Clinical question.

Following unsuccessful attempts at resuscitation in previously healthy children and young adults (<35 yo) with cardiac arrest (P), does consideration of a channelopathy as the etiology of the arrest (I), as compared with standard management (C), improve outcome (appropriate diagnosis and management, identification of at risk family members) (O)

Is this question addressing an intervention/therapy, prognosis or diagnosis? Prognosis

State if this is a proposed new topic or revision of existing worksheet:

Conflict of interest specific to this question

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? None

Search strategy (including electronic databases searched).

Database: Ovid MEDLINE(R) 1950 to Present with Daily Update

Search Strategy:

--------------------------------------------------------------------------------
1  Death, Sudden, Cardiac/ep, eh [Epidemiology, Ethnology] (1609)
2  limit 1 to (english language and humans and ("all child (0 to 18 years)" or "young adult (19 to 24 years)")(223)
3  exp Channelopathies/cn, ep, ge [Congenital, Epidemiology, Genetics] (59)
4  limit 3 to (english language and humans and ("all child (0 to 18 years)" or "young adult (19 to 24 years)")(12)
5  brugada syndrome/ or long qt syndrome/ or tachycardia, ventricular/ or torsades de pointes/ (13072)
6  limit 5 to (english language and humans and ("all child (0 to 18 years)" or "young adult (19 to 24 years)")(1731)
7  Ryanodine Receptor Calcium Release Channel/ (3646)
8  limit 7 to (english language and humans and ("all child (0 to 18 years)" or "young adult (19 to 24 years)")(130)
9  8 or 6 or 4 (1838)
10  exp Death, Sudden, Cardiac/ (7847)
11  10 and 9 (209)
12  *Death, Sudden, Cardiac/ep, eh and 2 (81)
13  11 or 12 (281)
14  from 13 keep 1-281 (281)

Cochrane Search History

ID Search Hits Edit Delete
#1 MeSH descriptor Heart Arrest explode all trees 824
#2 MeSH descriptor Channelopathies explode all trees 0
#3 MeSH descriptor Long QT Syndrome explode all trees 109
#4 MeSH descriptor Tachycardia, Ventricular explode all trees 445
#5 MeSH descriptor Torsades de Pointes explode all trees 22
#6 MeSH descriptor Ryanodine Receptor Calcium Release Channel explode all trees 1
#7 (catecholaminergic polymorphic ventricular tachycardia):ti,ab,kw 0
#8 MeSH descriptor Brugada Syndrome explode all trees 3
#9 (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8) 551
#10 (#1 AND #9) 86
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<th>Number of articles/sources meeting criteria for further review:</th>
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## Summary of evidence

### Evidence Supporting Clinical Question

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A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  
*Italics = Animal studies*

Note: The identification of affected individuals who die unexpectedly and affected family members both represent class E level of evidence as neither directly addresses the resuscitation process. Studies addressing the decedent, are classified as LOE 5 as they are indirectly related to the primary outcome.
## Evidence Neutral to Clinical question

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**Kimbrough, 2001E**

**Kaufman, 2008 E**

**Hendriks, 2008 E**

**Level of evidence**

- A = Return of spontaneous circulation
- C = Survival to hospital discharge
- E = Other endpoint
- B = Survival of event
- D = Intact neurological survival

**Italics = Animal studies**

### Evidence Opposing Clinical Question

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**Doolan, 2007 E**

**Level of evidence**

- A = Return of spontaneous circulation
- C = Survival to hospital discharge
- E = Other endpoint
- B = Survival of event
- D = Intact neurological survival

**Italics = Animal studies**
The incidence of sudden cardiac death in the young is 1 to 5 per 100,000 patient-years. No cause for death is found on routine autopsy for 10-30% of these individuals. [Chugh, 2000, 649-54, Eckart, 2004, 829-34, Puranik, 2005, 1277-82] Recent genetic investigation has led to better understanding of life threatening arrhythmias in the setting of a structurally and functionally normal heart. Mutations in genes coding for proteins that regulate sodium, potassium and calcium movement through “channels” in the cell membrane lead to an unstable electrical environment that is the substrate for these arrhythmias. Specific conditions include Long QT syndrome (LQTS), short QT syndrome, Brugada syndrome and Catecholaminergic polymorphic ventricular tachycardia (CPVT). As a group, these conditions are categorized as “channelopathies”. The primary source of these mutations is transmission from affected individuals, while fewer (8-10%) are due to de novo mutations.

Overall approximately 75% of those with channelopathies may be identified with genetic testing. It is presumed that affected individuals with negative results have mutations not yet recognized. Additional complexity arises related to penetrance and expressivity of these conditions. Penetrance refers to the likelihood of a clinical manifestation of disease in the presence of a genetic abnormality. A condition that is completely or 100% penetrant results in clinical manifestation for all individuals with the mutation. None of the above conditions are completely penetrant. While individuals with clinical manifestations of disease are clearly at risk, the risk assessment is less clear for individuals who have a positive genotype and normal phenotype. Further, the severity with which the condition is manifest (expressivity) varies among individuals with the same mutation and those in the same family.

The clinical diagnosis for a channelopathy phenotype is primarily based upon symptoms, documented arrhythmias and abnormalities on the resting ECG, and is supported by a family history of similarly affected individuals. Relevant family history includes syncope, seizures, sudden death (including SIDS), drowning and unexplained automobile accidents. There is no consensus on the extent of testing necessary for suspected channelopathies. While ECG is performed routinely, signal averaged ECG, exercise testing, Holter monitoring, echocardiography, epinephrine challenge, flecainide challenge, genetic testing and magnetic resonance imaging have been proposed but are not standard of care. The incremental cost benefit ratio of each clinical test has not been thoroughly studied. The NIH has established one its priorities related to channelopathies to be development, implementation and testing of new therapeutic approaches to identify, treat, and prevent inherited arrhythmias based on genetic, molecular, and cellular mechanisms”

The ideal network for first degree relatives of individuals dying unexpectedly begins with those involved in the unsuccessful resuscitation, but includes forensic pathologists, cardiologists, clinical geneticists and genetic counselors, diagnostic and research laboratories, and parent support groups.

Review of the literature indicates clear evidence that sudden unexpected death in young individuals (<35 years of age) is due to previously unrecognized channelopathies in up to 20%. A number of specific mutations have been identified in case series of autopsy negative sudden death [Ackerman, 2001, 2264-9], [Arnestad, 2007, 361-7], [d'Amati, 2005, 761-7], [Di Paolo, 2004, 182-4] [Nishio, 2006, 1402-6, Priori, 2000, 808-9, Tester, 2005, 596-600] [Tester, 2007, 240-6] (including sudden infant death syndrome (SIDS)[Schwartz, 2000, 262-7, Turillazzi, 2008, 209-16]). These include LQTS, short QT syndrome, Brugada syndrome, and CPVT.

The mechanism by which tissue and/or blood is preserved significantly impacts the ability to make a diagnosis and forensic pathologists should be aware of these requirements.

A single paper found the molecular autopsy to reveal no cases of channelopathy in a series of 59 patients with unexplained sudden death. [Doolan, 2008, 138-41]
Further, relatives of individuals who unexpectedly died suddenly are up to 8 times more likely to experience sudden death (Behr 2007). These family members frequently (12-56%) have clinically detectable evidence of these conditions (ie abnormal ECG) and/or carry mutations associated with these conditions [Behr, 2003, 1457-9] [Hofman, 2007, e967-73, Tan, 2005, 207-13] [Behr, 2008, 1670-80]

The identification of affected individuals who die unexpectedly and affected family members both represent class E level of evidence as neither directly addresses the resuscitation process. It is suggested for consideration that a category related to prevention be established for future reviews in this and related areas of investigation.

Overall the risk of sudden death due to channelopathies is mitigated with treatment, which includes behavioral/lifestyle modifications, medical therapy, left sympathectomy, catheter ablation of triggering foci and implantable defibrillators. Beta blockade and left sympathectomy can prevent sudden death in 96-97% of high risk patients with long QT syndrome. CPVT patients not treated with beta blockers had a hazard ratio of 5.48 compared to those who received these medications. [Hayashi, 2009, 2426-34]

One author [Di Paolo, 2004, 182-4] suggested neglecting to identify these potential diagnoses at autopsy, and thereby not providing the family with knowledge that others were at risk, may be sufficient grounds for litigation. It is logical to conclude that identification of affected family members would lead to improved outcomes.

There are several studies suggesting the investigation for a channelopathy may not be as beneficial as anticipated in all circumstances. One study found the severity profile of LQTS in a proband was not found to be useful in identifying the clinical severity of LQTS in affected first-degree relatives of the proband [Kimbrough, 2001, 557-62]. The same group further examined this issue and a clear benefit related to identification of disease due to a family member who succumbed was not proven [Kaufman, 2008, 831-6]. This was not a controlled trial and a number of confounding circumstances may have influenced the outcome. Additionally at least one study confirms that significant anxiety is generated in the testing following sudden death of a family member.[Hendriks, 2008, 719-24]

|Acknowledgements:|

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**Citation List**


LOE 5 - This study identifies likely causative mutations in a series of patients with SIDS. While it does not address the benefit provided to surviving family members (which is the population of interest), there is an implied benefit.

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LOE 5 - This study identifies likely causative mutations in a series of patients with SIDS. While it does not address the benefit provided to surviving family members (which is the population of interest), there is an implied benefit.


LOE 5 - This study directly assesses the population of interest and demonstrates that channelopathies may be present in first degree relatives of patients who die suddenly. It does not evaluate the benefit to these relatives.


LOE 4 - This study confirms the presence of channelopathies in first degree relatives of sudden death victims. It does not evaluate the benefit to these individuals, although one is implied.


LOE 5 - This study confirms the presence of channelopathies in first degree relatives of sudden death victims. It does not evaluate the benefit to these individuals, although one is implied.


LOE 5 - This study establishes the benefit of additional historical and laboratory data in the presence of a normal biopsy to establish a cause of sudden death. Channelopathy is not specifically evaluated, but other important causes are highlighted.


LOE 4 - This study establishes the benefit of additional historical and laboratory data in the presence of a normal biopsy to establish a cause of sudden death. Channelopathy is not specifically evaluated, but other important causes are highlighted.


LOE 4 - Case series of a family of sudden death victim. At least one first degree relative benefited with a reduction in exercise induced ectopy after treatment.


LOE 5 - Case series of a family of sudden death victim. At least one first degree relative benefited with a reduction in exercise induced ectopy after treatment.


LOE 5 - This is a case series showing LQTS as cause for unexplained sudden death. No data is presented regarding first degree relatives; benefit is implied from previous LQTS data in addition to suggesting liability for failure to identify channelopathy.


LOE 5 - This is a case series showing LQTS as cause for unexplained sudden death. No data is presented regarding first degree relatives; benefit is implied from previous LQTS data in addition to suggesting liability for failure to identify channelopathy.


LOE 5 - There were no disease causing mutations in a case series of autopsy negative sudden death. The sample is relatively small. As no mutations were identified, no benefit could be extrapolated to the population of interest.

LOE 5 - This large series details structural anomalies associated with sudden death, but confirms that autopsy alone does not explain 35% of these events, many of which are possibly due to channelopathy. The specific population of interest, first degree relatives, is not addressed.


LOE 4 - This case series showed benefit of beta blocker therapy in affected family members of probands with sudden death due to CPVT.


LOE 4 - This prospective analysis details an adverse impact on stress levels for family members of sudden death victims. While avoidance of sudden death in surviving family members is the real benefit to assess in this population, this represents a relatively less important, but significant, adverse result.


LOE 4 - Large case series identified disease in first and second degree relatives of SD victims. There was no assessment of benefit to the relatives other than the diagnosis, but a benefit is implied.


LOE 4 - Large retrospective review of LQT database was unable to demonstrate a survival benefit from the knowledge of death in a first or second degree relative. Results confounded by more aggressive treatment of relatives, but overall must be interpreted as a neutral result.


LOE 4 - Large retrospective review of LQT database demonstrated that affected mothers of SD victims have ongoing risk and implies a treatment benefit.


LOE - Small case series demonstrating ryanodine receptor mutation in SD victim with negative autopsy. There was no assessment of benefit to surviving family members, but one was implied.


LOE 5 - Small case series from a single family where mutation confirmed following suspicious ECG. No benefit to surviving relatives assessed, but one was implied.

LOE 5 - Retrospective review of database of sudden death presumed arrhythmia as etiology in absence of other findings. There was no assessment of relatives.


LOE 5 - Single case report of aborted SIDS victim subsequently shown to have channelopathy. Treatment benefit was present for proband, who was a spontaneous mutation. Therefore there was no benefit to first degree relatives.


LOE 4 - This is a prospective assessment of relatives of SD victims. Channelopathies were identified in 12/43 families. No treatment benefit was measured, but one was implied.


LOE 5 - This case series demonstrates potentially causitive channelopathies in 2 SD victims. No benefit to relatives is measured, but one is implied.


LOE 5 - This is a retrospective review of a large autopsy series demonstrating the presence of potentially causitive channelopathies. No treatment benefit was measured for relatives, but one was implied.


LOE 5 - Affected twins with SIDS subsequently demonstrated to have channelopathy, which may have been causitive. No benefit to realtives was measured, but one was implied.

**Supplemental Citations (Review articles)**


