**Supplemental Digital Content 7. Question 3a, (Queries 9, 10, 11): What morbidities are associated with an acute malignant hyperthermia (MH) event in the US and Canada? What is the MH morbidity rate in the US and Canada? What is the impact of dantrolene administration on MH morbidity in the US and Canada? Does the time of dantrolene or initial dantrolene dose affect likelihood of MH morbidity in the US and Canada?**

Records remaining after non-human, non-English abstracts, non US or Canadian experience, and duplicates removed (n=47)

(n = )

Full-text articles excluded (single case report, no data on morbidity, failure to meet MH definition (n=42)

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(n = 28)

Full-text articles assessed for eligibility
(n =47)

Studies included in qualitative synthesis
(n = 5)

Records identified through PubMed database searching
(n =657)

Additional records identified through other sources (Cochrane, EMBASE, and handsearch of personal files) (n=154)
(n =10)

## Included

## Eligibility

## Screening

## Identification

9. What morbidities are associated with an acute MH event in the US and Canada?

MH associated morbidities include: cardiac dysfunction including cardiac arrest, renal dysfunction, consciousness level change/coma, pulmonary edema, disseminated intravascular coagulation (**DIC**), and hepatic dysfunction. Other reported complications include development of compartment syndrome and pleural effusions. Some may consider recrudescence as a morbidity as well.

10. What is the MH morbidity rate in the US and Canada?

Complications not including recrudescence, cardiac arrest, or death ranged from 20% to 37% and are consistent over a significant time period that goes through 2012 and across 2 non-overlapping databases. Overall, the more severe the MH event (as determined by the MH clinical grading scale), the higher the morbidity rate. A North American Malignant Hyperthermia Registry of the Malignant Hyperthermia Association of the US (**NAMHR**) study of MH recrudescence found a 20% recrudescence rate.

11. What is the impact of dantrolene administration on MH morbidity? Does the time or initial dantrolene dose affect the likelihood of MH morbidity?

For the largest retrospective study of MH morbidity (excluding recrudescence, cardiac arrest), there was inadequate power to detect differences between the group receiving dantrolene and the one not receiving dantrolene.

Time of dantrolene administration: NAMHR studies showed that the likelihood of a MH complication increased 1.61 (1.16-2.25) times for every 30-minute increase in time between the first MH sign and the 1st dantrolene dose. The Canadian study also showed that the MH complication rate increased with increasing minutes to dantrolene use from the first MH sign. For each 10-minute delay in administration of dantrolene, complications increased substantially. When dantrolene was delayed beyond 50 minutes, complication rates increased to 100%.

Initial dantrolene dose amount: For the NAMHR data, the amount of initial dantrolene dose was examined and was not found to be significant for a model analyzing the likelihood of complications (odds ratio 1.13 (95% CI 0.96,1.33) P=1.000. For the group not experiencing complications the median initial dantrolene dose was 2.31 (1.47, 2.67) mg/kg and for the group experiencing complications, the median initial dose of dantrolene was 2.48 (2.00, 2.89) mg/kg.

For queries #9, 10, 11: A total of 5 references (all OCEBM level 3 or 4, retrospective studies) were available for analysis. Four of these references use the NAMHR database of predominantly US patients. One of these references derives from a Canadian database in which subjects MH events were both graded by the MH clinical grading scale and confirmed with a CHCT. There is no overlap between the NAMHR database and the Canadian database. For the Canadian database, dantrolene dose data for many subjects were not available even after examination of original anesthetic records. Limitations of all studies also include reporting, recall, and selection bias. Finally, associations may not imply causality.

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| Article Identifier | Morbidity Type Percentage  | Dantrolene | Classification of MH Event | Levelof Evidence | Bias | Other Comments |
| 1. Burkman JM, Posner KL, Domino KB: Analysis of the clinical variables associated with recrudescence after malignant hyperthermia reactions. Anesthesiology 2007;106:901-6 | Postoperative organ failure (49/308=16%) defined as evidence of: Cardiac dysfunction (11/308=4%), Cognitive dysfunction (22/308=7%) (change in consciousness or stroke), DIC (8/308=3%), hepatic dysfunction (10/308=3%), pulmonary dysfunction (14/308=5%)(prolonged intubation, pulmonary edema, pleural effusion), renal dysfunction (11/308=4%)See Table 4, p. 904 | No data on dantrolene dose and postoperative organ failure.Data regarding dantrolene dose only analyzed for its association with recrudescence and not for its association with postoperative organ failure.Where known (n=244), the initial dantrolene dose administered was similar between the two groups (those who recrudesced and those who did not recrudesce). | CGS\* score of >=20(MH rank >=4) (“somewhat greater than likely” MH)-clinical not contracture testing or genetic diagnosis | 3 | NAMHR\*\* data for AMRAs received from 1987 through 12/31/2004Reporting and recall bias; selection bias (death cases with initial episode were excluded)Not classic case control study and confounding is present; “associations do not imply causation”  | Analyzed in relationship to recrudescence; “Patients who recrudesced were more likely to experience postoperative organ failure than patients in the control group (P<0.01)However the analysis in column 2 is for those who both recrudesced and those that did not.Data has overlap with reference #2 with reference #1 having less stringent MH definition and fewer years.  |
| 2. Larach MG, Gronert GA, Allen GC, Brandom BW, Lehman EB. Clinical presentation, treatment, and complications of malignant hyperthermia in North America from 1987 to 2006. Anesth Analg 2010;110:498-507 | **Complications not including recrudescence, cardiac arrest, or death occurred in 63 of 181 MH events (34.8%)** The likelihood of any complication increased 2.9 times per 2°C increase in maximum temperature and 1.6 times per 30-minute delay in dantrolene use.See Table 6. p.503Consciousness level change/coma17/181 (9.4)Cardiac dysfunction 17/181 (9.4)Pulmonary edema15/181 (8.4)Renal dysfunction13/181 (7.2) % corrected by 1st authorDIC§13/181 (7.2)Hepatic dysfunction10/181 (5.6%)Other23/181 (12.7%) | Regarding the relationship between no dantrolene and the experience of MH complications: 2/11 MH cases who did not receive dantrolene but had information regarding MH complications experienced hepatic dysfunction with a peak CK\*\*\* of 37,911U/L and lower extremity soreness with a peak CK of 365,970. There was inadequate power to detect differences between the group receiving dantrolene (n=229) and the one not receiving dantrolene (n=22) for experience of MH complications. **The likelihood of a MH complication** **increased 1.61 (95% CI, 1.16-2.25) times for every 30-minute increase in time between the first MH sign and the first dantrolene dose** and 2.85 times (95% CI, 1.60-5.08) for every 2°C increase in maximum temperature.Hosmer-Lemeshow goodness of fit test for this model is P=0.140. Held even if removed 6 patients experiencing cardiac arrest. **Amount of initial dantrolene dose was examined and was not found to be significant for model (odds ratio 1.13 (95% CI 0.96,1.33) P=1.000. For group not experiencing complications the median initial dantrolene dose was 2.31 (1.47, 2.67) mg/kg and for the group experiencing complications, the median initial dose of dantrolene was 2.48 (2.00, 2.89) mg/kg** (median initial doses, 25%, 75%, odds ratio, 95% C.I., P values are from Erik B. Lehman, M.S., Department of Public Health Sciences, Penn State College of Medicine, Hershey, Pennsylvania, personal communication to M G Larach on May 26, 2009 from this dataset analysis.)  | CGS score of >=35 =Rank 5 and 6 or “very likely” or “almost certain” MH-no genotyping or contracture testing confirmation of MH susceptibility | 3 | NAMHR data for AMRAs received from 1/1/1987\* through 12/31/2006 Reporting and recall bias; selection bias Not classic case control study and confounding is present;“associations do not imply causation”\*Earliest AMRAs did not include complication question. | Complications defined as a change in consciousness level and/or coma; DIC, pulmonary edema, cardiac, renal or hepatic dysfunction, or “other” complication as specified by the reporting clinician. Many cases overlap with reference #1. Only 1.8% of cases from Canada. The rest were from U.S. |
| 3. Nelson P, Litman RS. Malignant hyperthermia in children: an analysis of the North American Malignant Hyperthermia Registry. Anesth Analg 2014;118:369-74 | “Other major complications were uncommon, with cardiac dysfunction having the highest incidence of 4.5%. 12/264. No further reference to what the other complications were.  | Impact of dantrolene on MH complications not examined. | CGS score =>35 (Rank 5 and rank 6); “very likely” or “almost certain” . Dataset restricted to < or =18 years. Events occurred between 1960 and 2011. | 3 | Reporting and recall bias; selection bias Not classic case control study and confounding is present;“associations do not imply causation”\*Earliest AMRAs did not include complication question. | Limited to **pediatrics**. Some of the dataset is a subset of reference # 2.Cardiac dysfunction in the pediatric population is 4.5% vs. all ages from reference #2 of 9.4%.  |
| 4. Riazi S, Larach MG, Hu C, Wijeysundera D, Massey C, Kraeva N. Malignant hyperthermia in Canada: characteristics of index anesthetics in 129 malignant hyperthermia probands. Anesth Analg 2014; 118:381-7. | 129 probands included in study. Table 4. p.384.Patients with 1 complication13/129 (10.1%)Patients with multiple complications13/129 (10.1%)**Patients with 1 or more complications****26/129 (20.2%)****In patients with CGS score of >=35, a complication was reported in 22/72 (30.6%). For patients with a CGS score of <35, a complication rate was 7.0%**Renal dysfunction19/129 (14.7%)Cardiac dysfunction (includes patients with cardiac arrest)7/129 (5.4%)DIC5/129 (3.9%)cardiac arrest5/129 (3.9%)pulmonary edema2/129 (1.6%)compartment syndrome1/129 (0.8%)hepatic dysfunction not examined because of insufficient data on bilirubin values to analyze hepatic dysfunction since increased transaminase levels may be secondary to rhabdomyolysis alone. | No data on actual dantrolene dose (often not recorded in the original anesthesia record). **When the time between onset of the first clinical sign and dantrolene administration was longer, the proportion of patients experiencing a complication was also larger (23.5 minutes vs 15.0 minutes, P=0.005)** **The exact Cochran-Armitrage trend test shows that complication rate increased with increasing minutes to dantrolene use, P<0.01.**Figure 1 (p.385) shows that for each 10-minute delay in administration of dantrolene, complications increased substantially. **When dantrolene administration was delayed beyond 50 minutes, complication rates increased to 100%.** | Surviving probands referred to Toronto General from 1992 to 2011 with dx of MH susceptible by contracture testing and anesthesia records.  | 3 | Data availability: specific dantrolene dose (amount) and type of temperature monitoring were lacking for majority of anesthetic records.Selection bias-had to survive to be referred for contracture testing. Varying severity of MH events but subgroup analysis helps correct this. | This dataset does not overlap with other references. Canadian patients only. |
| 5. Larach MG, Brandom BW, Allen GC, Gronert GA, Lehman EV: 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 (Other: NAMHR of MHAUS dataset)  | 31/84 or 36.9% complication rate Cardiac dysfunction 11/84 (13.1%)Renal dysfunction10/84 (11.9%)Consciousness level change/coma8/84 (9.5%)Pulmonary edema6/84 (7.1%)DIC\*6/84 (7.1%)Hepatic dysfunction4/84 (4.8%)Othercompartment syndrome1/84 (1.2%)pleural effusions1/84 (1.2%)No temperature probe or a skin temperature probe increased the likelihood of DIC P value 0.01, Odds ratio with 95% CI 12.4 (2.2, infinity)Recrudescence12/84 (16.4%) | Not published and untested for significant difference. Initial dose of dantrolene available for 74 of 84 in total dataset. Median of 2.46 mg/kg (180 mg) with lower quartile of 2.01 mg/kg (100 mg) and upper quartile of 2.61 mg/kg (240 mg) with minimum of 0.16 (12mg) and maximum of 10.15 mg/kg (660 mg). Total dose dantrolene available for 59 of 84 in dataset. Median of 7.0 mg/kg [467 mg] with lower quartile of 3.00 mg/kg [180mg] and upper quartile of 10.00 mg/kg [810 mg]. Range 1.01 mg/kg [48 mg] to 16.71 mg/kg [1700 mg]. (Personal communication from Erik B. Lehman, M.S., Department of Public Health Sciences, Penn State College of Medicine, Hershey, Pennsylvania, to M G Larach on February 7, 2014 from this dataset analysis.) | ‘very likely’ or ‘almost certain’ MH event | Not applicable | NAMHR data for AMRAs received from 1/1/2007 through 12/31/2012 Reporting and recall bias; selection bias Not classic case control study and confounding is present;“associations do not imply causation” | Not published as part of a paper but drawn from analysis of the dataset for this paper. Personal communication from M.G. Larach on June 12, 2016. Based on reporting of individual completing AMRA. Usually no hospital charts available to review. |
| **Summary**References All but reference #4 being drawn from the NAMHR database. Reference#4: no overlap of events with the other references and has both CGS score with CHCT confirmation.  | Morbidity type/percentageRef #1: n=308**16%** postoperative organ failure when D4-6 MH events analyzedRef#2: n=181**34.8%** complications when D5-D6 events 1987-2006Ref#5 unpublished data: **36.9%** same analysis but D5-D6 events from 2007-2012Ref#4: n=129**20.2%** but increases to **30.6%** when only D5 and D6 events included in the analysis of patients who were all CHCT+. CHCT between 1992 to 2011 and referred to Toronto GeneralOverall: The more severe the event, the higher the morbidity rate. Reference #4 and #11-Other demonstrate that complication rate consistent in spite of different time periods. | DantroleneRef#2: Unpublished data: Amount of initial dantrolene dose was examined and was not found to be significant for model analyzing likelihood of complications (odds ratio 1.13 (95% CI 0.96,1.33) P=1.000. For group not experiencing complications the median initial dantrolene dose was 2.31 (1.47, 2.67) mg/kg and for the group experiencing complications, the median initial dose of dantrolene was 2.48 (2.00, 2.89) mg/kgRef#2: The likelihood of a MH complication increased 1.61 (1.16-2.25) times for every 30-minute increase in time tween the first MH sign and the 1st dantrolene doseAmount of initial dantrolene dose was examined and was not found to be significant for model (odds ratio 1.13 (95% CI 0.96,1.33) P=1.000.Ref#4: Complication rate increased with increasing minutes to dantrolene use from first MH sign. For each 10-minute delay in administration of dantrolene, complications increased substantially. When dantrolene was delayed beyond 50 minutes, complication rates increased to 100%. | Classification of MH EventRef#1: D4-D6Ref#2: D5-D6Ref#4: CHCT+ with 72/129 (55.8%) D5-D6, range of all 129=D3-D6Ref#5: D5-D6 | Level of EvidenceAll references are level 3 or 4 | BiasIncomplete data possible,No classic case control studiesReporting and recall bias; selection bias (especially ref#4 because had to survive and be well enough to go on for CHCT), confounding, associations do not imply causality | CommentsReferences #1, #2, #3, #5 primarily US cases.Reference #4: Canadian cases |

\* CGS=Clinical Grading Scale

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

\*\*\* CK=creatine kinase

§ DIC=disseminated intravascular coagulation