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| White Paper Report on Excited Delirium Syndrome |
| ACEP Excited Delirium Task Force |
| **September 10, 2009** |

*Report to the Council and Board of Directors on Excited Delirium at the Direction of Amended Resolution 21(08)*

# TASK FORCE CHAIR

## Mark L. DeBard, MD, FACEP, Chair

Professor of Emergency Medicine

Ohio State University College of Medicine Columbus, Ohio

# TASK FORCE MEMBERS

## Jason Adler, MD

Emergency Medicine Resident University of Maryland Baltimore, Maryland

## William Bozeman, MD, FACEP

Associate Professor of Emergency Medicine Director of Prehospital Research

Wake Forest University Winston Salem, North Carolina

## Theodore Chan, MD, FACEP

Professor of Clinical Medicine

Medical Director, Dept of Emergency Medicine University of California at San Diego

San Diego, California

## Stewart Coffman, MD, FACEP

Assistant Clinical Professor of Emergency Medicine EMS Medical Director

Chair, Dept. of Emergency Medicine UTSW Dallas, Lewisville, TX - ED Lewisville, Texas

**Melissa Wysong Costello, MD, FACEP** Associate Professor of Emergency Medicine University of South Alabama

Mobile, Alabama

## Michael D. Curtis, MD, FACEP

EMS Medical Director St. Michael’s Hospital

Stevens Point, Wisconsin St. Clare’s Hospital Weston, Wisconsin

**Fabrice Czarnecki, MD, MA, MPH** Director of Medical-Legal Research The Gables Group, Inc.

St. Joseph Medical Center Towson, Maryland

## Donald Dawes, MD, FACEP

Assistant Professor, University of Louisville Department of Physiology and Biophysics Louisville, Kentucky

Attending Physician, Lompoc Valley Medical Center Lompoc, California

Police Officer, Santa Barbara Police Department Santa Barbara, California

## Christine Hall, MD, MSc, FRCPC

Clinical Assistant Professor, Faculty of Medicine University of British Columbia

Victoria, British Columbia Canada Associate Professor, Faculty of Medicine Department of Community Health Sciences University of Calgary

Calgary, Alberta Canada

**Joseph Heck, DO, FACOEP, FACEP** Adjunct Professor of Emergency Medicine Touro University – Nevada

Medical Director, Las Vegas Metropolitan Police Dept. Henderson, Nevada

## Sean Henderson, MD, FACEP

Associate Professor of Emergency Medicine and Preven- tive Medicine

Vice Chair, Dept. of Emergency Medicine

Keck School of Medicine of the University of Southern California

Los Angeles, California

## Jeffrey Ho, MD, FACEP

Associate Professor of Emergency Medicine

Hennepin Co. Medical Center/University of Minnesota Minneapolis, Minnesota

Deputy Sheriff, Meeker County Sheriff’s Office Litchfield, Minnesota

## Deborah C. Mash, PhD

Professor of Neurology and Molecular and Cellular Pharmacology

Miller School of Medicine University of Miami Miami, Florida

## Mary Jo McMullen, MD, FACEP

Professor of Emergency Medicine

Northeastern Ohio University College of Medicine Akron, Ohio

## Jeffery Metzger, MD

Assistant Professor, Division of Emergency Medicine University of Texas, Southwestern Medical Center Medical Director, Dallas Police Department

Dallas, Texas

**James Roberts, MD, FACEP, FACMT** Professor and Vice-Chair Department of Emergency Medicine

Senior Consultant, Division of Toxicology Drexel University College of Medicine Philadelphia, Pennsylvania

Chair, Department of Emergency Medicine Mercy Catholic Medical Center Philadelphia, Pennsylvania

**Matthew Sztajnkrycer, MD, PhD, FACEP** Associate Professor of Emergency Medicine Mayo School of Medicine

Rochester, Minnesota

**Gary Vilke, MD, FACEP** Professor of Clinical Medicine Chief of Staff

University of California at San Diego Medical Center Director, Clinical Research for Emergency Medicine University of California at San Diego

San Diego, California

## ACEP Board Liaison

**David C. Seaberg, MD, FACEP**

Dean, University of Tennessee College of Medicine Chattanooga, Tennessee

ACEP Staff Liaison

## Rick Murray, EMT-P

Director, EMS & Disaster Preparedness Dept Dallas, Texas

ACEP Staff Support

## Denise Fechner

EMS & Disaster Preparedness Dept Dallas, Texas



**Excited Delirium Task Force**

**White Paper Report to the Council and Board of Directors September 10, 2009**

# PREAMBLE

The 2008 Council of the American College of Emer- gency Physicians (ACEP) adopted Amended Resolu- tion 21(08), “Excited Delirium,” which was then adopted by the ACEP Board of Directors:

“RESOLVED, that ACEP study:

1. The existence of “excited delirium” as a dis- ease entity (or not);
2. Characteristics that help identify the pres- entation and risk for death; and
3. Current and emerging methods of control and treatment.

And be it further RESOLVED,

That ACEP develop and disseminate a white paper on findings to appropriate entities (e.g., EMS, law enforcement).”

# INTRODUCTION

In response to this resolution, ACEP convened a Task Force of nineteen experts in what the Task Force has chosen to call Excited Delirium Syndrome (ExDS). Eighteen of these experts are emergency physician members of ACEP and one is a PhD re- searcher. The Task Force was charged to examine the available literature and existing data and use their expert experience and consensus to deter- mine:

1. if the entity commonly referred to as “excited delirium” exists, and
2. if so, whether it could be better defined, identi- fied, and treated.

## It is the consensus of the Task Force that ExDS is a unique syndrome which may be identified by the presence of a distinctive group of clinical and be- havioral characteristics that can be recognized in the pre-mortem state. ExDS, while potentially fat- al, may be amenable to early therapeutic interven- tion in some cases.

The term “Excited Delirium” has been used to refer to a subcategory of delirium that has primarily been described retrospectively in the medical examiner literature. Over time, the concept of excited deli- rium has made its way into the emergency medi- cine, psychiatric, law enforcement, prehospital and medicolegal literature. It has generally been used to describe a small group of patients with a set of symptoms that has eluded a unifying, prospective clinical definition. The Task Force debated the me- rits of renaming the syndrome in a medically more descriptive way. However, it was decided that the literature and general understanding in the health care and law enforcement fields of the term “Ex- cited Delirium” favored retention of the traditional- ly understood word for research and clinical pur- poses. It was incorporated into the described syn- drome as “Excited Delirium Syndrome (ExDS).”

The difficulty surrounding the clinical identification of ExDS is that the spectrum of behaviors and signs overlap with many clinical disease processes*.* ExDS is not intended to include these diseases, except insofar as they might meet the definition of ExDS. Treatment interventions targeted at one of these alternate diagnoses may potentially alleviate or ex- acerbate ExDS, thus further confounding the diag- nosis. Faced with the lack of a clear definition and cause, the decision to identify ExDS as a syndrome instead of a unique disease is similar to the dec-

ades-long controversy over the causes of Sudden Infant Death Syndrome.

Despite increased research, the exact pathophysiol- ogy of ExDS remains unidentified. Some recent re- search in the area of fatal ExDS points to dopamine transporter abnormalities. Eventually, there might be found a genetic susceptibility, an enzyme excess or deficiency, an overdose or withdrawal state, or some other multifactorial trigger, including a variety of medical and psychiatric conditions.

At present, physicians and other medical and non- medical personnel involved in personal interactions with these patients do not have a definitive diag- nostic “test” for ExDS. It must be identified by its clinical features. This also makes it is very difficult to ascertain the true incidence of ExDS.

While not universally fatal, it is clear that a propor- tion of patients with ExDS progress to cardiac arrest and death. It is impossible at present to know how many patients receive a therapeutic intervention that stops the terminal progression of this syn- drome. While many of the current deaths from ExDS are likely not preventable, there may be an unidentified subset in whom death could be averted with early directed therapeutic intervention.

In this paper, the Task Force provides a review of the history and epidemiology of ExDS, clinical pers- pectives, and a discussion of its potential pathophy- siology, diagnostic characteristics, differential diag- noses, and clinical treatment. Ultimately, the goals are to raise awareness of the existence of this syn- drome to medical and public entities, to aid law en- forcement, Emergency Medical Service (EMS) per- sonnel, physicians, health care providers, correc- tions officers and others in the recognition of ExDS, and to identify best practices to deal with this true medical emergency.

# HISTORY

For more than 150 years, there have been case re- ports that do not use the exact term “excited deli- rium,” yet describe a similar constellation of symp-

toms and features. These cases discuss clinical be- havior and outcomes that are strikingly similar to the modern day concept of ExDS.

These historical cases occurred primarily within in- stitutions that housed mentally disturbed individu- als in protective custody largely because of the lack of effective pharmacologic treatment available dur- ing that time period. The behavior seen in these cases has been called “Bell’s Mania,” named after Dr. Luther Bell, the primary psychiatrist at the McLane Asylum for the Insane in Massachusetts. Dr. Bell was the first to describe a clinical condition that took the lives of over 75% of those suffering from it. Based on the clinical features and outcomes of the institutionalized cases from the 1800s when com- pared to the presently accepted criteria known to accompany ExDS, it is believed that Bell’s Mania may be related to the syndrome of ExDS that we witness today.

Historical research indicates that the worrisome behaviors and deaths following uncontrolled psy- chiatric illness described in the 1800s seemed to decline drastically by the mid-1950s. This is largely attributed to the advent of modern antipsychotic pharmaceutical therapy that changed psychiatric practice from one of custodial patient control to a goal of de-institutionalization and patient place- ment within normal community settings.

There is only one reference before 1985 known to mention the exact term “Excited Delirium.” In this reference, the words “excited” and “delirium” were combined to describe the condition of a patient just prior to death following a hemorrhoid operation by an accomplished surgeon. At the time, it was felt that the operation somehow damaged the patient’s nervous system, and lead to acute psychiatric de- compensation and death.

In the 1980s, there was a dramatic increase in the number of reported cases with behavior similar to an uncontrolled psychiatric emergency. While some seemed to be unchecked psychiatric disease, most of these cases were found to be associated with the introduction and abuse of cocaine in North America. Since then, this connection between ExDS and co-

caine has continued. Additionally, ExDS has now been recognized to occur in association with other illicit drugs of abuse, as well as with certain types of mental illness and their associated treatment medi- cations.

Before 1985, there was no single unifying term to describe the clinical pattern seen in these patients. In 1985 a subset of cocaine deaths was described by Wetli and Fishbain in a seminal paper which for the first time used the term “excited delirium.”

The typical course of a published ExDS patient in- volves acute drug intoxication, often a history of mental illness (especially those conditions involving paranoia), a struggle with law enforcement, physical or noxious chemical control measures or electrical control device (ECD) application, sudden and unex- pected death, and an autopsy which fails to reveal a definite cause of death from trauma or natural dis- ease.

As a consequence of the circumstances surrounding the death and the lack of a definitive cause on au- topsy, there has been continued debate about the validity of the term “excited delirium.” This debate continues today. There are those who believe it to be a convenient term used to excuse and exonerate authorities when someone dies while in their cus- tody. It is articulated by some that ExDS is a term or concept that has been “manufactured” as a law en- forcement conspiracy or cover-up for brutality.

This argument mainly centers on the fact that most organized medical associations (e.g., American Medical Association) and medical coding reference materials (e.g., International Classification of Dis- eases, Ninth Revision, or ICD-9) do not recognize the exact term “excited delirium” or “excited deli- rium syndrome.” The countering argument is that there are organized medical associations that do recognize ExDS as an entity (e.g., National Associa- tion of Medical Examiners) and references such as the ICD-9 contain several codes that can be used to describe the same entity as ExDS, albeit with differ- ent wording such as:

 296.00S Manic Excitement

 293.1J Delirium of Mixed Origin

 292.81Q Delirium, drug induced

 292.81R Delirium, induced by drug  307.9AD Agitation

 780.09E Delirium

 799.2AM Psychomotor Excitement

 799.2V Psychomotor Agitation

 799.2X Abnormal Excitement

This issue of semantics does not indicate that ExDS does not exist, but it does mean that this exact and specific terminology may not yet be accepted within some organizations or references.

# EPIDEMIOLOGY

The exact incidence of ExDS is impossible to deter- mine as there is no current standardized case defi- nition to identify ExDS. In addition, since ExDS is mainly discussed in the forensic literature and is a diagnosis of exclusion established on autopsy, there is little documentation about survivors of the syn- drome. A published observational study suggests that the incidence of death among patients mani- festing signs and symptoms consistent with ExDS is 8.3%. Some Task Force members have cared for multiple individual patients with ExDS who have survived.

Stimulant drug use, including cocaine, methamphe- tamine, and PCP, demonstrates a well established association with ExDS and is usually associated with cases of ExDS death.

A review of the literature reveals common characte- ristics among patients identified post-mortem as suffering from ExDS. More than 95% of all pub- lished fatal cases are males with a mean age of 36. These subjects are hyperaggressive with bizarre be- havior, and are impervious to pain, combative, hyperthermic and tachycardic. There is typically a struggle with law enforcement that involves physi- cal, noxious chemical, or ECD use followed by a pe- riod of quiet and sudden death. The majority of

cases involve stimulant abuse, most commonly co- caine, though methamphetamine, PCP, and LSD have also been described. At least in the setting of cocaine use, the episode of ExDS usually appears to occur in the context of a cocaine binge that follows a long history of cocaine abuse.

Persons with psychiatric illnesses comprise the second largest but a distinctly smaller cohort of ExDS cases and deaths. The literature on ExDS fre- quently cites abrupt cessation of psychotherapeutic medications as a cause. This raises the question of whether the behavioral changes seen in this context represent withdrawal syndromes characteristic of the medications involved, central nervous system adaptations to medications, or recrudescence of underlying disease. Since medication noncom- pliance is common in psychiatric patients, health care providers should be aware of this potential cause of delirium-like behavior. Less commonly, persons with new-onset psychiatric disease (mania or psychosis) will present with ExDS. In most cases, the underlying disease will be untreated at the time of presentation, but in some cases the disease may be partially treated or mistreated.

Over a two-year period, presence or absence of 10 potential clinical features of ExDS was recorded by Canadian police for over 1 million police-public inte- ractions (C. Hall, personal communication).

Of the 698 encounters involving use of force, 24 probable cases were identified, based upon the presence of perceived abnormal behavior and at least 6 of 10 potential clinical criteria for ExDS. These represent 3.4% (or 2-5%) of the use of force cohort. For the individuals manifesting 7 or more features including tactile hyperthermia, **Table 1** lists the occurrence of all 10 potential features with their frequencies and 95% confidence intervals. (Note that the oft-reported mirror or glass attrac- tion is rather infrequent). These represent 2.7% (or 1-3.5%) of the use of force cohort, a not inconse- quential number given the potential for sudden un- expected death.

Although no deaths occurred in this collection pe- riod, the 97.5% one sided confidence interval for

the absence of death still implies that up to 14% of these individuals could experience sudden death, a number in line with the previously mentioned and published observational study.

**Table 1: ExDS Prehospital Potential Features and Frequencies with 95% Confidence Intervals**

|  |  |
| --- | --- |
| **FEATURE** | **FREQUENCY****% (95% CI)** |
| Pain Tolerance | 100 (83-100) |
| Tachypnea | 100 (83-100) |
| Sweating | 95 (75-100) |
| Agitation | 95 (75-100) |
| Tactile Hyperthermia | 95 (75-100) |
| Police Noncompliance | 90 (68-99) |
| Lack of Tiring | 90 (68-90) |
| Unusual Strength | 90 (68-90 |
| Inappropriately Clothed | 70 (45-88) |
| Mirror/Glass Attraction | 10 |

# PATHOPHYSIOLOGY

The pathophysiology of ExDS is complex and poorly understood. The fundamental manifestation is deli- rium. There are several different potential underly- ing associations or causes, including stimulant drug abuse, psychiatric disease, psychiatric drug with- drawal, and metabolic disorders. Unknown mechan- isms lead from these conditions to the overt ExDS state. Specific manifestations vary among different cases. We do not fully understand why some cases progress to death and why some do not.

Although our knowledge concerning the etiology and pathophysiology of ExDS is limited, basic science and clinical studies have provided some in- sight. Stimulant drug use, especially cocaine, is as- sociated with ExDS. Of note, post-mortem toxico- logical analysis of fatal cocaine-associated ExDS pa- tients demonstrates cocaine concentrations similar to those found in recreational drug users and less

than those noted in acute cocaine intoxication deaths, suggesting a different mechanism of death.

Subsequent anatomic and molecular characteriza- tion of this group of fatal ExDS patients has focused primarily on postmortem brain examination. Results from this increasingly robust body of work demon- strate a characteristic loss of the dopamine trans- porter in the striatum of chronic cocaine abusers who die in police custody from apparent ExDS. This suggests that one potential pathway for the devel- opment of ExDS is excessive dopamine stimulation in the striatum, but the significance of this in the larger context of ExDS unrelated to chronic cocaine abuse remains unknown.

Making a central dopamine hypothesis more ap- pealing is the fact that hypothalamic dopamine re- ceptors are responsible for thermoregulation. Dis- turbances of dopamine neurotransmission may help explain the profound hyperthermia noted in many ExDS patients. Post-mortem studies in these pa- tients have demonstrated elevated levels of heat shock proteins (HSP). The central dopamine hypo- thesis also provides a link to psychiatric etiologies of ExDS.

While the specific precipitants of fatal ExDS remain unclear, epidemiologic and clinical reports provide some understanding of the underlying pathophysi- ology. When available, cardiac rhythm analysis de- monstrates bradyasystole; ventricular dysrhythmias are rare, occurring in only a single patient in one study. The majority of lethal ExDS patients die shortly after a violent struggle. Severe acidosis ap- pears to play a prominent role in lethal ExDS- associated cardiovascular collapse.

While attention has focused largely upon cases of fatal ExDS in humans, it must be noted that a similar syndrome, termed capture myopathy, has been re- ported in the veterinary literature. Clinically, it is characterized by prolonged neuromuscular activity, acidosis, and rhabdomyolysis.

# CLINICAL PERSPECTIVES

## Law Enforcement

In modern times, a law enforcement officer (LEO) is often present with a person suffering from ExDS because the situation at hand has degenerated to such a degree that someone has deemed it neces- sary to contact a person of authority to deal with it. LEOs are in the difficult and sometimes impossible position of having to recognize this as a medical emergency, attempting to control an irrational and physically resistive person, and minding the safety of all involved.

Given the irrational and potentially violent, danger- ous, and lethal behavior of an ExDS subject, any LEO interaction with a person in this situation risks sig- nificant injury or death to either the LEO or the ExDS subject who has a potentially lethal medical syndrome. This already challenging situation has the potential for intense public scrutiny coupled with the expectation of a perfect outcome. Anything less creates a situation of potential public outrage. Un- fortunately, this dangerous medical situation makes perfect outcomes difficult in many circumstances.

It is important for LEOs to recognize that ExDS sub- jects are persons with an acute, potentially life- threatening medical condition. LEOs must also be aware that remorse, normal fear and understanding of surroundings, and rational thoughts for safety are absent in such subjects.

ExDS subjects are known to be irrational, often vio- lent and relatively impervious to pain. Unfortunate- ly, almost everything taught to LEOs about control of subjects relies on a suspect to either be rational, appropriate, or to comply with painful stimuli. Tools and tactics available to LEOs (such as pepper spray, impact batons, joint lock maneuvers, punches and kicks, and ECD’s, especially when used for pain compliance) that are traditionally effective in con- trolling resisting subjects, are likely to be less effec- tive on ExDS subjects.

When methods such as pain compliance maneuvers or tools of force fail, the LEO is left with few op-

tions. It is not feasible for them to wait for the ExDS subject to calm down, as this may take hours in a potentially medically unstable situation fraught with scene safety concerns.

Some of the goals of LEOs in these situations should be to 1) recognize possible ExDS, contain the sub- ject, and call for EMS; 2) take the subject into cus- tody quickly, safely, and efficiently if necessary; and

3) then immediately turn the care of the subject over to EMS personnel when they arrive for treat- ment and transport to definitive medical care.

LEOs should be trained to recognize and manage subjects with ExDS. Officers should attempt to en- sure that the tactile temperature of these subjects is documented and request EMS to measure it. In fatal cases, a significantly elevated temperature may suggest that a life-threatening disease or con- dition was present, and that the death was inde- pendent of the police intervention.

## Emergency Medical Services

EMS dispatch personnel need to recognize clues from calls or radio traffic that personnel may be responding to a case of ExDS. This should trigger multiple law enforcement personnel responding in addition to EMS.

EMS personnel need to be trained in the recogni- tion of the signs and symptoms of ExDS. They are in a difficult position because they need to recognize the heightened personal safety risks that ExDS sub- jects represent to them but they also have a duty to provide timely care. They need to understand and practice their expected interaction with LEOs.

It is the role of LEOs to control the person with po- tential ExDS. However, as soon as control has been obtained, it is the role of EMS to recognize that this is a medical emergency and to assume responsibili- ty for assessment and care of the patient.

## Emergency Department (ED)

Emergency Physicians (EP’s) should be educated about the clinical features of ExDS and should in-

clude this in the differential diagnosis of any patient with altered mental status and agitation (either at the time of presentation or by history). There should be an increased index of suspicion for ExDS in agitated patients that present in the custody of law enforcement; however, this is a clinical entity that can enter the ED from any source (EMS, Law Enforcement, ED triage, etc).

EP's should recognize that this syndrome seems to be a multifactorial interaction of delirium and agita- tion, leading to hyperthermia and profound acide- mia, often in the setting of stimulant drug abuse. Regardless of etiology, ExDS may be fatal in some patients. EP’s should consider the possibility of ExDS in the evaluation of younger patients that present in cardiac arrest, especially in the setting of profound metabolic acidosis and hyperthermia. The physician should also initiate the documentation of clinical signs and the collection of specimens for research and diagnosis.

## Medical Examiners

Medical Examiners are often required to render a decision as to the cause of death in cases that in- volve patients in police custody with multiple con- founding variables such as pre-existing health con- ditions, concomitant illicit substance use, and un- derlying psychiatric conditions. Lack of complete prior medical information, especially underlying cardiac and metabolic pathology, hampers the as- certainment of the actual cause of death when only autopsy results are interpreted.

For example, an unknown case of Brugada syn- drome (a genetic abnormality of sodium ion chan- nels leading to sudden death from ventricular fibril- lation) may be the actual cause of cardiac arrest in an individual under the influence of cocaine, even absent excessive LEO force. Without prior electro- cardiograms, this condition would be entirely missed. Likewise, premortem potassium and glu- cose levels, and even basic vital signs (temperature and blood pressure) cannot possibly be investigated via autopsy.

The importance of a skilled investigation of the

scene of death cannot be overestimated. Crucial information such as subject behavior, drug use his- tory, a history or presence of psychosis, or the pres- ence of hyperthermia, can facilitate the determina- tion of whether the clinical features of ExDS were present.

The time, quantity, and chronicity of drug ingestion cannot always be reliably determined by toxicology alone. Significant postmortem redistribution of drugs makes interpretation of blood levels found at autopsy fraught with speculation. Tolerance to many drugs of abuse can confound interpretation of blood or tissue levels. Specific drug levels may not correlate with acute drug toxicity or poisoning. While the majority of cases of ExDS appear to occur in the presence of or with a history of cocaine or other stimulants, their presence is not required for this syndrome to occur. Psychiatric cases not involv- ing drugs of abuse have been reported. There is no current gold standard test for the diagnosis of ExDS. The presence of the hallmark clinical findings along with the presence of some type of centrally acting stimulant strongly suggests the diagnosis. Current understanding of pathophysiology suggests that the collection of various specimens (particularly brain tissue in fatal cases) is beneficial both for potential diagnosis confirmation and research.

# CLINICAL CHARACTERISTICS

Because ExDS resulting in death does not currently have a known specific etiology or a consistent single anatomic feature, it can only be described by its epidemiology, commonly described clinical presen- tation, and usual course. The minimum features for ExDS to be considered include the presence of both delirium and an excited or agitated state. As de- scribed in the DSM-IV-R, the features of delirium are constant and defined by a disturbance of con- sciousness (reduced clarity of the awareness of the environment) with reduced ability to focus, sustain or shift attention. The perceptual disturbance de- velops over a short period of time (usually hours to days), may fluctuate during the course of a day, and is not accounted for by underlying dementia.

Because of varied underlying medical conditions that may generate ExDS, there is also variation in the specific symptom cluster. As in any disorder that affects mental status, there is no assumption that each subject’s presentation will occur as a com- pletely discrete entity with absolute boundaries. The consistency lies with subjects who are delirious with evidence of psychomotor and physiologic exci- tation.

The combination of delirium, psychomotor agita- tion, and physiologic excitation differentiates ExDS from other processes that induce delirium only. Similarly, subjects who are agitated or violent but who do not also demonstrate features of delirium simply do not meet the definition of ExDS.

Until wider recognition of ExDS began, most publi- cations about it were found in the forensic patholo- gy literature and there was little publication interest in cases of ExDS that did not end catastrophically. The high reported frequency of death is likely in- creased by measurement and reporting bias since pathologists who first identified the unifying pro- drome of ExDS that leads to sudden unexpected death necessarily encountered only those subjects who died. At least one author (a forensic patholo- gist) describes the combination of a prodrome of excited delirium plus unanticipated sudden death as “excited delirium syndrome,” with invocation of the term syndrome only if the subject died.

When death occurs, it occurs suddenly, typically following physical control measures (physical, nox- ious chemical, or electrical), and there is no clear anatomic cause of death at autopsy. In cases in which a subject dies following the application of control measures, many or most of the following features are found:

male subjects, average age 36

destructive or bizarre behavior generating calls to police,

 suspected or known psychostimulant drug or alcohol intoxication,

suspected or known psychiatric illness, nudity or inappropriate clothing for the en- vironment,

 failure to recognize or respond to police presence at the scene (reflecting delirium), erratic or violent behavior,

unusual physical strength and stamina, ongoing struggle despite futility, cardiopulmonary collapse immediately fol- lowing a struggle or very shortly after quiescence,

inability to be resuscitated at the scene, and inability for a pathologist to determine a specific organic cause of death,

 attraction to glass or reflective surfaces (less frequent than all others per the Cana- dian data).

## Table 2: ExDS Features by Literature Review (n=18)

Subjects are incoherent and combative, and the struggle is more severe than anyone anticipates. Many have already sustained traumatic injuries be- fore the arrival of law enforcement and still exhibit intense struggling even when a struggle is futile and self mutilation is a result.

|  |  |
| --- | --- |
| **Features in History** | **# Articles** |
| Male gender | **16** |
| Mean age ~30’s | **16** |
| Sudden onset | **4** |
| History of Mental Illness | **8** |
| History of Psychostimulant abuse | **11** |
|  |  |
| **Features evident at scene** | **# Articles** |
| Call for disturbance/psychomotor agita- tion/excitation | **18** |
| Violent/combative/belligerent/assault call | **11** |
| Not responding to authorities/verbal com- mands | **1** |
| Psychosis/delusional/paranoid/fearful | **13** |
| Yelling/shouting/guttural sounds | **7** |
| Disrobing/inappropriate clothing | **5** |
| Violence toward/destruction of inanimate objects | **7** |
| Walking/running in traffic | **3** |
| Subject Obese | **5** |
|  |  |
| **Features evident on contact** | **# Articles** |
| Significant resistance to physical restraint | **11** |
| Superhuman strength | **8** |
| Impervious to pain | **3** |
| Continued struggle despite restraint | **7** |
| Profuse sweating/clammy skin | **3** |
|  |  |
| **Features with clinical assessment** | **# Articles** |
| Tachypnea | **1** |
| Tachycardia | **7** |
| Hyperthermia | **12** |
| Hypertension | **3** |
| Acidosis | **3** |
| Rhabdomyolysis | **5** |
|  |  |

**Table 2** lists the features of excited delirium syn- drome based on a review of the medical literature including 18 articles. The table is divided to indicate features based on the medical history of the sub- ject, features that are observed in the company of the subject, features that are evident upon physical contact, features that are only evident with clinical assessment (i.e. vital signs), features that are de- scribed if the subject dies, and finally, features that are described on autopsy. A limitation of this analy- sis is that not all of these publications are observa- tional studies and there is significant overlap of publications that reference each other to derive the most common clinical presentation.

## Differential Diagnosis

|  |  |
| --- | --- |
| **Features of death** | **# Articles** |
| Period of tranquility/”giving up” | **4** |
| Sudden collapse after restraint | **12** |
| Respiratory Arrest described | **5** |
| Cardiac rhythm brady-asystole or PEA | **4** |
| Aggressive Resuscitation unsuccessful | **5** |
|  |  |
| **Features on autopsy** | **# Articles** |
| Drug screen Positive for psychostimulants | **9** |
| Drug levels lower than anticipated | **3** |
| No anatomic correlate for death | **6** |
| Dopamine transporter disregulation | **2** |

**Overview of delirium and altered mental status**

Almost any drug, toxin, extraneous substance, psy- chiatric or medical condition, or biochemical or phy- siologic alteration in the body can cause acute changes in behavior or mental status. The general public, law enforcement, EMS, and even highly trained medical personnel may not be able to readi- ly discern the cause of an acute behavioral distur- bance, or differentiate a specific organic disease from ExDS.

## Conditions that cause altered mental status

Emergency clinicians and prehospital care providers are anecdotally aware that not all ExDS cases end in death. However, publication of nonfatal case re- ports or cohort studies remains infrequent. There is currently a paucity of literature to describe the epi- demiology of ExDS if it is not accompanied by sud- den death.

In the previously described Canadian data, 24 indi- viduals demonstrated 6 or more of the clinical fea- tures found in **Table 1**. Prehospital ExDS may be reasonably presumed in subjects displaying 6 or more features of excited delirium (perhaps exclud- ing attraction to reflective surfaces), thereby pro- viding a potential case definition for future investi- gations. It is particularly likely if the subject displays constant or near constant physical activity, pain to- lerance, superhuman strength, sweating, rapid breathing, tactile hyperthermia, and a failure to re- spond to police presence.

In summary, the clinical picture is one of an agitated and delirious state with autonomic dysregulation. It manifests through sympathetic hyper-arousal with frequent hyperthermia, vital sign abnormalities, and metabolic acidosis. For some, the clinical syndrome progresses to death.

Altered mental status may be associated with a wide range of clinical signs and symptoms. The condition can range from coma to mild or profound confusion to uncontrolled agitation and delirium. A limited differential diagnosis of altered mental sta- tus is provided by the mnemonics AEIOU TIPS (**Ta- ble 3**), or SMASHED 2 (**Table 4**). Some etiologies may be suggested by clinical observation, obvious toxidromes, past medical history, patient age, or circumstances surrounding the acute event. Exten- sive testing and protracted evaluation and observa- tion are often required to fully unravel the etiology of the acutely altered sensorium. As such, lifesaving interventions should be initiated prior to obtaining a specific diagnosis.

## Table 3: AEIOU TIPS Mnemonic for Abbreviated Differential Diagnosis of Altered Mental Status

|  |  |
| --- | --- |
| **Letter** | **Description** |
| A | Alcohol |
| E | Endocrine, Encephalopathy, Electrolytes |
| I | Insulin (hypoglycemia) |
| O | Oxygen (hypoxia), Opiates (drugs of abuse) |
| U | Uremia |
|  |  |
| T | Toxins, Trauma, Temperature |
| I | Infection |
| P | Psychiatric, Porphyria |
| S | Stroke, Shock, Subarachnoid Hemorrhage,Space-Occupying CNS Lesion |

**Table 4: SMASHED 2 Mnemonic for Differential Diagnosis of Altered Mental Status**

|  |  |  |
| --- | --- | --- |
| **Letter** | **Title** | **Description** |
| **S** | **Substrates** | glucose (high/low), thia-mine deficiency |
|  | **Sepsis** |  |
| **M** | **Meningitis** | all CNS infections, AIDS dementia, encephalitis, brain abscess or toxop-lasmosis |
|  | **Mental illness** | acute psychosis, medica- tion noncompliance, ma- nia, depression, malin- gering, rage, suicide in-tent (via police) |
| **A** | **Alcohol** | Intoxication, withdrawal |
|  | **Accident** | head trauma, CVA, cere- bral contusion, subduralor epidural hematoma |
| **S** | **Seizing** | or postictal |
|  | **Stimulants, hallucinogens, anticholiner- gics** | Cocaine, amphetamines, caffeine, PCP, LSD, keta- mine, psilocybin, antihis- tamines, atropine, scopo-lamine, jimson weed |
| **H** | **Hyper** | hypertension, hyperthy- roidism, hypercarbia, hy-perthermia |
|  | **Hypo** | hypotension, hypothy- roidism, hypoxia, hypo-thermia |
| **E** | **Electrolytes** | hyper/hyponatremia,hypercalcemia |
|  | **Encephalopa- thy** | hepatic, HIV, uremic, hypertensive, lead, Reye's syndrome, CNStumor |
| **D** | **Drugs** | Intoxication or with-drawal |
|  | **Don't forget other drugs** | carbon monoxide, li- thium, steroids, salicy- lates, designer/street drugs, theophylline, MDMA, antipsychotics, toxins not on routinedrug screen, others |

Several specific entities which cause altered mental status and may mimic ExDS deserve specific men- tion:

* Diabetic hypoglycemic reactions have been asso- ciated with outbursts of violent behavior and an appearance of intoxication. Diagnosis may be rapid- ly and conclusively made by determination of blood glucose and response to glucose administration.
* Heat stroke may manifest as tactile hyperthermia, rhabdomyolysis, and delirium, and may be asso- ciated with neuroleptic use and mental illness. A profound acidosis is often not present.
* Serotonin syndrome and neuroleptic malignant syndrome (NMS) may share some clinical characte- ristics with ExDS. However, they usually do not share the aggressive violent behavior manifested by patients with ExDS.
* Psychiatric issues may mimic ExDS. Some patients experience behavioral disturbances directly due to psychotropic drug withdrawal or noncompliance. Substance abuse is also very common in psychiatric patients. Many psychiatric conditions themselves, including acute paranoid schizophrenia, bipolar dis- order, and even emotional rage from acute stressful social circumstances, may mimic an ExDS-like state. Untreated or poorly controlled psychiatric illness may also result in poor compliance with manage- ment of acute or chronic medical conditions. In *Phillips v Milwaukee*, a man who died in police cus- tody of apparent ExDS was found at autopsy to have untreated thyrotoxicosis, as well as being non- compliant with his psychiatric medications.

## Conditions that cause sudden death

Sudden unexpected death is the hallmark of fatal ExDS. The differential diagnosis for sudden death includes ischemic or drug induced sudden cardiac death, stress (Takotsubo) cardiomyopathy, inhe- rited or acquired Long QT Syndrome, Brugada syn- drome, and less common entities such as Cannon’s Voodoo Death, Lethal Catatonia, and sudden unex- plained death in epilepsy (SUDEP).

## Treatment and Protocols

In the absence of clearly stated case definitions and prospective clinical studies, treatment of ExDS re- mains largely speculative and consensus-driven, directed towards supportive care and reversal of obvious clinical and laboratory abnormalities. The specific circumstances under which medical inter- ventions will provide benefit are currently unclear. Nonetheless, there are current medical approaches that have consensus support. Most authorities, in- cluding this Task Force, posit the beneficial use of aggressive chemical sedation as first line interven- tion. As with any critically ill patient, treatment should proceed concurrently with evaluation for precipitating causes or additional pathology.

In subjects who do not respond to verbal calming and de-escalation techniques, control measures are a prerequisite for medical assessment and interven- tion. When necessary, this should be accomplished as rapidly and safely as possible. Recent research indicates that physical struggle is a much greater contributor to catecholamine surge and metabolic acidosis than other causes of exertion or noxious stimuli. Since these parameters are thought to con- tribute to poor outcomes in ExDS, the specific phys- ical control methods employed should optimally minimize the time spent struggling, while safely achieving physical control. The use of multiple per- sonnel with training in safe physical control meas- ures is encouraged.

After adequate physical control is achieved, medical assessment and treatment should be immediately initiated. Indeed, because death might occur sud- denly, EMS should ideally be present and prepared to resuscitate before definitive LEO control meas- ures are initiated.

Initial assessment should include assessment of vital signs, cardiac monitoring, IV access, glucose mea- surement, pulse oximetry and supplemental oxy- gen, and careful physical examination. While the need for LEO control measures may initially prec- lude some or all of these interventions, they should be performed as soon as safely possible.

Agitation, hyperthermia, and acidosis are all major components of ExDS which can be effectively ma- naged using traditional medical interventions. The approach to each of these components is described below.

### *Agitation*

LEO control measures should be rapidly supple- mented with sedation in the setting of acutely agi- tated, combative patients displaying signs of ExDS. While the intravenous (IV) route is preferred if available, intramuscular (IM) or intranasal (IN) transmucosal administration of sedative agents may be needed initially in order to facilitate IV place- ment. Commonly used agents and their doses are listed in **Table 5** and include benzodiazepines, anti- psychotics, and the dissociative agent ketamine. Suggested doses are based upon consensus opinion. The actual effective dose of all suggested medica- tions is unknown due to a paucity of research.

Because these agents have respiratory and cardi- ovascular effects, continuous monitoring of both should be performed as soon as feasible whenever parenteral sedation is administered. When appro- priate safety systems are in place, one should be aware of manufacturers suggested dosing recom- mendations for other uses, but be prepared to use clinically effective doses for the management of this condition.

## Table 5. Sedation Agents for ExDS–type symptoms

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Class** | **Agent (Trade Name)** | **Available Routes** | **Dosing (mg)\*** | **Onset (min)** | **Duration (min)** |
| Midazolam (Versed) | IN | 5 | 3-5 | 30-60 |
| IM | 5 | 10-15 | 120-360 |
| IV | 2 - 5 | 3-5 | 30-60 |
| Lorazepam (Ativan) | IM | 4 | 15-30 | 60-120 |
| IV | 2 - 4 | 2-5 | 60-120 |
| Diazepam (Valium) | IM | 10 | 15-30 | 15-60 |
| IV | 5 - 10 | 2-5 | 15-60 |
| †Haloperidol (Haldol) | IM | 10– 20 | 15 | 180-360 |
| ††IV | 5 – 10 | 10 | 180-360 |
| †Droperidol (Inapsine) | IM | 5 | 20 | 120-240 |
| IV | 2.5 | 10 | 120-240 |
| Ziprasidone(Geodon) | IM | 10– 20 | 10 | 240 |
| Olanzapine(Zyprexa) | IM | 10 | 15-30 | 24 hrs |
| Ketamine (Ketaset, Ketalar) | IM | 4-5mg/kg | 3-5 | 60-90 |
| IV | 2mg/kg) | 1 | 20-30 |

IN: Intranasal; IM: Intramuscular; IV: Intravenous

\* Typical adult dosing for severe agitation.

† The Food and Drug Administration has issued “Black Box” warnings regarding potential serious adverse effects (QT pro- longation and torsades de points) with these agents. Clinicians should use their clinical judgment regarding the risk / benefit ratio on a case by case basis.

†† Though widely used in clinical practice, Haloperidol is not FDA approved for intravenous administration.

(*For adequate control of ExDS, the above doses are conservative and describe a reasonable starting point. Clinical effect in ExDS may require doses greatly in excess of those for traditional med- ical use in other conditions*).

Benzodiazepines are familiar, commonly available sedative agents which can be administered by the IM or IV routes. Midazolam is also available and ra- pidly absorbed by the intranasal route, making it attractive for use in situations such as ExDS when rapid treatment is essential but IV access may not be available. Benzodiazepines are often preferred if

stimulant drug overdose is suspected. Potential dis- advantages include relatively slow onset and un- predictability of action if not given IV, the need for repeat doses in many cases to achieve adequate sedation, and the potential for respiratory suppres- sion. Often benzodiazepine doses many times the traditional suggested dose for sedation are re- quired, and there is likely no maximum dose limit for benzodiazepines when facilities for respiratory and blood pressure support are available.

Antipsychotic agents are commonly used for seda- tion of agitated psychiatric patients, and can be administered by the IV or IM route. There is some concern for potential rare cardiac conduction ef- fects such as QT prolongation with all of these agents, which may result in ventricular dysrhyth- mias such as torsades de pointes. These concerns, combined with a preexisting risk for sudden death among ExDS patients, official “black box” warnings from the FDA regarding QT prolongation with halo- peridol and droperidol, and a slower onset of action than benzodiazepines by the IV or IM route, have led some clinicians to avoid this class of agents in suspected ExDS. Others have noted the potential for anticholinergic effects producing hyperthermia, and a mechanism of action involving central neuro- transmitter systems (which may be markedly ab- normal in some patients presenting with ExDS) as reasons to consider other agents.

The dissociative agent ketamine can also be admi- nistered by the IV or IM route and appears advan- tageous due to very rapid onset (especially by the IM route when compared to other medications), and lack of significant respiratory and cardiovascu- lar effects. Case reports have indicated excellent results and safety when used in ExDS patients. Po- tential disadvantages include rare side effects such as increased oral secretions, laryngospasm, hyper- tension, and distress from emergence phenomena.

In some circumstances, sedation and paralysis with rapid sequence intubation and respiratory support may be necessary to control agitation in patients with ExDS. In these cases, standard techniques and medications may be utilized at the clinician’s discre- tion.

### *Hyperthermia*

Empiric treatment for hyperthermia may be in- itiated based on qualitative assessment (i.e. tactile hyperthermia) when needed, though core tempera- ture measurement is preferred when available and practical. Basic cooling methods include removal of clothing and placement in a cool environment. Ac- tive external cooling may be initiated, with misting of water on exposed skin, providing air flow to en- hance evaporative cooling, and placement of ice packs at the neck, axillae, and groin. Rapid cooling by infusion of cold saline IV has been shown to be effective in a number of other settings and can also be used. Care must be taken to avoid treatment “overshoot” leading to hypothermia.

Once the patient is stabilized in the ED or hospital setting, additional measures may be considered. In refractory or severe cases, immersion in cool water can rapidly reduce core body temperature, though this may present some difficulty with monitoring and treatment. A variety of external and internal temperature control devices are now available and may also be considered. If NMS or malignant hyper- thermia is suspected, dantrolene may be indicated.

### *Acidosis*

Metabolic acidosis and hypovolemia are thought to be common in ExDS. If suspected based on the clini- cal situation or physical exam, fluid resuscitation with intravenous fluids is prudent. In severe cases, sodium bicarbonate may be used either empirically or based on laboratory results revealing significant acidosis. Controversy exists regarding empiric use of sodium bicarbonate; the efficacy of supplemental sodium bicarbonate is unknown, and has not been supported as routine therapy for the metabolic aci- dosis of cardiac arrest. It is approved by some EMS agencies, but not by others (**Table 6**). Sodium bicar- bonate may be administered by bolus injections or as a continuous infusion. Hyperventilation is the body’s normal compensatory mechanism for cor- recting acidosis. Control measures that might inter- fere with ventilation should be avoided.

### *Other*

Other components of ExDS may include rhabdo- myolysis and hyperkalemia. Rhabdomyolysis is in- itially managed by fluid administration and urine alkalinization with sodium bicarbonate. These inter- ventions may have already been initiated empirical- ly for other components of ExDS before laboratory results allow confirmation of rhabdomyolysis. Hyperkalemia may also be treated with traditional ACLS interventions based on characteristic EKG changes and laboratory results.

Many EMS systems already have protocols in place that incorporate these recommendations, allowing treatment of the clinical signs and symptoms of ExDS in the prehospital setting. While some agen- cies have adopted specific ExDS protocols, others place the interventions within traditional headings such as agitation and hyperthermia. Several pre- hospital protocols are summarized in **Table 6**.

## Table 6. Sample EMS Protocols for ExDS symptoms

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **City,****State** | **Sedation** | **Fluids** | **Hyper-****thermia** | **Other** |
| Miami, | Midazolam | Normal | Cold | Sodium |
| FL | (Versed)5mg IN | Saline1 liter | (<60°F) IVfluid | Bicarb.1 amp (50 |
|  | [max 20mg] | bolus IV | Cold packs | mEq) per |
|  |  |  |  | liter of |
|  |  |  |  | Normal |
|  |  |  |  | Saline |
| Nash- | Midazolam | Normal | Evapora- |  |
| ville, | (Versed) | Saline | tive Cool- |
| TN | 2mg IV or5mg IM | @ 500cc/hr IV | ingCold packs |
|  | [may repeat] |  |  |
| Clark | Midazolam | Normal | Evapora- |  |
| County | (Versed) | Saline | tive Cool- |
| (Las Vegas),NV | 2mg IV or5mg IM / IN [may repeat] |  | ingCold packs |
| Colum- | Midazolam | Normal | Evapora- | Sodium |
| lum- | (Versed) | Saline | tive Cool- | Bicarb. |
| bus, OH | 2- 5mg IN,IV, pr[max 10 mg] | 500ccover 20min | ingCold packs | ½ amp (25mEq) perliter of |
|  |  |  |  | Normal |
|  |  |  |  | Saline |
| Min- | Ketamine | Normal | Evapora- | Sodium |
| neapo- | 5 mg/kg IM | Saline | tive Cool- | Bicarb. |
| lis, MN | or 2 mg/kgIV | up to 2liter | ingCold packs | 2 amps(100 mEq) |
|  |  | bolus IV |  | IV push |
| Roche- | Lorazepam | Normal | Evapora- | Sodium |
| ster, | (Ativan) | Saline | tive Cool- | Bicarbo- |
| MN | 1-4 mgIV/IM or |  | ingCold Packs | nate1mEq/kg |
|  | midazolam |  |  | IV push in |
|  | (Versed) |  |  | cardiac |
|  | 1-5 mg |  |  | arrest |
|  | IV/IM |  |  |  |

IV: Intravenous; IM: Intramuscular; IN: Intranasal; pr: per rec- tum; Normal Saline: 0.9% Sodium Chloride

# LIMITATIONS OF CURRENT KNOWLEDGE AND RECOMMENDATIONS FOR FUTURE RESEARCH

The primary issues surrounding identifying and studying ExDS and subsequent therapeutic inter- ventions are the lack of well-defined, consistent epidemiological case definition and overlap with other established diseases.

In those cases where a death occurs while in custo- dy, there is the additional difficulty of separating any potential contribution of control measures from the underlying pathology. For example, was death due to the police control tool, or to positional as- phyxia, or from ExDS, or from interplay of all these factors? Even in the situation where all caregivers agree that a patient is in an active delirious state, there is no proof of the most safe and effective con- trol measure or therapy for what is most likely an extremely agitated patient. However, the existence of multiple EMS protocols as well as expert consen- sus suggests that there are practical and agreed- upon methods of therapy that are believed to lower morbidity or mortality. Sedative or dissociative agents such as benzodiazepines, major tranquiliz- ers, and ketamine are suggested but there is no evi- dence yet to prove that these will result in a lower morbidity or mortality.

Future research should focus on several areas. An- imal models should be developed to begin to better understand the pathophysiology of ExDS.

In humans, a consistent case definition should be developed and applied in a large epidemiologic prospective study or from a national or internation- al database of all suspected cases, including those who survive. At a molecular level, and based upon post-mortem cocaine-associated ExDS brain tissue, a Genome Wide Association Scan may be per- formed to identify susceptibility genes.

Development of a national orphan case report regi- stry is recommended. This registry would be impor- tant in beginning to define the course of ExDS, and might eventually provide for earlier recognition of individuals at risk. It would also allow the scientific community to begin the process of identifying common characteristics on a large scale as well as comparing therapies. Without including suspected cases and survivors, no meaningful conclusions can be reached that would allow the development of case definitions, etiologies, and treatments.

Studies should address the role of law enforcement control techniques and devices in the death of sub-

jects with ExDS. Finally, research is needed to es- tablish field protocols and techniques that allow police, EMS and hospital personnel to interact with these agitated, aggressive patients in a manner safe both for the patients and the providers.

# SUMMARY

Based upon available evidence, it is the consensus of the Task Force that ExDS is a real syndrome of uncertain etiology. It is characterized by delirium, agitation, and hyperadrenergic autonomic dysfunc- tion, typically in the setting of acute on chronic drug abuse or serious mental illness.

Research suggests the pathophysiology may include genetic susceptibility and chronic stimulant-induced abnormalities of dopamine transporter pathways, along with elevation of heat shock proteins in fatal cases. There is insufficient data at this time to de- termine whether fatal ExDS is preventable, or whether there is a point of no return after which the patient will die regardless of advanced life sup- port interventions.

The risk of death is likely increased with physiologic stress. Attempts to minimize such stress are needed in the management of these patients. Ideally, any necessary law enforcement control measures

should be combined with immediate sedative medi- cal intervention to attempt to reduce the risk of death.

There are well-documented cases of ExDS deaths with minimal restraint such as handcuffs without ECD use. This underscores that this is a potentially fatal syndrome in and of itself, sometimes reversi- ble when expert medical treatment is immediately available.

For research and diagnostic purposes, thorough do- cumentation of the patient’s signs and symptoms along with appropriate testing should occur. This includes the presence of sweating or muscle rigidi- ty, temperature, pulse, respiratory rate, blood pres- sure, venous blood gases, urine and serum toxicolo- gy, thyroid functions, and blood and (if fatal) ana- tomic brain specimens for genetic, heat shock pro- teins, and neurochemical analyses.

The ante-mortem diagnosis in the prehospital or emergency department setting depends upon clini- cal characteristics and the exclusion of alternative disease processes. It is our consensus that rapid and appropriate but limited control measures, and im- mediate administration of IV benzodiazepines or ketamine, IM ketamine, or intranasal midazolam, can be lifesaving.

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