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Trends and Outcomes of Malignant Hyperthermia in the United States, 2000 to 2005

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Background: **Malignant hyperthermia (MH) is a potentially fatal pharmacogenetic disorder with an estimated mortality of less than 5%. The purpose of this study was to evaluate the current incidence of MH and the predictors associated with in-hospital mortality in the United States.**

Methods: **The Nationwide Inpatient Sample, which is the largest all-payer inpatient database in the United States, was used to identify patients discharged with a diagnosis of MH during the years 2000–2005. The weighted exact Cochrane-Armitage test and multivariate logistic regression analyses were used to assess trends in the incidence and risk-adjusted mortality from MH, taking into account the complex survey design.**

Results: **From 2000 to 2005, the number of cases of MH increased from 372 to 521 per year. The occurrence of MH increased from 10.2 to 13.3 patients per million hospital discharges ($P = 0.001$). Mortality rates from MH ranged from 6.5% in 2005 to 16.9% in 2001 ($P < 0.0001$). The median age of patients with MH was 39 (interquartile range, 23–54 yr). Only 17.8% of the patients were children, who had lower mortality than adults (0.7% *vs.* 14.1%, $P < 0.0001$). Logistic regression analyses revealed that risk-adjusted in-hospital mortality was associated with increasing age, female sex, comorbidity burden, source of admission to hospital, and geographic region of the United States.**

Conclusions: **The incidence of MH in the United States has increased in recent years. The in-hospital mortality from MH remains elevated and higher than previously reported. The results of this study should enable the identification of areas requiring increased focus in MH-related education.**

MALIGNANT hyperthermia (MH) is a rare, potentially fatal complex genetic disorder of skeletal muscle that manifests as a hypermetabolic crisis in susceptible patients.[1,2] An MH episode is characterized by hyperthermia, hypercarbia, muscle rigidity, and rhabdomyolysis. The episodes are usually associated with the administration of inhalation anesthetics or succinylcholine.[1,2]

Mortality from MH was reported to be as high as 70% before the introduction of dantrolene and end-tidal carbon dioxide monitoring.[1] Because of this high mortality rate and the fact that susceptible patients are otherwise healthy, MH was referred to as a "hidden killer." According to some European reports, mortality from MH is now estimated to be less than 5%.[3,4] Although a recent study from the North American Malignant Hyperthermia Registry (NAMHR) reported a mortality rate associated with MH in the United States of 1.4%;[5] this rate, however, remains controversial.[6]

The aim of this study was to use an administrative national database representative of the United States hospital discharges to determine the incidence of MH and risk-adjusted in-hospital mortality associated with a diagnosis of MH in the United States population during the years 2000 to 2005. In addition, the predictors of MH-related mortality were also examined.

Materials and Methods

Data from the Nationwide Inpatient Sample (NIS) from the Healthcare Cost and Utilization Project was used for this study. The NIS is the largest all-payer inpatient database in the United States. It represents a 20% stratified sample of inpatient discharges from United States academic, community, and acute care hospitals, accounting for approximately 1,000 hospitals in 35 states; excluding federal and prison hospitals.‖

Discharge data collected include demographics, primary and 14 different secondary diagnoses, primary and 14 different secondary procedures per patient as identified by the *International Classification of Diseases, 9th Revision, Clinical Modification* codes, length of stay, hospital charges, and clinical outcomes. In addition, the NIS provides information on admission profiles, hospital profiles, and vital status at discharge (whether the patient died or did not die during hospitalization). Sampling weights are provided in the database to facilitate the production of national estimates based on the complex survey design. To estimate the sampling weights, each hospital and discharge were weighted to the number of hospitals and discharges estimated to be in the corresponding target universe of hospitals. In brief, the sample design of the NIS is as follows: The hospital universe is defined by all hospitals that were designated as community hospitals in the American Hospital Association Annual Survey of Hospitals, excluding rehabilitation hospitals. Hospitals are stratified by region, location and teaching status (within region), bed size category (within region and location and teaching status), and ownership (within region, location and teaching status,

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‖ http://www.hcup-us.ahrq.gov/nisoverview.jsp. Accessed January 4, 2008.

and bed size categories). Within each stratum, a systematic random sample equivalent to 20% of the hospitals for that stratum was drawn, and all the discharges from the sampled hospitals were included in the NIS. Because NIS data are publicly available and contains no personal identifying information, this study was exempt from institutional review board approval.

Since October 1997, the *International Classification of Diseases, 9th Revision, Clinical Modification* coding system has provided a specific diagnosis code for MH as a result of anesthetics (*International Classification of Diseases, 9th Revision, Clinical Modification* 995.86). The NIS core inpatient files were used to identify all hospital discharge records with a diagnosis of MH during the years 2000 through 2005. Patients with primary or secondary diagnostic codes for other conditions associated with hyperthermia such as heat stroke, neuroleptic malignant syndrome, sepsis, thyrotoxicosis, and neurologic disorders were identified and excluded from the analyses to avoid confounding. The incidence rate of MH was calculated as the number of MH episodes per million hospital discharges per year.

Patient comorbidity load was calculated using the modified Charlson Comorbidity Index (CCI). The CCI was calculated using up to 15 *International Classification of Diseases, 9th Revision, Clinical Modification* diagnosis codes for each patient and the clinical classification software (Agency for Healthcare Research and Quality; Rockville, MD) coding system included in the data.# The index is a validated measure for use with administrative data that correlates with in-hospital morbidity and mortality after surgical procedures.[7] The measure comprises 19 comorbid conditions, each assigned a weight according to its potential for influencing postoperative mortality. The index is the sum of the weighted comorbidities and accounts for the number and seriousness of the conditions. The ability of the CCI to predict in-hospital mortality was initially assessed. Once validated, the CCI was further used for risk-adjusted mortality analyses.[8–10]

The primary outcome endpoint was risk-adjusted in-hospital mortality associated with a diagnosis of MH. Mortality data were available directly from the dataset. Weighted analyses for predictors of in-hospital mortality included demographic data, hospital characteristics, source of admission to hospital, preoperative comorbidities, and risk stratification based on the comorbidity index. Hospital characteristics such as bed size, location (urban or rural), and teaching status (teaching or nonteaching) were coded in the NIS dataset. The geographic region of the hospital was defined in the database according to the four region categories of the United States census (Northeast, Midwest, South, and West). Source of admission to hospital was categorized as follows: emergency department; another hospital, including transfers from an acute care hospital or from a rural primary care hospital; other health facility, including ambulatory surgery centers, skilled nursing facilities, and long-term care facilities; and routine admissions, including physician referrals, outpatient or clinic referrals, and Health Maintenance Organization referrals.

http://www.hcup-us.ahrq.gov/db/quality.jsp. Accessed January 2, 2008.

Statistical Analysis

Descriptive statistics for categorical variables were presented as relative frequencies (percentages), and were analyzed using the chi-square test (chi-square for independent groups, two-tailed *P* value). Continuous variables were expressed as medians and interquartile ranges. The Cochran-Armitage trend test was used to evaluate trends in the incidence of MH episodes during the study period. In-hospital mortality was adjusted for patient age, sex, hospital characteristics, and CCI using multivariate logistic regression analyses. Findings were considered statistically significant for the primary end point; *i.e.*, risk-adjusted in-hospital mortality, if the resulting *P* value was less than 0.05. Multivariate odds ratios were reported with 95% CIs.

In our statistical analysis, we calculated frequencies of the primary outcome for each year and determined if there were any trends in outcomes from 2000 to 2005. The number of states that made their data available for inclusion in the NIS increased from 28 in 2000 to 37 in 2005. To adjust for this change in the sampling frame, the NIS Trends Supplemental Files provided by the Healthcare Cost and Utilization Project were used in further statistical analyses that spanned multiple years and included the whole dataset. SAS version 9.1 software (SAS Institute Inc.; Cary, NC) was used for data analyses. The SURVEYFREC, SURVEYMEANS, and SURVEYLOGISTIC procedures of the SAS software were used in the analyses to account for the complex sampling design of the NIS.

Results

A total of 3,082 cases with a principal or secondary *International Classification of Diseases, 9th Revision, Clinical Modification* diagnosis code for MH were identified during the 5-yr study period. Of these, 529 cases also had one or more diagnosis of other conditions associated with hyperthermia (table 1). After the exclusion of patients with other conditions associated with hyperthermia that could have been misdiagnosed as MH, 2,553 records were included in the analyses.

The number of MH patients increased from 372 cases in 2000 to 521 cases in 2005. The estimated incidence rate of MH episodes per million of hospital discharges increased from 10.2 in 2000 to 13.3 in 2005 (*P* for trend = 0.001)

Table 1. Patients with Diagnosis of Malignant Hyperthermia with and without Other Conditions Associated with Hyperthermia

Diagnosis	Number
Patients with principal or secondary diagnosis of MH	3,082
Patients with concomitant diagnosis of MH and other conditions associated with hyperthermia	529
MH without concomitant diagnosis of other conditions associated with hyperthermia	2,553
Conditions associated with hyperthermia in patients with diagnosis of MH*	
Sepsis	428
Neuroleptic malignant syndrome	37
Heat stroke	43
Thyrotoxicosis	4
Traumatic brain injury	35
Central nervous system infections	16
Brain tumors	10

* Total adds to greater than 529 because some patients had more than 1 diagnosis.

MH = malignant hyperthermia.

Table 3. Characteristics of Patients with Diagnosis of Malignant Hyperthermia, Excluding Those with Other Causes of Hyperthermia

Characteristic	Number (n = 2,553)	Percent
Sex		
Male	1,471	57.6
Female	1,082	42.4
Age category (yr)		
Children (< 18 yr)	454	17.8
Adults (18 yr or older)		
18–44	1,047	41.0
45–64	646	25.3
>64	406	15.9
Total adults	2,099	82.2
Charlson Comorbidity Index		
0	1,660	65.0
1	469	18.4
2	239	9.4
3 or greater	185	7.2

(table 2). Median age of patients was 39 yr (interquartile range 23–54 yr); 58% were men. Patient characteristics are listed in table 3. Overall, 11.7% of patients with a diagnosis of MH died during hospitalization. Mortality rate significantly decreased from 12.5% in 2000 to 6.5% in 2005 (*P* for trend <0.0001).

Univariate analyses demonstrated that mortality was associated with age, comorbidity burden, type of admission, source of admission, and location of hospital (table 4). Mortality rate was higher in patients 18 yr or older (14.1%) than in those younger than 18 yr (0.7%) (chi-square test, $P < 0.0001$). Mortality significantly increased as the number and severity of comorbidities increased (*P* for trend < 0.0001). For instance, the mortality rate was 7.5% in patients with a CCI of 0, and 36.8% in those with a CCI of 3 or more.

Patients with a diagnosis of MH admitted to rural hospitals had significantly higher mortality than those admitted to urban hospitals (16.2% *vs.* 11.0%, respectively; $P = 0.006$). A stratified analysis by geographic region of hospital showed that mortality in patients who had a diagnosis of MH was significantly higher (15.8%) in hospitals located in the South region of the United States, and lower (7.0%) in hospitals located in the West ($P < 0.0001$). The mortality rate was higher in patients admitted from other health facilities (19.8%) or from other hospitals (13.6%), as compared with routine admissions (5.4%), ($P < 0.0001$). Mortality was significantly higher for emergency admissions (20.2%) as compared with elective admissions (3.0%, $P < 0.0001$). A high proportion of patients admitted from other hospitals and from other health care facilities had emergency or urgent admissions (80.0% and 76.4%, respectively). The mortality rate among patients urgently or emergently admitted from other hospitals or from other health facilities was 17% (19 out of 113 patients died) and 20% (12 out of 60 patients died), respectively. Conversely, the mortality rate was 0% in patients with elective admissions, whether they were admitted from other hospitals (n = 28) or other health facilities (n = 21). Other factors such as bed size of hospital and teaching status of hospital were not associated with differences in mortality rates.

Multivariate logistic regression analyses identified older age, gender, higher CCI, admission source, and geographic region of the United States as significant and independent factors associated with in-hospital mortality in patients with a diagnosis of MH (table 5). After adjust-

Table 2. Incidence and Mortality Associated with Malignant Hyperthermia by Year

Year	Frequency of MH Patients	95% CI for Frequency*	Total Hospital Discharges	MH Patients per Million Hospital Discharges	Death during Hospitalization, n (%)
2000	372	282.4–461.3	36,417,565	10.21	47 (12.5)
2001	384	293.0–475.1	37,187,641	10.33	65 (16.9)
2002	391	294.7–486.6	37,804,021	10.33	52 (13.4)
2003	437	332.2–541.5	38,220,659	11.43	59 (13.4)
2004	448	343.3–552.9	38,661,786	11.59	41 (9.2)
2005	521	402.7–640.0	39,163,834	13.30	34 (6.5)
Total	2,553	2,304–2,802	227,455,506	11.22	298 (11.7)

* 95% CI, confidence intervals for the weighted frequency of cases with diagnosis of malignant hyperthermia.

MH = malignant hyperthermia.

Table 4. Mortality Associated with Malignant Hyperthermia Episodes by Patient and Hospital Characteristics, Univariate Analysis

Characteristic	Patients with Diagnosis of MH, n (%)	Death in Hospital, n (%)	*P* Value
Gender			0.09
Female	1,082 (42.4)	140 (13.0)	
Male	1,471 (57.6)	158 (10.8)	
Age			<0.0001
<18 yr	454 (17.8)	3 (0.7)	
18–44 yr	1,047 (41.0)	99 (9.5)	
45–64 yr	646 (25.3)	117 (18.2)	
65+ yr	406 (15.9)	78 (19.4)	
Charlson Comorbidity Index			<0.0001
0	1,660 (65.0)	124 (7.5)	
1	469 (18.4)	72 (15.3)	
2	239 (9.4)	34 (14.1)	
3 or greater	185 (7.2)	68 (36.8)	
Teaching status of hospital			0.62
Nonteaching	1,266 (49.6)	144 (11.4)	
Teaching	1,287 (50.4)	154 (12.0)	
Admission type			<0.0001
Emergency	1,020 (45.0)	206 (20.2)	
Urgent	482 (21.3)	43 (8.9)	
Elective	761 (33.7)	23 (3.0)	
Admission source			<0.0001
Emergency department	1,062 (41.9)	189 (17.8)	
Another hospital	142 (5.6)	19 (13.6)	
Other health facility	81 (3.2)	16 (19.8)	
Routine admission	1,250 (49.3)	67 (5.4)	
Geographic region			<0.0001
Northeast	399 (15.6)	29 (7.3)	
Midwest	507 (19.9)	54 (10.6)	
South	1,129 (44.2)	178 (15.8)	
West	518 (20.3)	37 (7.0)	
Hospital location			0.006
Rural	329 (12.9)	53 (16.2)	
Urban	2,224 (87.1)	245 (11.0)	
Hospital bed size			0.68
Small	315 (12.4)	32 (10.3)	
Medium	652 (25.5)	75 (11.6)	
Large	1,586 (62.2)	190 (12.0)	

MH = malignant hyperthermia.

ing for age, sex, and comorbidity index, hospital location (*i.e.*, urban *vs.* rural) was not found to be independently associated with increased mortality in patients with a diagnosis of MH. The odds of in-hospital mortality in patients with a diagnosis of MH were increased almost 30% for every 10-yr increase in age (odds ratio, 1.27; 95% CI, 1.19–1.36), and almost 40% for every point increase in the CCI (odds ratio, 1.38; 95% CI, 1.28–1.49). Women had significantly higher mortality than men (odds ratio, 1.36; 95% CI, 1.03–1.79). Adjusted mortality was more than 3 times higher in hospitals located in the southern United States, compared with hospitals located in the western region of the country (odds ratio, 3.17; 95% CI, 2.06–4.88). Patients admitted from the emergency department, from another hospital, or from other health facilities had significantly higher adjusted mortality than patients who had routine admissions (physician, clinics, or Health Maintenance Organization referrals).

Table 5. Multivariate Analysis of Variables Associated with Mortality from Malignant Hyperthermia*

Variable	Odds Ratio†	95% CI
Age (per 10-yr increase)	1.27	1.19–1.36
Sex (female *vs.* male)	1.36	1.03–1.79
Charlson Comorbidity Index	1.38	1.28–1.49
Source of admission		
Emergency department *versus* routine	4.06	2.97–5.54
Another hospital *versus* routine	3.30	1.84–5.90
Other health facility *versus* routine	4.07	2.11–7.84
Geographic region		
Northeast *versus* West	1.16	0.68–1.97
Midwest *versus* West	1.22	0.75–1.97
South *versus* West	3.17	2.06–4.88
South *versus* Northeast	2.55	1.72–3.79
Midwest *versus* Northeast	1.05	0.63–1.77

* Variables entered into the multivariate regression model were selected by stepwise selection, if P value < 0.05. † Odds ratio of in-hospital mortality. CI = confidence interval.

Discussion

This study suggests that the incidence of MH in the United States between 2000 and 2005 has increased. The mortality rate decreased during the study period, probably because of increased index of suspicion, leading to early identification and treatment. The overall nationwide mortality rate in patients with a diagnosis of MH in this study was 11.7%, which is higher than that previously reported. Textbooks and review articles often state that current mortality from MH is less than 5%, probably based on data from the Danish Malignant Hyperthermia Register.[3,4] However, these data were published more than 10 yr ago and were collected from Denmark, a country with a predominantly Caucasian population. These data may, therefore, not be generalizable to the ethnically diverse population of the United States. Other investigators in Asia have reported MH-related mortality rates that are comparable or higher than those found in our study. A study from Japan reported that 383 cases of MH occurred between 1961 and 2005, with a mortality rate of 42.3% between 1961 and 1984, which decreased to 15% between 1995 and 2005, when dantrolene became readily available.[11] Similarly, a survey of 102 hospitals in Taiwan reported a 28.6% mortality rate from MH between 1994 and 2003.[12] Interestingly, a recent study from the NAMHR reported 299 cases of MH between 1987-2006 with a mortality rate of only 1.4%.[5] Because the NAMHR depends completely upon voluntary reporting, the significantly lower incidence and mortality rate in the NAMHR study may be due to under-reporting of MH cases.

This study is consistent with previous reports that have found gender differences in the incidence of MH.[3,13,14] MH episodes occurred more frequently in males than in females; however, after adjusting for age and comorbidities the mortality rate was significantly higher in females. The reasons for a higher mortality rate in females remain

unclear; however, contributing factors may include differences in pathophysiological mechanisms, differential exposure to triggering agents, information bias (*i.e.*, diagnosis bias), and disease management.

We also found that 18% of the MH episodes occurred in pediatric patients in contrast to previous studies reporting up to 50% rate in this population.[2] The NIS is a representative sample of inpatient discharges including pediatric hospitals, but it is possible that the NIS data may not have captured all pediatric patients which could explain the lower rates that we found. In addition, the NIS data might have missed pediatric MH cases that occurred in outpatient surgical settings. It is also possible that the incidence of MH in pediatric population may have decreased in recent years due to increased provider awareness and avoidance of triggering agents (*e.g.*, succinylcholine) in this population.[15] We speculate that anesthesiologists who care for children are presumably more attuned to the diagnosis of MH and are more likely to promptly recognize and treat the syndrome given that they are more likely to encounter children with undiagnosed neuromuscular disorders who have higher susceptibility to MH. Thus, provider awareness is higher in this group of anesthesiologists. This earlier diagnosis and treatment may explain the lower mortality rate found in pediatric patients (0.7%) compared to adults (14.1%). The pediatric mortality rate found in this study is similar to that found in the NAMHR study.[5] Overall, there appears to be a shift in the age distribution of MH cases from children to older age groups. These results imply that anesthesiologists need to be vigilant for MH signs in adult patients exposed to triggering agents, as mortality in this age group is substantially high.

Not surprisingly, mortality in patients with a CCI equal or greater than 3 was more than twice that of patients with a CCI of 2, and 4 times greater than that of patients with no comorbidities. Most MH patients (83%) had a low comorbidity load with a CCI of 1 or less. Nevertheless, mortality in this low risk group was 9.2%.

Geographic differences in the prevalence of MH susceptibility have been previously reported.[16,17] It is not clear if different geographical prevalence rates of MH susceptibility influence the rate of mortality from this condition. Our findings indicate that after adjusting for age, sex, comorbidities, and hospital characteristics, mortality was significantly higher in the south, as compared with the West and Northeast regions of the United States (table 4). The differences in mortality in patients with a diagnosis of MH in the different geographical regions cannot be explained from the data available in the NIS data set.

The multivariate logistic regression model showed that the source of admission is an independent factor associated with mortality after adjusting for age, sex, and comorbidities. The higher mortality found in patients admitted through the emergency room and those transferred from other health facilities could be explained by factors such as the increased use of succinylcholine in patients admitted for emergency procedures, as compared with those admitted for elective surgery. It is also possible that diagnosis and treatment may have been delayed in patients transferred from other health facilities.

The limitations of our study are related to the nature of the administrative database. First, the NIS database relies heavily on *International Classification of Diseases, 9th Revision, Clinical Modification* codes, and lacks information such as the type of anesthesia, intraoperative temperature, end-tidal carbon dioxide levels, and the use of dantrolene. Therefore, patients with hyperthermic syndromes as a result of causes other than MH may have been misdiagnosed as cases of MH. Consequently, we excluded all patients with other conditions associated with hyperthermia from our analysis. Because of the nature of the database, information to confirm the diagnosis of MH, such as the *in vitro* muscle contracture test or at least an MH clinical grading scale score, were not available.[18] In addition, the total annual number of patients exposed to MH triggering agents cannot be calculated from the NIS data set; therefore, the "true" incidence of MH episodes in the United States could not be determined with certainty in this study. Nevertheless, our results underscore the magnitude of the clinical problem, in view of the fact that patients with a diagnosis of suspected MH should be treated as MH-susceptible until proven otherwise. Since our data provides information on inpatient discharges only, it presumes that most patients who may have developed MH in outpatient settings would be transferred to hospitals with intensive care unit capabilities and captured by the NIS data set. However MH patients who were not transferred or died in the ambulatory or office setting would not be captured in the database. Furthermore, patients who were transferred from other health care facilities and died in the emergency room before admission to the hospital are not included in the database.

Despite these limitations, the large sample size of the NIS database enables analyses of rare conditions, such as MH. In contrast to the NAMHR database which is collected from voluntary reports, the NIS dataset is subject to minimal reporting bias, and all information is coded independently of the individual practitioner, making it a potentially more reliable source.

In summary, this is the first study, to our knowledge, to report nationwide data on acute MH incidence and mortality in the United States. Adjusted mortality in patients with a diagnosis of MH is higher in women, adults, patients with higher comorbidities, and in those admitted through the emergency department or transferred from other health care facilities. Mortality associated with MH is higher in the South and lower in the West regions of the United States. In conclusion, the incidence of MH in the United States appears to have in-

creased in recent years. NIS data analysis suggests that in-hospital mortality from MH remains elevated and higher than previously reported. The results of this study should enable the identification of areas requiring increased focus in MH-related education.

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