**Supplemental Digital Content 8. Question 3b, (Query 7): What is the malignant hyperthermia (MH) mortality rate in the U.S. and Canada?**

Full-text articles assessed for eligibility
(n =16)

Studies included in qualitative synthesis
(n = 7)

Records identified through PubMed database
(n =122)

Additional records identified through Embase/MEDLINE

(n=221)

Records after duplicates removed

(n=272)

## Included

## Eligibility

## Screening

## Identification

Full-text articles excluded (case series, no data on mortality, not North American)

(n = 9)

(n = 28)

**Summary:** There are 3 Oxford Centre for Evidence−Based Medicine (**OCEBM**) level 3 studies of MH mortality derived from the North American Malignant Hyperthermia Registry of the Malignant Hyperthermia Association of the United States (**NAMHR**) with 1 of these 3 studies having an overlapping dataset. Mortality rates ranged from 1.4% to 9.5% in predominantly US cases. (Reference 1, 3, 5) There are also unpublished NAMHR deaths (3/75) from 2013 through 2016. (Communication from B.W. Brandom M.D., NAMHR Director, February 21, 2018.) For the years 1987 through 2016, a total of 15 (n=450 MH events) deaths were reported to the NAMHR database. Four of 15 MH triggering anesthetics were administered in freestanding facilities. NAMHR studies are limited by possible selection bias, reporting, and recall bias. ICD-9 based MH studies do not differentiate between MH events and MH susceptible individuals, therefore, the 4.6% - 15.1% mortality rates may represent overestimates for US populations.

Literature search: PubMed and Embase/MEDLINE.

Free text: “malignant hyperthermia” AND mortality

Filters: Journal Article, Abstract, Publication date from 01/01/1969 to 12/31/2017, Humans, English.

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| Article Identifier | Database search | Findings | Mortality Rate | Level of Evidence | Bias |
| **1.**  Larach MG, Brandom BW, Allen GC, Gronert GA, Lehman EB: Malignant hyperthermia deaths related to inadequate temperature monitoring, 2007-2012: a report from the North American Malignant Hyperthermia Registry of the Malignant Hyperthermia Association of the United States.Anesth Analg 2014; 119:1359-66 | NAMHR\*  | - Searched for AMRA -US and Canada-Dates Jan. 1, 2007 – Dec. 31, 2012-189 total reports -84 events identified as MH CGS \*\*“very likely” or “almost certain”-Out of 84 events: 7 cardiac arrests, 8 deaths with 4/8 anesthetics occurring in a freestanding facility. 6/8 had post-mortem genetic studies: 3/8 MH-causative *RYR1* mutations and 3/8 with *RYR1* variants of uncertain significance. | 9.5% | 3 | Selective reportingRegistry data dependent on voluntary reporting, therefore not all events captured. Also, those reporting may have incomplete/ misdiagnosed patient event. Also, no confirmatory testing for MH is conducted for every reported event.  |
| **2.**  Salazar JH, Yang J, Shen L, Abdullah F, Kim TW:Pediatric malignant hyperthermia: risk factors, morbidity, and mortality identified from the Nationwide Inpatient Sample and Kids' Inpatient Database.Paediatr Anaesth 2014;24:1212-6 | Nationwide Inpatient Sample and Kid’s Inpatient Database | -Searched **ICD-9 code** (995.86) for MH-US; ages 0-17 y-1998 – 2010; non overlapping years-310 pediatric admissions-9 deaths | Pediatric2.9%\_\_\_\_\_\_\_\_\_\_\_\_Adult18.2%\_\_\_\_\_\_\_\_\_\_\_\_Combined15.1% | 3 | Selective reportingHCUP§ data is national sampling, not complete for US. Represents only inpatient discharges, therefore does not capture deaths prior to admission. Assumes correct ICD-9 coding/diagnosis by MD. Also, no confirmatory testing for MH is conducted for every data patient.  |

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| **3.**  Nelson P, Litman RS:Malignant hyperthermia in children: an analysis of the North American Malignant Hyperthermia Registry.Anesth Analg 2014;118:369-74  | NAMHR | -Searched for AMRA-US and Canada-351 Pediatric pts (<18 y) from 1960 - 2011-264 reports-Identified event as MH CGS “very likely” or “almost certain”-3 cohorts: 0-24 m,25 m– 12 y, 13 – 18 y-10 deaths: 6 in 25 m-12 y, 4 in 13-18 y | 25 mo – 12 y3.7%\_\_\_\_\_\_\_\_\_\_\_\_\_13 – 18 y6.1%Overall death rate was 10/264=3.8% with all deaths occurring between 1990 and 2010 | 3 | Selective reportingRegistry data dependent on voluntary reporting, therefore not all events captured. Also, those reporting may have incomplete/ misdiagnosed patient event. Also, no confirmatory testing for MH is conducted for every registered event. Dataset overlaps partially with reference #1 and #5 |
| **4.**  Li G, Brady JE, Rosenberg H, Sun LS: Excess comorbidities associated with malignant hyperthermia diagnosis in pediatric hospital discharge records.Paediatr Anaesth 2011;21:958-63 | Kids’ Inpatient Database | -Searched **ICD-9 code** for MH-Dates 2000,2003,2006-Patients <21 y-175 patient diagnosis MH | 4.6% | 3 | Selective reportingHCUP data is national sampling, not complete for US. Represents only inpatient discharges, therefore does not capture deaths prior to admission. **Assumes correct ICD-9 coding/**diagnosis by MD. Also, no confirmatory testing for MH is conducted for every data patient.  |
| **5.**  Larach MG, Brandom BW, Allen GC, Gronert GA, Lehman EB: Cardiac arrests and deaths associated with malignant hyperthermia in North America from 1987 to 2006: a report from the North American Malignant Hyperthermia Registry of the Malignant Hyperthermia Association of the United States.Anesthesiology 2008;108:603-11  | MHAUSMH Registry | -Searched for AMRA -US and Canada-Dates Jan. 1, 1987 – Dec. 31, 2006-597 total reports -291 events identified as MH CGS “very likely” or “almost certain”-Out of 291 events: 8 cardiac arrests, 4 deaths-No Canadian deaths or cardiac arrests  | 1.4% | 3 | Selective reportingRegistry data dependent on voluntary reporting, therefore not all events captured. Also, those reporting may have incomplete/ misdiagnosed patient event. Also, no confirmatory testing for MH is conducted for every registered event.  |
| **6.**  Rosero EB, Adesanya AO, Timaran CH, Joshi GP:Trends and outcomes of malignant hyperthermia in the United States, 2000 to 2005. Anesthesiology 2009; 110:89-94  | Nationwide Inpatient Sample | -Searched **ICD-9** code for MH-Dates 2000 – 2005-3,082 cases total cases-2553 MH cases identified without concomitant diagnosis of other conditions associated with hyperthermia-3 pediatric deaths (<18 yo)-294 adult deaths (>18 yo)-297 deaths overall | Pediatrics0.7%\_\_\_\_\_\_\_\_\_\_\_\_\_Adults14.1%\_\_\_\_\_\_\_\_\_\_\_\_\_Combined11.7% | 3 | Selective reportingHCUP data is national sampling, not complete for US. Represents only inpatient discharges, therefore does not capture deaths prior to admission. Assumes correct ICD-9 coding/diagnosis by MD. Also, no confirmatory testing for MH is conducted for every data patient.  |
| **7.**  Lu Z, Rosenberg H, Li G:Prevalence of malignant hyperthermia diagnosis in hospital dischargerecords in California, Florida, New York, and WisconsinJ Clin Anesth 2017; 39:10-14 | HCUP§ SID§§ for California (2011), Florida(2011), New York (2012) and Wisconsin (2012). | - Searched **ICD-9** code for MH- California during 2011, Florida during 2011, New York during 2012, and Wisconsin during 2012.- total of 164 hospital discharges- 18 deaths | Combined11.0% | 3 | Selective reportingHealthcare Cost and UtilizationProject (HCUP) State Inpatient Database (SID) for California (2011),Florida (2011), New York (2012) and Wisconsin (2012) HCUP data is national sampling, not complete for US. Represents only inpatient discharges, therefore does not capture deaths prior to admission. Assumes correct ICD-9 coding/diagnosis by MD. Also, no confirmatory testing for MH is conducted for every data patient.  |
| **Summary of Published References** | Reported to the NAMHR from 1990 to 2017 | Registry reported deaths=15 individuals | If one excludes references dependent only on ICD9 code for MH, then left with 2 Registry published studies and preliminary Registry data only. Mortality rates that range from 1.4 – 9.5%.  | Predominantly 3 | Predominantly US estimates- selective reporting-possible incomplete or misdiagnosed anesthetic event- |
|  | Nationwide Inpatient Sample, Kid’s Inpatient Database (1998 – 2010);Kids’ Inpatient Database (2000,2003,2006);Nationwide Inpatient Sample (2000-2005);HCUP§ SID§§ for California (2011), Florida(2011), New York (2012) and Wisconsin (2012). | Deaths reported by selected studies:2. NIS +KIDS = 9 deaths4. KIDS report only death rate 4.6% 6. NIS = 297 deaths7. HCUP§ SID §§ = 18 deaths | ICD-9 based MH studiesOverlapping yrs of studies using multiple databases with inherent flaws to data extraction make it difficult to make an accurate assessment of deaths. If accept references with ICD9 code definition of MH, then mortality rate varies form 4.6% - 15.1% | 3 | Predominantly US estimates- selective reporting-possible incomplete or misdiagnosed anesthetic event- |
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| Other: NAMHR unpublished data | 1/1/2013-12/31/2016 | Total number of CGS ≥ 20 or “fulminant” cases=75- 3 deaths  | Mortality rate4.0% |  | Personal Communication from Barbara W. Brandom, Past NAMHR Director to M.G. Larach, February 22, 2018 |

\* NAMHR=North American Malignant Hyperthermia Registry (Registry) of the Malignant Hyperthermia Association of the US

\*\*CGS=Clinical Grading Scale

§ HCUP= Healthcare Cost and Utilization Project

§§SID=State Inpatient Database