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Consensus Guideline for Care of Patients in the Prehospital and Aerospace Settings with Exposures to Hydrazine and Hydrazine Derivatives

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ABSTRACT

OBJECTIVES: Hydrazine (HZ) and Hydrazine Derivative (HZ-D) exposures pose health risks to people in industrial and aerospace settings. Several recent systematic reviews and case series have highlighted common clinical presentations and management strategies. Given the low frequency at which HZ and HZ-D exposures occur, a strong evidence base on which to develop an evidence-based guideline does not exist at this time. Therefore, the aim of this project is to establish a consensus guideline for prehospital care of patients with exposures to HZ and HZ-Ds.

METHODS: A modified Delphi technique was used to develop clinical questions, obtain expert panel opinions, develop initial patient care recommendations, and revise the draft into a final consensus guideline. First, individuals (Emergency Medical Services (EMS) physicians and hazardous materials technicians) with experience in management of HZ and HZ-Ds identified relevant clinical questions. An expert panel was then convened to make clinical recommendations. In the first round, the panel voted on clinical care recommendations. These recommendations were drafted into a guideline that expert panel members reviewed. After review, additional unanswered questions were discussed electronically by expert panel members, and electronic votes were cast. Ultimately, patient care recommendations were condensed into a concise, consensus guideline.

RESULTS: Eight clinical questions regarding treatment of patients with HZ and HZ-D exposures were identified. These questions were reviewed by the expert panel which included 2 representatives from: aerospace medicine, military medicine, EMS medicine, paramedicine, pharmacy, and toxicology. Draft patient care recommendations generated three additional questions which were discussed electronically and voted on. These recommendations were then

formatted into a guideline outlining recommendations for care prior to decontamination, during decontamination, and after decontamination.

CONCLUSIONS: The consensus guideline for clinical care of patients with exposure to HZ/HZ-Ds is as follows: Prior to decontamination, use appropriate personal protective equipment, and when necessary, support ventilation using a bag-valve-mask and administer midazolam intramuscularly for seizures. After decontamination, provide supplemental oxygen; consider selective advanced airway management when indicated; administer inhaled beta-agonists for wheezing; and, for seizures unresponsive to multiple doses of benzodiazepines that occur during pre-planned, high-hazard activities, such as spacecraft recovery, consider intravenous or intraosseous pyridoxine.

Keywords: hydrazine, guideline, prehospital, toxicity

INTRODUCTION

Hydrazine (HZ) and hydrazine derivatives (HZ-D) play an integral role in the aerospace industry. Chosen for their high energy yield and hypergolic properties, their utility spans a range of aerospace applications, including the propulsion of the F-16 aircraft's emergency power unit (EPUs) and the fueling of satellite and crew module thrusters for spaceflight orbital adjustments and attitude control (1-6). The use of HZ/HZ-Ds in pivotal space missions, such as the Apollo Lunar Module and Mars rovers, underscores their significance in the realm of space exploration (7,8).

In manned aerospace flight, HZ/HZ-Ds pose considerable safety challenges. Not only are they extremely flammable and explosive, but they also have significant potential toxicity and possible human carcinogenicity (9-11). Hydrazine is a colorless, oily liquid with an ammonia-like odor. The odor threshold is 3.0 - 4.0 ppm, far higher than the Permissible Exposure Limit (PEL) of 1 ppm, established by the United States (U.S.) Occupational Safety and Health Administration (OSHA) (12), the Immediately Dangerous to Life and Health (IDLH) concentration is 50 ppm. To ensure the safety of astronauts and recovery personnel, stringent safety and contingency protocols are essential. These include comprehensive environmental monitoring, the use of personal protective equipment (PPE), and thorough decontamination procedures (13). With the emergence of the commercial space sector, the use of HZ/HZ-Ds, and the need for Emergency Medical Services (EMS) clinicians to manage very rare, but also life-threatening illness after exposure to HZ/HZ-D, prehospital patient care guidelines are needed. Two recent systematic reviews and a reported large case series have highlighted both the toxicity observed after HZ or HZ-D exposure as well as hospital-based treatment recommendations (14-16). The aim of this

project is to summarize that evidence, and, when lacking, make consensus recommendations in a consensus guideline for the prehospital care of individuals with HZ/HZ-D exposures (Figure 1).

Exposure to HZ/HZ-Ds can lead to severe health complications. Symptoms of acute HZ/HZ-D toxicity are commonly grouped into four areas: skin and mucosal injury (including respiratory system injury), neurologic sequelae, hepatotoxicity, and hematotoxicity (14,15).

As strong bases, HZ/HZ-Ds can cause corrosive injury to the skin and act as an irritant aerosols or vapors. The most commonly reported symptoms occur when mucous membranes are exposed, and patients experience eye irritation, and upper airway burns. Common patient presentations include: conjunctival irritation, throat irritation, mucosal blistering, and epistaxis (14,17,18). Lower airway injury can also occur, with symptoms ranging from bronchospasm to pulmonary edema and pulmonary hemorrhage (19,20). Skin contact can lead to irritation, blistering, and chemical burns (20-22).

Despite skin and mucosal injury causing the majority of symptoms following HZ/HZ-D exposures, a significant focus of the care for patients with hydrazine exposure falls on the monitoring and treatment of neurologic complications. Neurologic symptoms in humans following HZ/HZ-D exposure have been reported to range from lethargy to acute agitation (23-25), while animals with extensive HZ/HZD exposure have been observed to have excitation and seizures (26,27). Somewhat uniquely, agitation and seizure in patients with HZ/HZ-D exposure are thought to be due to HZ/HZ-D interference with gamma-aminobutyric acid (GABA)

synthesis, a pyridoxine-dependent reaction (14,28). Therefore, some treatment guidelines recommend the administration of both benzodiazepines and pyridoxine in patients with neurologic symptoms following HZ/HZ-D exposure (14,28,29).

Hematotoxicity and hepatotoxicity are also concerns. Several hematologic dose-dependent changes are seen in animals, including methemoglobinemia (MtHb) and hemolytic anemia (14,30). Historically, some have suggested treating possible MtHb with methylene blue (14,30). However, the development of MtHb appears to be species-specific, and no clinically significant case of human MtHb has been described (17,31). Hepatotoxicity has been documented in humans following HZ/HZ-D exposure with the most common finding being mild transaminitis without clinical symptoms or identifiable/treatable prehospital conditions (18).

The existing literature leaves the treatment of patients with HZ/HZ-D exposure largely up to the expertise of aerospace medicine physicians, clinical toxicologists, and poison control centers (16). However, with the expansion of commercial space flight and military aircraft operating in civilian airspace, EMS physicians and specially trained paramedics need to be prepared to manage patients with HZ/HZ-D exposures.

METHODS

This prehospital consensus guideline was developed according to the Recommendations for Improving the Quality of Prehospital Evidence-Based Guidelines (32). First, relevant clinical questions were identified by experienced prehospital clinicians with both clinical and operational experience in the management of HZ/HZ-D exposure. Clinical questions were grouped, *a priori*,

into clinical care provided prior to decontamination (hot zone care), during decontamination (warm zone care), and after decontamination (cold zone care). Second, recent systematic reviews and published case series were used to answer clinical questions with supporting, peer-reviewed, clinical evidence. To identify any new evidence the search term “Hydrazine” and “Toxicity” were searched in PubMed from Jan 2023 forward, the time at which the most recent systematic review was published. Third, when strong supporting evidence was not available to answer clinical questions, a multidisciplinary panel of individuals with expertise on HZ/HZ-Ds was convened to review unanswered clinical questions and provide consensus recommendations on care.

Emergency Medical Services physicians were asked to review existing literature on both HZ/HZ-D exposures and related clinical conditions (airway management, seizure management, etc.). Based on that evidence, the group was asked to identify any clinical questions that could be answered using existing evidence-based guidelines (EBGs) or high-quality evidence. Finally, if unable to answer the clinical questions using existing evidence, the group referred the clinical questions to the multidisciplinary expert panel to make consensus recommendations using a communication technique known as the Delphi method. This is a structured communication technique to achieve a converged consensus among a panel of experts using iterative rounds of discussion and feedback. Recognizing the complexity of managing HZ/HZ-D exposures, the research team selected a diverse group of specialists to form the expert panel. This panel was composed of two professionals in each category: aerospace medicine, toxicology, EMS, military medical operations, and pharmacology, ensuring a comprehensive range of knowledge and experience. The inclusion of specialists from these fields was strategic, aiming to cover the

multifaceted aspects of HZ/HZ-D exposures, from their chemical properties and potential health impacts to logistical and practical challenges of emergency response in aerospace contexts.

To reach consensus, multidisciplinary panel members were asked to review the recent published literature on the care of patients with HZ or HZ-D exposures and consider relevant clinical questions. After reviewing the most current literature, a consensus panel meeting was held in which initial unanswered clinical questions were discussed and experts voted on the most appropriate clinical care recommendations. When consensus could not be reached, recommendations were made based on the opinion of the majority of participants and notation of the differing expert recommendations made on the final treatment protocol. To ensure all comments and considerations were captured and incorporated, the dialogue from these meetings were recorded and transcribed. This approach ensured that the context of expert insights was captured in full, allowing for an accurate representation of the discussions.

Following the initial consensus panel meeting, a draft guideline was created, and the revision phase was initiated. During the revision phase, panel members had the opportunity to review the guideline and suggest additional discuss areas that may have been missed. When unable to reach a clear consensus, a specific follow-up question was generated, and an electronic discussion occurred with a vote on recommendations. This revision cycle continued until all relevant clinical questions or controversies were answered.

RESULTS

Identification of clinical questions

Initially, the existing literature was reviewed by three EMS physicians (AH, AR, and SM), two HZ management experts (JD and MS), one paramedic (ML), and one toxicologist (FW). This "initial review group" identified eight primary clinical care questions (1-8 in Table 1) and four additional follow-up questions (5a, 6a, 7a, and 7b in Table 1). The initial review group evaluated these questions in the context of the most recent systematic reviews and case series to determine if the question was answered by the existing literature or if consensus panel members would need to review available evidence and vote on clinical care recommendations. Eleven of the 12 expert panel members were available to meet for the first expert panel session (one provided written responses prior to the meeting). Following that meeting a draft guideline was shared among expert panel members and three follow-up or clarifying questions were identified (2a, 3a and 6c). Those three questions were reviewed by panel members and votes collected with discussion facilitated electronically.

Expert panel assembly and demographics

The composition of the expert panel was identified *a priori* with twelve members. Expert panel members were identified by JG and FW based on their relevant experience and published work in this area. Panel members included: military aerospace medicine physicians (MT, HN), NASA aerospace medicine physicians (SG, RC), clinical toxicologists with expertise in hazardous materials management (FS, BW), pharmacists with experience in hazardous materials

management (CE, DH), EMS physicians with expertise in hazardous materials management and aerospace medicine (MK, RF), and hazardous materials response technicians (AY, JW).

Expert panel recommendations

Question 1: During the expert panel meeting, panel members unanimously agreed that HZ (anhydrous hydrazine) and HZ-Ds used as propellants produce similar toxicities and should be covered by these guidelines. Propellent HZ-Ds included in these guidelines are monomethylhydrazine [$N_2H_3(CH_3)$] and unsymmetrical dimethylhydrazine [$H_2NN(CH_3)_2$; UDMH], and any future HZ-D with similar properties.

Question 2: During the expert panel meeting, panel members unanimously agreed that intramuscular (IM) midazolam should be considered for patients with seizures in the hot zone when prolonged decontamination or extrication is likely.

Question 2.a: After review of draft patient care guidelines, it was unclear what the dosing frequency of midazolam should be. Therefore, follow-up question 2a was sent to panel members for review. Panel members recommended treatment of seizures be similar to prehospital treatment of other types of seizure. Given that clinical practice is largely based on evidence from the RAMPART study, and they voted eleven to one for the following care: in adults, an initial 10mg midazolam by the IM route. That dose should be repeated if the seizure continues for 5 minutes after the initial dose has been given. The one dissenting vote favored dosing of midazolam every 3-5 minutes rather than every 5 minutes.

Question 3: The panel recommended unanimously that: prior to decontamination or in the hot zone airway management should be limited to BVM airway management on room air until decontamination has been initiated. There is risk with both the use of oxygen and advanced airways in the hot zone. EMS clinicians should consider the risk of oxygen causing a fire or an explosive event and avoid taking oxygen into the hot or warm zones. After decontamination, in the cold zone EMS clinicians should consider advanced airway management.

Question 3a: After initial guideline review, a concern was raised that insertion of a supraglottic airway (SGA) could cause harm in a patient with thermal or caustic upper airway injuries. The expert panel agreed, ultimately voting seven to one (four abstaining) to avoid SGA placement.

The panel highlighted one specific exception for this recommendation: For providers trained in the placement of advanced airways while wearing PPE and responding to a scene in which they are either the only provider or extraction from the hot zone is prolonged, advanced airway management might be considered.

Question 4: Following HZ/HZ-D exposures, patients can develop bronchospasm. The expert panel unanimously recommended that inhaled beta-agonists (nebulized or by metered dose inhaler (MDI)) be used to treat irritant gas-related bronchospasm caused by HZ and HZ-D exposure.

Question 5: The expert panel unanimously recommended that the administration of dexamethasone should be deferred until the patient has arrived at the point of definitive care.

Question 6: The panel then addressed the administration of midazolam in the cold zone after decontamination. First addressing the question: In patients with continued seizure activity after an initial dose of 10 mg of IM Midazolam, should an Intravenous (IV) / intraosseous (IO) catheter be placed, and additional midazolam given IV/IO, or should midazolam continue to be given by the IM route? The panel voted unanimously to recommend that IV or IO access be obtained as soon as possible after decontamination. However, treatment of seizure occurring in the cold zone should not be delayed. Therefore, initial doses of midazolam should be given IM, and after IV or IO access is established, subsequent doses given IV or IO.

Question 6a: After reviewing the draft guideline, the expert panel considered the dosing of midazolam when given IV or IO in the cold zone. All panel members voted electronically to recommend that treatment for seizures in the cold zone initially follow existing EBG recommendations for the care of adults with seizures in the prehospital setting, using midazolam 10 mg IM or 5mg IV/IO in adult patients, repeating every 5 minutes as in other published EBGs.

Question 7: The panel recommends that for patients with seizure, refractory to benzodiazepines after HZ or HZ-D exposure, 5g of pyridoxine should be given over 5 minutes. It should be noted that in many scenarios it is not practical or possible to make pyridoxine available in the prehospital setting due to the large dose of pyridoxine required and need to carry multiple vials. However, when possible (during pre-planned, high-hazard activities), this medication should be used. Otherwise, administration of pyridoxine can be delayed until arrival at the hospital.

Question 7a & 7b: In summary, 11 panel members voted to recommend that, when available, 5 g of pyridoxine should be administered for benzodiazepine-refractory seizures in adults. Benzodiazepine refractory seizures were defined as seizures that continue after two doses of midazolam. Because of the very large dose of pyridoxine required, providers should start preparing the medication after the first dose of midazolam is administered and give the pyridoxine after the second dose of midazolam has been administered. The recommended rate of pyridoxine administration is 5g over 5 minutes, i.e. at a maximum rate of 1g/minute. There was one dissenting vote who favored pyridoxine administration but recommended holding off on administration until after arrival at the hospital and consultation with a toxicologist.

Question 7.c: During the initial panel meeting, the group unanimously supported an initial dose of pyridoxine at 70 mg/kg, with a maximum dose of 5g administered at a rate of 1g/minute. In review of the draft guideline, an alternative dosing strategy was proposed of 4g IV followed by 1g every 30 minutes after the initial dose until the seizure stops. This alternative dosing was discussed, and ultimately the panel voted 7:3 with one abstention to recommend 5g IV administered at a rate of 1g per minute.

Question 8: The panel unanimously voted that, although exposure to HZ and HZ-Ds carries the theoretical risk of MtHb, there is no human data to suggest this risk is substantial and therefore recommends against including methylene blue in these treatment guidelines.

Guideline development and revision:

Recommendations of the expert panel were condensed into an operationally friendly (brief) consensus guideline. That guideline was reviewed by all panel members and feedback incorporated. The final guideline is illustrated in Figure 1.

DISCUSSION:

Question 1: Should EMS guidelines focus solely on HZ exposure, or is it clinically relevant to expand the scope to cover treatment for exposure to HZ-Ds, such as methylhydrazine?

Discussion on question one centered on the published evidence that HZ and HZ-Ds are widely used as propellants and, when used as propellants, have similar properties. For example, HZ is currently used in operations on spacecraft, while HZ hydrate is used for the F-16's Emergency Power Unit. Hydrazine and HZ-Ds are also found naturally in tobacco and mushrooms that contain monomethylhydrazine (33,34). Isoniazid is an antitubercular medication that is a hydrazide that can be synthesized from hydrazine hydrate. These orally ingested HZ and HZ-Ds have similar mechanisms of toxicity but different clinical presentations, as exposure does not include potential inhalation, thermal, and dermal routes and associated symptoms. Ultimately, the panel felt that it would serve civilian responders to have one broad guideline to address propellent-based HZ and HZ-Ds exposure, rather than creating multiple sets of guidelines to address subtle differences.

Question 2: Prior to decontamination, should IM midazolam be administered to a patient exposed to HZ or HZ-Ds and seizing? Discussion regarding if midazolam should be given for seizure in the hot zone centered on the likelihood of seizures after exposure to high concentrations of HZ/HZ-D and limitations to patient care while wearing PPE in the hot and warm zones. Although rare, exposures to HZ.HZ-Ds is associated with seizures in humans case reports (16). Management of seizure using both benzodiazepines and phenobarbital has been well described in the literature for seizures associated with hydrazine and its derivatives. Operational considerations, such as the inability to establish an IV in the hot and warm zones, limit the use of

medications to those that can be given IM. Therefore, from a practical standpoint, midazolam was the preferred medication to manage seizures.

One significant limitation noted by the panel was that midazolam commonly comes in very small vials containing a small volume, making drawing up medication while wearing PPE difficult. Currently, there are no autoinjectors available for midazolam. Therefore, the panel recommends that a preloaded midazolam syringe with 10 mg in each syringe be brought into the hot zone if significant exposures are anticipated.

Question 2.a: Clarifying question added after draft guideline review: If midazolam is administered after HZ or HZ-Ds exposure, should RAMPART midazolam dosing and frequency be followed? Discussion around the dose of midazolam to be administered highlighted the observation that exact interval for doses of benzodiazepines has not been well described. The Neurological Critical Care Society suggests an interval of 3–5 minutes between doses for the management of emergency status epilepticus (35). However, the onset of midazolam can be 15 minutes in an adult patient. The expert panel discussed increasing the time interval to 10–15 minutes between doses due to concerns about respiratory depression. However, the RAMPART trial found that the mean time to seizure resolution after medication administration was 3.3 minutes (36). While EBGs for the care of patients with seizure recommend re-dosing at an interval of 5 minutes (37,38). Since existing EBG for the care of patients with seizures contain a dosing interval of every 5 minutes, this same dosing interval was recommended for inclusion in this guideline.

Question 3: Considering the constraints of responders' PPE and the complexities of decontamination, should airway management for an apneic patient be confined to bag-valve-mask ventilation using room air, postponing more advanced procedures until the patient is decontaminated and in a controlled environment? The panel first addressed airway management in the hot zone and subsequently in question 3a in the cold zone. Panel discussion on airway management in the hot zone centered around when and where to preform airway interventions (endotracheal intubation (ETI), SGA, or cricothyrotomy). Panel members highlighted the need to balance the difficulty of preforming airway management skills while in PPE, and the risk of contamination with the risk of apnea and difficulty in managing the airway using only a BVM until the patient is decontaminated and is in a controlled environment.

During the initial panel meeting, panel members highlighted the benefit of a definitive airway in providing ventilation through the decontamination process. However, that benefit was offset by the possibility of advanced airway contamination and airway injury. This risk, in combination with the need to preform rapid extrication from the hot zone decreasing the concentration-time product were key topics in discussions. Ultimately, the panel voted to recommend ventilation using a BVM only in the hot zone, acknowledging that in some situations, extrication from the hot zone may be prolonged, and when trained to preform airway management in PPE, using an endotracheal tube (ETT) or cricothyrotomy may be considered.

Question 3a: Clarifying question added after draft EBG review, considering the risk of chemical airway injury / burns should advanced airway management be limited to ETI or cricothyrotomy,

to avoid converting a partially obstructed airway to a completely obstructed airway with a SGA device? Addressing airway management after decontamination the panel members raised the concern of airway injury after HZ/HZ-D exposures. In such patient's insertion of a SGA may cause further airway damage. The panel ultimately voted to avoid insertion of a SGA in these patients, as evaluation of the upper airway for chemical burns prior to SGA insertion is likely impractical in the field.

Question 4: Should nebulized beta-agonist be used to treat irritant gas related bronchospasm caused by HZ or HZ-D exposures? HZ and HZ-Ds are irritants and can act as irritant gases when inhaled. Irritant gases are well described to cause bronchospasm that than bronchospasm, which can improve when treated with inhaled beta-agonists. The expert panel noted that in the field, beta-agonists are primarily driven with oxygen rather than air; therefore, unless the patient can use a multidose inhaler (MDI), administration of inhaled beta-agonist should be limited to after patient decontamination in the cold zone to limit the risk of explosion or fire.

Question 5: In addressing complications such as upper airway burns or bronchospasm seen in HZ or HZ-D exposures, should dexamethasone or other steroids be administered to potentially mitigate inflammation and improve airway patency? Panel discussion centered around the lack of data to suggest that use of dexamethasone is beneficial in chemical burns of the airway or chemical pneumonitis (14). There are conflicting case reports, some of which suggest superimposed bacterial infections occur after steroid use for chemical pneumonitis, while other case studies suggest glucocorticoids are beneficial in chemical pneumonitis (16,25). Additionally, dexamethasone administration is not a time-critical intervention. Most steroids,

including dexamethasone, require approximately 12–24 hours for peak effect. Therefore, administration of this medication can wait until the patient arrives at the point of definitive care.

Question 6 & 6a: In patients with continued seizure activity after an initial dose of 10 mg of IM Midazolam, should an IV/IO be placed, and additional midazolam given IV/IO, or should midazolam continue to be given by the IM route? If additional doses of midazolam are to be given by the IV or IO route at what dose and what dosing interval for continued seizing after exposure to HZ or HZ-Ds? In question 6 the panel addressed how seizures should be managed after decontamination, assuming an initial dose of IM midazolam has been administered and a patient continued to seize. The expert panel felt strongly that an IV or IO should be placed as quickly as possible after decontamination. However, given that decontamination would likely take some time, administration of midazolam should not be delayed for IV / IO access and the initial dose(s) given by the IM route prior to IV / IO access. The panel did not initially consider how much midazolam to administer after decontamination. After a brief online discussion, the panel agreed unanimously that initial seizure management in the field should follow EBG recommendations for the care of adults with seizures. This includes administration of 10 mg of midazolam IM followed by IV or IO placement and administration of subsequent midazolam doses at 5 mg IV /IO every 5 minutes until seizure activity stops.

Question 7, 7a, & 7b: Should intravenous pyridoxine be administered in cases where patients present with seizures that are unresponsive to benzodiazepine treatment? If so, at what interval after administration of a benzodiazepine should pyridoxine be administered? If so, what dose of pyridoxine should be administered and at what rate or intervals? Panel discussion surrounding

the administration of pyridoxine centered around evidence suggesting that pyridoxine may be beneficial in patients with seizure after HZ and HZ-D exposures when seizures are refractory to benzodiazepines. The panel acknowledged the limited and contradictory data (23,39-41). Ultimately, the majority (11:1) of panel members felt that the potential benefit (seizure cessation and decreased neurologic sequelae) outweighed the risk (peripheral neuropathy). The dissenting vote cited the low frequency of seizure in patients following HZ/HZ-D exposures and the lack of definitive evidence that pyridoxine improves seizures as reasons not to include administration of the medication in the guideline.

Additionally, the panel highlighted some operational reasons pyridoxine is not an ideal medication for prehospital administration. Primarily, multiple vials of pyridoxine must be used for a single dose. Indeed, an initial 5g dose may require the administration of 50 vials of pyridoxine. Even if providers were able to draw this medication up very quickly (10s per vial), preparing a single dose would take over 8 minutes. In addition to the time limitations, in the prehospital setting, space limitations may also preclude the ability to carry this quantity of medication. Therefore, the panel modified its recommendation to give pyridoxine in situations in which there is a planned response for a situation in which HZ/HZ-D exposures are a known risk, such as a planned spacecraft landing or at flight shows or exhibits in which aircraft with HZ or HZ-D will be present.

Discussion surrounding when to administer pyridoxine focused on the need to ensure patients with seizures have received benzodiazepine treatment prior to pyridoxine, the need to establish an IV prior to pyridoxine administration, and the time needed to draw up 50 vials of pyridoxine.

Given the above limitations, the panel unanimously agreed that pyridoxine should not be given until two doses of midazolam have been administered, separated by 5 minutes with the patient continuing to seize thereafter. This was defined as a "benzodiazepine-refractory seizure."

Question 7c: Two dosing strategies for pyridoxine have been identified: A) 5g, administered at a rate of 0.5 - 1.0 g/minute. B) 4g IV at a rate of 0.5 – 1.0 g/minute, then 1g IM every 30 minutes as needed at a rate of 0.5 – 1.0 g/minute. As outlined above, during the initial panel meeting, the group unanimously supported an initial dose of pyridoxine at 70 mg/kg, with a maximum dose of 5g administered at a rate of 1g/minute (42). An alternative dosing strategy of 4g IV followed by 1g every 30 minutes after the initial dose until seizure stops was later proposed (23). Electronic discussion surrounding pyridoxine dosing centered on the low risk of patients developing peripheral neuropathy at a pyridoxine dose of 5g (24) and the difficulty of carrying, drawing up, and administering additional doses of pyridoxine during EMS transport. Ultimately, the panel voted to recommend 5g IV administered at a rate of 1g per minute.

Question 8: Should methylene blue be considered as a treatment option for the possibility of MtHb in the context of HZ or HZ-D exposures? There is a theoretical risk of MtHb following exposure to HZ and HZ-Ds (15). However, there are no human cases of MtHb following HZ, HZ-Ds, or isoniazid exposures. Additionally, HZ and HZ-D are reducing agents, which makes methylene blue unlikely to be necessary. In contrast, studies by the U.S. Department of Defense on in vitro human red blood cells exposed to HZ-D for a period of 4 hours produced greater than 30% methemoglobin (26). However, it is unlikely that an inhalation exposure would yield a blood concentration high enough to pass this threshold. There does not appear to be clear

biochemical basis or sufficient case literature to support recommending the administration of methylene blue to address theoretical HZ or HZ-D induction of MtHb. The panel did note that rocket fuel may be paired with nitrogen tetroxide or nitrogen dioxide, or other strong oxidizers. These agents may pose methemoglobin risks. However, this panel is only addressing the potential of MtHb in the setting of HZ or HZ-D exposures.

Finally, dissemination of this guideline will be important. Just in time access to recommendations included here might be helpful for NASA, DOD, and civilian stakeholders who work in areas where HZ and HZ-Ds might be encountered. Potential methods of dissemination include incorporation in future revisions of the Emergency Response Guidebook (ERG), Chemical Hazards Emergency Medical Management (CHEMM), Wireless Information System for Emergency Responders (WISER), etc. as well as into instructional resources for hazardous materials response teams.

LIMITATIONS

There are several limitations that should be considered in the development of this guideline. First, there have been no published clinical trials or other evidence outside of case reports and animal studies on which to base these clinical recommendations. Similar to many rare hazardous materials exposure incidents, prehospital systems must be prepared to care for individuals with rare chemical exposures and provide care based on limited evidence. The goal of this consensus guideline was to provide those recommendations for prehospital systems who are called to respond with little or no warning. Second, HZ and HZ-D exposures are rare events, and the operational environments in which HZ/HZ-D exposures occur are unique. Some of these unique

environments include combat zones and other scenarios in which specially trained responders may be forced to provide care in the hot zone for a prolonged period. This guideline is not intended for use under those unique circumstances. Finally, this guideline is intended to serve as a reference for EMS system leaders who plan for events with a potential risk of HZ/HZ-D exposures or EMS clinicians who are responding to a known HZ/HZ-D incident. In many scenarios, responders will not initially know they are providing care for a patient exposed to HZ/HZ-D. In that case, supportive care that follows established guidelines for managing respiratory distress and seizures will suffice, in addition to early consultation with the local poison control center.

CONCLUSIONS

The consensus guidelines for clinical care of patients with exposure to HZ/HZ-Ds are as follows: Prior to decontamination, use appropriate PPE, and when necessary, support ventilation using a BVM and administer midazolam, 10 mg IM for seizures. After decontamination, provide supplemental oxygen; consider selective advanced airway management when needed; administer inhaled beta-agonists for wheezing; and, for seizures unresponsive to multiple doses of benzodiazepines that occur during pre-planned, high-hazard activities, such as spacecraft recovery, consider 5 g intravenous or intraosseous pyridoxine.

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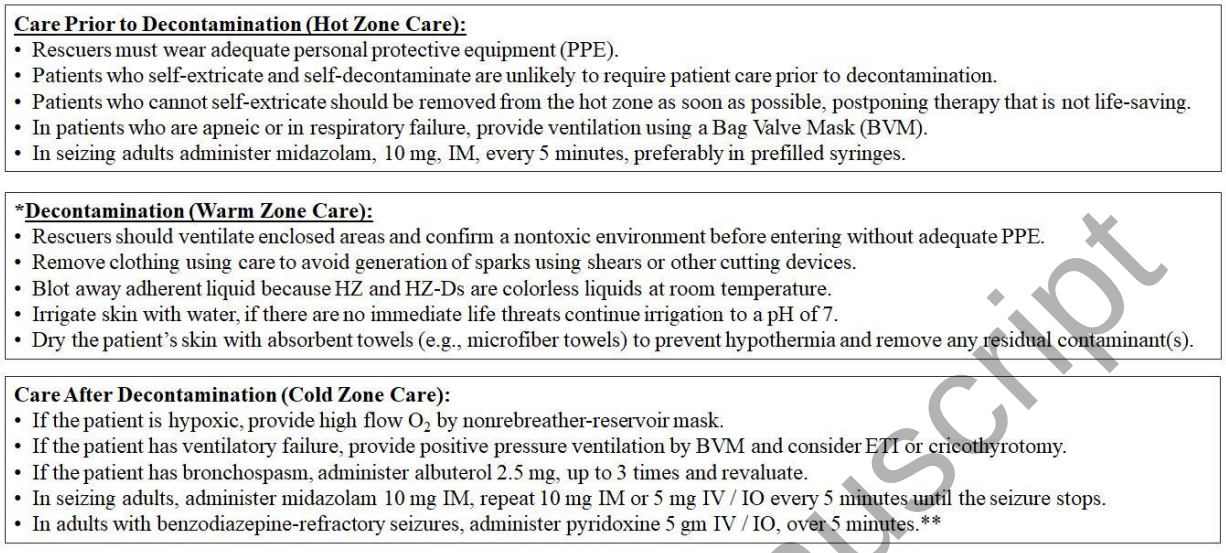
Figure 1: Consensus Guidelines for the Prehospital Care of Patients with Hydrazine (HZ) or Hydrazine Derivative (HZ-D) Exposures



*Recommendations on decontamination procedures are outside of the scope of this project.

** Due to the large dose of pyridoxine required and need to carry multiple vials, this medication should only be used in the prehospital setting during pre-planned, high-hazard activities. Otherwise, administration of pyridoxine can be delayed until arrival at the hospital.

Table 1: Clinical questions regarding care of patients with exposures to hydrazine (HZ) or hydrazine derivatives (HZ-Ds).

	Location of Care	Question	Existing Evidence	Pannel Vote
1	General Care	Should EMS guidelines focus solely on anhydrous hydrazine (HZ) exposure, or is it clinically relevant to expand the scope to cover treatment for exposure to hydrazine derivatives (HZ-Ds), such as methylhydrazine?	None	12 votes in favor of both HZ & HZ-Ds
2	Prior to Decontamination	Prior to decontamination, should intramuscular (IM) midazolam be administered to a patient exposed to HZ or HZ-Ds and seizing?	None	12 votes affirmative
2.a	Prior to Decontamination	Clarifying question added after draft EBG review: If midazolam is administered after HZ or HZ-Ds exposure, should RAMPART midazolam dosing and frequency be followed?	Limited	11 votes affirmative, 1 vote opposed.
3	Prior to Decontamination	Considering the constraints of responders' PPE and the complexities of decontamination, should airway management for an apneic patient be confined to bag-valve-mask ventilation using room air, postponing more advanced procedures until the patient is decontaminated and in a controlled environment?	None	12 votes affirmative, with conditions
3a	After Decontamination in the Field	Clarifying question added after draft EBG review: Considering the risk of chemical airway injury / burns should advanced airway management be limited to endotracheal intubation (ETI) or cricothyrotomy, to avoid converting a partially obstructed airway to a completely obstructed airway with a supraglottic airway (SGA) device?	None	7 votes to limited use of SGAs with cautions, 1 vote to include SGAs, 4 abstained
4	After Decontamination in the Field	Should nebulized beta-agonist be used to treat irritant gas related bronchospasm caused by HZ or HZ-D exposures?	None	12 votes affirmative
5	After Decontamination in the Field	In addressing complications such as upper airway burns or bronchospasm seen in HZ or HZ-D exposures, should dexamethasone or other steroids be administered to potentially mitigate inflammation and	None	12 votes opposed

		improve airway patency?		
6	After Decontamination in the Field	In patients with continued seizure activity after an initial dose of 10 mg of IM Midazolam, should an IV/IO be placed, and additional midazolam given IV/IO, or should midazolam continue to be given by the IM route?	Yes	12 votes affirmative
6.a	After Decontamination, in the Field	If additional doses of midazolam are to be given by the IV or IO route at what dose and what dosing interval for continued seizing after exposure to HZ or HZ-Ds?	Weak Evidence	12 votes for 5mg midazolam IV or IO every 5 minutes
7	After Decontamination in the Field	Should intravenous pyridoxine be administered in cases where patients present with seizures that are unresponsive to benzodiazepine treatment?	None	11 votes affirmative, 1 opposed
7.a	After Decontamination in the Field	If so, at what interval after administration of a benzodiazepine should pyridoxine be administered?	None	11 votes for after 2nd dose of midazolam, 1 abstention
7.b	After Decontamination in the field	If so, what dose of pyridoxine should be administered and at what rate or intervals?	None	12 votes for 5g over 5 minutes
7.c	After Decontamination in the field	Clarifying question added after draft EBG review: Two dosing strategies for pyridoxine have been identified: A) 5 grams, administered at a rate of 0.5 – 1.0 gm / minute. B) 4 g IV at a rate of 0.5 – 1.0 gm / minute, then 1 g IM every 30 min as needed at a rate of 0.5 – 1.0 gm / minute. Which dosing strategy should be used in the prehospital setting?	None	7 votes for 5gm dose, 3 votes for 4g dose, 1 abstained
8	After Decontamination in the field	Should methylene blue be considered as a treatment option for the possibility of methemoglobinemia in the context of HZ or HZ-D exposures?	None	12 votes opposed