented minimal bibasilar rales and a II/VI systolic ejection murmur. The patient spontaneously moved all extremities, but muscular rigidity and “cog-wheeling” were demonstrable in both upper extremities.

Repeat laboratory studies revealed an arterial blood gas of pH 7.25; Pco2, 13 mm Hg; and Po2, 80 mm Hg. A chest x-ray demonstrated postmedian sternotomy changes and old granulomatous disease. An electrocardiogram documented sinus tachycardia with left ventricular hypertrophy and repolarization abnormalities. The patient's hemogram showed a hematocrit of 44%, a white blood cell count of 24,000/μL, and a platelet count of 373,000/μL. Serum chemistries manifested the following values: Na, 155 mEq/L; K, 5.2 mEq/L; Cl, 122 mEq/L; HCO3-, 4.5 mEq/L; creatinine, 4.9 mg/dL; and lactate dehydrogenase, 1,160 IU/L (nl. 91 to 180). Serum glucose was 271 mg/dL and Ca was 7.8 mg/dL, whereas Po2 was 3.1 mg/dL. Urinalysis initially documented the following: specific gravity, 1.011; pH 6; 1+ blood on dipstick analysis with 0 to 4 white blood cells per high-power field and rare red blood cells per high-power field. The patient received 15 additional mg of haloperidol (im) and 2 mg of lorazepam for her agitation and was admitted to the intensive care unit.

Her past medical history was remarkable for coronary artery disease, for which she had undergone coronary artery bypass grafting. She also had a history of hypertension, congestive heart failure, and type II diabetes mellitus. Additionally, she suffered from major depression. Her usual medications consisted of isradipine, 5 mg twice daily; furosemide, 40 mg daily; trazodone, 50 mg daily; imipramine, 75 mg each evening; ranitidine, 150 mg two times a day; and digoxin, 0.125 mg daily.

Because of progressive fatigue and agitation, the patient was electively intubated. Further laboratory studies were obtained. These showed the following: CPK, 5,552 IU/L (nl. 22 to 269); lactate, 6.4 mmol/L; aspartate aminotransferase, 153 IU/L (nl. 10 to 42); alanine aminotransferase, 285 IU/L (nl. 10 to 60); and γ-glutamyltransferase, 123 IU/L (nl. 7 to 64). The prothrombin time was 16.7 s with a control of 11.1 s; the APTT was within normal limits. Urine chemistries showed urine sodium of 88 mEq/L, urine chloride of 99 mEq/L, and urine potassium of 27 mEq/L. Urine ketones were trace positive on dipstick, but serum ketones were negative. A noncontrasted computed tomographic scan of the brain showed only a mild increase in ventricular size. A lumbar puncture was subsequently performed, and cerebrospinal fluid studies were all within normal limits.

Intravenous therapy was begun with 0.45% saline and bicarbonate replacement (50 mmol/L) at 250 mL/h. The patient also received iv bolus therapy with bicarbonate (100 mmol/L HCO3-) in 5% glucose and 2 L of 0.9% saline. Crystalloids were administered iv. The patient’s oliguria occurred on the next 12 h. Serial CPK determinations rose to 59,860 IU/L and peaked at 76,080 IU/L 24 h after admission. Serum creatinine showed a concomitant rise to 5.7 mg/dL during the same period. Urine myoglobin 24 h after admission was negative. Chemistries at that time revealed serum uric acid of 21 mg/dL, Ca of 6.8 mg/dL, and PO4 of 3.6 mg/dL. Additional laboratory abnormalities showed a fall in hematocrit to 34.4% with a decline in platelets to 153,000/μL.

For the next 3 days, the patient’s urine output averaged 5,100 mL/day. She did not receive any further neuroleptic medication. Her fever abated by her second hospital day, and she remained afebrile. Her blood pressure gradually declined and by the third hospital day averaged 142/76 mm Hg. Values for serum creatinine during these 3 days returned toward baseline, 1.3 mg/dL, as did liver function tests, CPK levels, and other serum chemistries. Blood, urine, and cerebrospinal fluid cultures remained negative. The patient’s hematocrit and platelet count increased to 36.6% and 241,000/μL, respectively, and her prothrombin time returned to normal. The patient was successfully extubated and subsequently discharged from the hospital off of all neuroleptic medications.

**DISCUSSION**

With no history of muscle trauma or excessive muscle activity, this patient abruptly developed nontraumatic rhabdomyolysis with acute renal failure.
Neuroleptic-Induced Rhabdomyolysis

Such a clinical course has been reported with variable frequency in the literature. Grossman et al. recognized a 34% incidence of nontraumatic rhabdomyolysis among 44 patients with myoglobinuria and acute renal failure (3). Similarly, Koffler et al. identified acute renal failure in 21 patients with concomitant nontraumatic rhabdomyolysis (5). In both studies, the authors noted elevations in serum creatinine concentrations disproportionate to other serum chemistries. They also recognized electrolyte abnormalities in these patients, characterized by early hypocalcemia and followed later by hypercalcemia and hyperuricemia. Finally, both groups emphasized the excellent prognosis associated with this form of renal failure. Mortality was minimal; only 1 of the cumulative 36 patients died.

Multiple factors were implicated as causes for rhabdomyolysis in each report. These included myopathies, grand mal seizures, coma, strenuous exercise, drug overdose, viral illness, and unspecified causes. Certainly, hyperpyrexia, vascular catastrophes, carbon monoxide poisoning, electrolyte abnormalities, e.g., hypokalemia, and even diabetic ketoacidosis have also been associated with nontraumatic rhabdomyolysis and subsequent acute renal failure (1).

Obviously, many of these possibilities could be readily excluded in the aforementioned case history. There was no history of myopathy, strenuous exercise, or seizures, nor findings consistent with limb ischemia. Similarly, the absence of profound electrolyte abnormalities and ketonemia eliminates these entities as causes of rhabdomyolysis in this case.

Our patient's compelling historical features (treatment with haloperidol), physical examination findings (fever, hypertension, muscle rigidity), and elevated CPK values support the diagnosis of NMS. Her clinical improvement after the discontinuation of the neuroleptic medication and her concomitant recovery of renal function further substantiate the diagnosis of NMS-induced rhabdomyolysis and renal failure.

This disease entity, NMS, was first described in the American literature in 1968 by Delay and Deniker (6). It has been characterized as an idiosyncratic drug reaction during therapy with neuroleptic agents or similar compounds. The prevalence has been estimated at 0.5 to 1.5% of all neuroleptic treatment episodes (7). Several congruent definitions of this syndrome have been proposed. All share certain criteria including hyperpyrexia, muscle rigidity, alterations in consciousness, and autonomic dysfunction. Levenson has subdivided these signs and symptoms into major and minor diagnostic criteria (8). Major criteria consist of fever, muscle rigidity, and elevated CPK. The minor criteria encompass tachycardia, tachypnea, blood pressure alterations, altered mental status, diaphoresis, and leukocytosis. For diagnosis, all three major criteria must be present or two major criteria plus three minor criteria.

NMS arises during treatment with antipsychotic agents, regardless of their duration of use. In 10% of patients with NMS, symptoms develop within 24 h of their first dose of medication. Of the remaining 90% of cases, symptoms arise within 2 wk after the initiation of medication. In rare instances, months or even years may elapse before the onset of NMS. The compounds most frequently associated with NMS are shown in Table 1. Notably, haloperidol, the agent administered to our patient, is the most common offending agent. In addition, benzodiazepines and substituted benzamide derivatives may also contribute to the genesis of NMS.

This syndrome classically develops over 24 to 72 h but may take up to 10 days before manifesting its complete symptomatology. Patients most frequently present with fever and may have extreme pyrexia (temperatures higher than 41°C). They also display variable degrees of muscular rigidity, cog-wheeling, and muscle contraction. Frequently, these patients will also be hypertensive. Several factors can precipitate NMS, including the baseline degree of psychomotor agitation, the dose and/or number of IM injections, other medications, and the rate of drug administration (7).

The pathogenesis of this disorder centers around central nervous system (CNS) dopamine depletion. Neuroleptic agents effectively block CNS dopamine receptors in the hypothalamus and corpus striatum and throughout the spine. This results in acute dopamine depletion with attendant fluctuations in body temperature, vasomotor instability, and sympathetic activity. Extensive muscular contractions contribute significantly to heat production. Marked vasoconstriction and dysregulation of central dopaminergic pathways also figure prominently in fever generation (9).

Rhabdomyolysis in NMS probably results from extensive muscle contractions. Our patient certainly demonstrated these findings. She also received IM injections, another risk factor for muscle injury.

TABLE 1. Compounds frequently associated with NMS

<table>
<thead>
<tr>
<th>Compound</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Haloperidol (Haldol)</td>
<td>42.7%</td>
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<tr>
<td>Chlorpromazine (Thorazine)</td>
<td>20.9%</td>
</tr>
<tr>
<td>Thioridazine (Mellaril)</td>
<td>5.7%</td>
</tr>
<tr>
<td>Trifluoperazine (Stelazine)</td>
<td>4.8%</td>
</tr>
<tr>
<td>Thiothixene (Navane)</td>
<td>4.3%</td>
</tr>
<tr>
<td>Promethazine (Phenergan)</td>
<td>1.3%</td>
</tr>
<tr>
<td>Other medications</td>
<td>20.3%</td>
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</tbody>
</table>

*Trade names in brackets; analysis of 330 cases, modified from reference 9.*
Other risk factors include hyperthermia and immobilization. All contribute proportionately to this generalized muscle damage. Few studies have examined the pathologic changes underlying this form of drug-induced rhabdomyolysis. The data suggest that there is little to differentiate this form of muscle damage from other forms of rhabdomyolysis. Stricken myocytes in NMS demonstrate focal necrosis, edema, and muscle fiber hypercontractions, as well as glycogen and lipid depletion (10). This muscle injury extends to the sarcoplasmic membrane and impairs Na-K-ATPase activity. This attenuates sodium extrusion from the sarcoplasm, thereby also limiting calcium efflux, and triggers the activation of proteases that disrupt myofibrils and induce further muscle damage (11).

The association of NMS with acute renal failure appears throughout the literature (12). Eiser et al. reported three cases of acute myoglobinuric renal failure as a result of NMS (13). Each patient received treatment with phenothiazines or haloperidol, and two were also treated with amitriptyline, a tricyclic antidepressant and neuroleptic use. The authors concluded that there may be an increased risk of rhabdomyolysis and renal failure in NMS in the setting of combined tricyclic antidepressant and neuroleptic use.

NMS may result in other abnormalities in addition to rhabdomyolysis. Mental status changes and fluctuating levels of consciousness have been described in NMS (7). Motor abnormalities range from tremors to akinesia. Increased muscle tone may become so problematic that chest wall excursion is reduced and mechanical ventilation becomes necessary.

Serum chemistries reflect many of the aforementioned abnormal values. Hyperkalemia and hypernatremia may be present, as well as elevations in serum creatinine and CPK values. Hypocalcemia, hyperuricemia, and hyperphosphatemia may also occur.

Our patient demonstrated nearly all of these findings. Most are accounted for by the muscle injury and/or resultant renal failure. Her hypernatremia, however, is notable. Patients who sustain muscle injury of any nature can develop severe intravascular volume depletion, and hypernatremia may reflect this phenomenon. Similarly, neuroleptic medications may impair central thirst mechanisms, and hypernatremia, in this instance, can arise from simple dehydration.

Liver function abnormalities have also been reported in NMS (7). These are characterized by elevated levels of transaminases, lactate dehydrogenase, and alkaline phosphatase. The pathogenesis of these abnormalities remains hypothetical and may reflect fatty liver changes (14).

### DIFFERENTIAL DIAGNOSIS

Alternative diagnostic considerations must be entertained when one is confronted with the clinical findings present in this case: hyperpyrexia, autonomic instability, agitation, and biochemical evidence of muscle damage. The differential diagnosis in this setting ranges from primary thermoregulatory failure to drug-induced syndromes (Table 2).

Extreme pyrexia (temperature higher than 41.1°C) is an important clinical sign for conditions mimicking NMS. Hyperpyrexia may result from a variety of causes including infection, impaired thermoregulation, and heat stroke (15). It may actually be very common, secondary simply to strenuous exercise. Knochel and others have noted marked heat production from skeletal muscle during sustained exercise and intense physical work (16).

Other physiologic and metabolic factors also affect the body’s ability to dissipate heat. Age, cardiovascular and endocrine function, and chronic illness may affect thermoregulation. In an environment with elevated ambient temperatures, these factors can influence the development of classic heat stroke. Active perspiration ceases and body temperature increases, heralding a syndrome of hot, dry skin and CNS abnormalities. Hypokalemia may be present, but other electrolyte abnormalities are less common or less profound. Prodromal symptoms may never appear, and sudden collapse may be the first manifestation of heat stroke. In general, acute renal failure occurs in less than 5% of patients and rhabdomyolysis, if present, may be minimal (16).

Exertional heat stroke may occur in younger, healthier individuals, even in the presence of marked perspiration. Acidosis, acute renal failure, and rhabdomyolysis are more likely to result, as is disseminated intravascular coagulation (DIC). Hypotension and hypoglycemia often accompany these cases. Renal damage is more evident in patients with this form of heat stroke: the incidence of acute renal failure approximates 25% (16). Interestingly, reports of exertional heat stroke and rhabdomyolysis are rare.

<table>
<thead>
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<th>TABLE 2. Differential diagnosis of NMS</th>
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<tr>
<td>Phenothiazine-Induced Heat Stroke</td>
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<tr>
<td>Lethal Catatonia</td>
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<td>Drug Interactions with Monoamine Oxidase Inhibitors</td>
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<td>Central Anticholinergic Syndrome</td>
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<td>MH Associated With Anesthesia</td>
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<td>Infections of the CNS</td>
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in women (17). This fact argued strongly against exertional heat stroke as the cause of our patient's illness.

Patients with quadriplegia or paraplegia who develop septicemia can display markedly elevated body temperatures. This may be secondary to alterations in temperature homeostasis resulting from the spinal cord injury. Nonetheless, these patients fail to display other symptoms as noted above and respond quickly to cooling measures.

Select endocrinopathies can result in hyperpyrexia with some of the aforementioned findings. Thyroid storm can generate marked fevers with diaphoresis as a result of an overwhelming increase in total body metabolism. Cases of diabetic ketoacidosis may also display extreme pyrexia and, with the marked acidosis, evidence of CNS abnormalities and electrolyte disturbances. Less commonly, pheochromocytomas may yield a similar clinical picture, highlighted by significant unremitting hypertension. Finally, hyperpyrexia can complicate insulinoma resection. Although its occurrence is rare, it follows a severe course similar to heat stroke and can result in death.

Other patients may develop a drug-related or toxin-related syndrome with fever and rhabdomyolysis. Primary drug- or toxin-induced rhabdomyolysis refers to a direct myotoxic effect from a specific agent. Certain snake venoms, *e.g.*, *Enhydrina schistosa*, contain myotoxins that result in muscle damage. Antihyperlipidemics such as human menopausal gonadotropin—coenzyme A reductase inhibitors, e.g., penicillamine, are rare causes of muscle damage. Antihyperlipidemics also include a number of injuries to skeletal muscle. These effects differ from rhabdomyolysis secondary to muscle ischemia related to drug overdose. This form of muscle damage usually results from direct muscle compression in coma or through seizure activity.

Drugs associated with polymyositis and/or dermatomyositis, *e.g.*, penicillamine, are rare causes of drug-induced muscle damage. Drug-related vasculitides contain myotoxins as well. Muscular rigidity, the central anticholinergic syndrome, but can progress to hyperpyrexia, agitation, and muscular rigidity. The central anticholinergic syndrome, an array of findings resulting from the use of anticholinergic agents, presents with typical symptoms including dry, warm skin, temperature elevation, and confusion. Patients may manifest other signs of cholinergic blockade such as dilated pupils, dry mouth, and urinary retention. Treatment with physostigmine often relieves these symptoms—a response not seen when the same therapy is offered for NMS.

Malignant hyperthermia (MH) may be the clinical entity most akin to NMS. This disorder arises after exposure to inhalational as well as depolarizing anesthetic agents. MH, which has a genetic inheritance in at least 50% of cases, is characterized by marked hyperthermia, hypercapnia, elevated CPK values, and frequently, DIC. Muscle biopsies examined histologically demonstrate findings similar to those seen in NMS (18). Linkage studies in MH families have implicated mutations in the ryanodine receptor gene mapped to q 13.1 of chromosome 19 as the molecular nidus of MH (19).

**TREATMENT**

The recognition of NMS and rhabdomyolysis should prompt the clinician to engage in several therapeutic maneuvers. The rationale for expedient action lies in the significant morbidity and mortality associated with this disorder. Generalized mortality in NMS is variable, ranging from 11.6 to 25% (20).

However, the concomitant presence of rhabdomyolysis and renal failure increases the mortality risk to nearly 50% (20). Thus, therapy aimed at preventing renal failure in this setting is prudent.

Initial treatment should address reversing the hyperthermia of NMS. Antipyretic agents, cooling blankets, and even ice packs all help to dissipate heat and attenuate the morbidity associated with NMS. Simple measures such as placing the patient in an air-conditioned environment can further aid recovery in NMS.

The next goal should be the assessment and treatment of rhabdomyolysis. Therapy for nearly all forms of rhabdomyolysis consists of early interventions to halt muscle destruction and avert renal failure. Better and Stein have outlined thorough guidelines for treating patients subjected to catastrophic traumatic rhabdomyolysis (21). The applicability of these recommendations in the setting of nontraumatic rhabdomyolysis, however, remains to be fully evaluated. Treatment modalities oriented more specifically for drug- or toxin-induced rhabdomyolysis have been suggested by Curry et al. (4) (Table 3). Notably, both Better and Stein and Curry et al. strongly advocate the use of IV bicarbonate therapy. Clinical evidence
supporting sodium bicarbonate use in conjunction with mannitol comes, in part, from data reported by Eneas et al. (22). In 20 cases of myoglobinuria, patients were given mannitol (20 of 20) and sodium bicarbonate (19 of 20) as components of therapy. Nine of the 20 patients responded to the mannitol bicarbonate infusion with improvements in renal function and urine output. Additional reports by Ron et al., as well as studies by Zager, have corroborated the renal protective effects of these maneuvers (23, 24).

Acetazolamide has been advocated as possible therapy when arterial pH exceeds 7.45. This drug will alkalinize the urine (pH > 6.5 to 7.0), but it carries with it the danger of inducing systemic metabolic acidosis. Therefore, its use is not recommended.

Frequent monitoring of serum electrolytes is mandatory. Hyperkalemia may be life threatening, and standard modes of therapy including sodium bicarbonate, glucose, insulin, sodium polystyrene sulfonate (Kayexalate), calcium, and even dialysis.

Hypocalcemia, although frequently present, rarely becomes symptomatic. The extent of hypocalcemia can, in fact, worsen during therapy to correct the metabolic acidosis. Yet, the injudicious administration of calcium to correct a serum value to normal may exaggerate the rebound hypercalcemia often seen in this disorder. Most authors suggest cautious calcium replacement as adjunctive therapy for the treatment of hyperkalemia or symptomatic hypocalcemia. The rebound hypercalcemia, witnessed during the recovery phase of rhabdomyolysis-induced renal failure, gradually resolves over 2 to 3 wk and rarely requires therapy. Other systemic abnormalities, such as DIC and cardiopulmonary dysfunction, tend to resolve in conjunction with the therapy for the rhabdomyolysis itself.

Strategies for the specific management of NMS have focused on agents to diminish the extrapyramidal symptoms as well as the fever. Discontinuing neuroleptic medications is imperative. Algorithms developed by Gratz et al. also support the use of anticholinergic agents (25). Supportive medical therapy and monitoring should be provided as necessary. The use of dantrolene or bromocriptine is best reserved for patients with severe symptomatology and marked hyperthermia.

These particular drugs have been strongly advocated as possible therapies for NMS. Dantrolene sodium was chosen on the basis of its efficacy in treating MH, the disorder most similar to NMS. It acts as a peripheral muscle relaxant, interfering with calcium efflux from the sarcoplasmic reticulum. Bromocriptine, a D2 receptor agonist, has also been proposed as therapy on the basis of the presumed pathophysiology of NMS. Its postsynaptic site of action affords it greater effectiveness than similar agents that act presynaptically.

Data from Rosenberg and Green substantiate the early use of these compounds in NMS (26). Those authors examined whether treatment with either agent hastened recovery in NMS. They defined clinical response as either a persistent decrease in rigidity or fever. Patients treated with bromocriptine or dantrolene demonstrated a mean time to clinical response of either 1.03 ± 0.55 or 1.72 ± 1.15 days, respectively. Patients treated with supportive therapy alone took 6.80 ± 2.68 days to reach a clinical response. Additionally, the time to complete resolution of symptoms was greater in patients treated with supportive care alone compared with either of the other two modalities.

The marked trend in clinical improvement in patients treated with dantrolene or bromocriptine suggests that these drugs might be of benefit in NMS. To date, only small prospective trials have examined the utility of either drug and/or dosages and those results remain equivocal. If either compound is to be instituted as therapy, however, appropriate dosages should be used (Table 3).

Overall mortality in NMS may actually be diminishing with earlier recognition of this syndrome; however, renal failure still confers a significant mortality risk in NMS. Thus, the rapid identification of NMS is mandatory for clinicians, especially if the history, examination, and laboratory findings suggest oliguria, myoglobinuria, or azotemia. Aggressive therapy with the modalities described above and even dialysis, if necessary, are warranted. Our patient was fortunate; her renal failure resolved with vigorous

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<th>TABLE 3. Recommended therapy for NMS with rhabdomyolysis and renal failurea</th>
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<tr>
<td>1. Discontinue Neuroleptic Medication</td>
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<tr>
<td>2. Attempt Rapid Cooling With Antipyretic Agents, Cooling Blankets, and/or Ice Bags</td>
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<tr>
<td>3. Establish Circulatory Stability, Then Volume Replacement, With Isotonic Saline Infusion at 2.5 to 5 mL/kg per hour</td>
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<td>4. Treatment of Hyperkalemia, If Present</td>
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<tr>
<td>5. IV NaHCO3 Therapy (Initial Dose, 1 mmol/kg body wt) To Achieve Arterial pH = 7.45</td>
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<tr>
<td>6. IV Mannitol Infusion, 1 g/kg body wt over 30 min</td>
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<tr>
<td>7. Serial Arterial pH Measurements, Electrolyte and Urine Measurements Every 2 to 4 h</td>
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<tr>
<td>8. IV Dantrolene Sodium (1 mg/kg per day, up to 4 to 8 mg/kg per day Divided Four times daily or Bromocriptine (5 mg po every 6 to 8 h, up to 15 to 20 mg three or four times daily)</td>
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<tr>
<td>9. Anticholinergic Medications as Needed To Relieve Muscular Rigidity</td>
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a Modified from references 4 and 25.
supportive measures. Nevertheless, this form of drug-induced rhabdomyolysis carries with it definite, even fatal, consequences. Each clinician should be aware of its course and prognosis, especially if renal failure complicates NMS.

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REFERENCES