REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Toxidrome Recognition in Chemical-Weapons Attacks

Gregory R. Ciottone, M.D.

From Beth Israel Deaconess Medical Center, Harvard Medical School, Boston. Address reprint requests to Dr. Ciottone at Beth Israel Deaconess Medical Center, Dept. of Emergency Medicine, Rosenberg Building, 1 Deaconess Rd., Boston, MA 02215, or at gciotton@bidmc.harvard.edu.

N Engl J Med 2018;378:1611-20.
DOI: 10.1056/NEJMra1705224

Terrorist attacks are increasing in both frequency and complexity around the world. In 2016 alone, there were more than 13,400 terrorist attacks globally, killing more than 34,000 people.[1] Of equal concern, chemical-warfare agents that were developed for the battlefield are being used on civilians in major cities and conflict zones. The recent sarin attacks in Syria,[2,3] the latest in a series of chemical attacks in that region,[3,4] along with the use of the nerve agent VX in the assassination of Kim Jong-nam in Malaysia and the Soviet-era agent Novichok in the poisoning of Sergei Skripal in the United Kingdom,[5] all represent a worrisome trend in the use of deadly chemical agents by various rogue groups in civilian settings. In light of the rise in coordinated, multimodal terrorist attacks in Western urban centers,[6,7] concern has been expressed about an increase in the use of chemical agents by terrorists on civilian targets around the world. Such attacks entail unique issues in on-the-scene safety[8,9] and also require a rapid medical response.[10] As health care providers, we must be proactive in how we prepare for and respond to this new threat.

This article reviews the toxidromes (constellations of signs and symptoms that are characteristic of a given class of agents) for known and suspected chemical-warfare agents that have properties that are well suited for terrorist attacks — namely, high volatility and rapid onset of incapacitating or lethal effects.[11] Poison-control procedures currently use toxidromes to identify specific classes of agents. Although symptoms such as eye irritation and coughing are common to a number of classes, specific clinical findings, including fasciculations, hypersecretions, early seizure, and miosis or mydriasis, can be rapidly identified as part of an acute-phase triage system and used to differentiate among classes of agents. This should lead to reduced morbidity and mortality while also decreasing the risk to responding health care workers.[12] The combined group of chemical-warfare agents examined here includes nerve agents, asphyxiants (blood agents), opioid agents, anesthetic agents, anticholinergic (antimuscarinic) agents, botulinum toxin, pulmonary agents, caustic agents (acids), riot-control agents, T-2 toxin, and vesicants (Table 1).

HISTORY

Chemical warfare is not new. As early as 10,000 B.C., rival tribes used various poisons derived from plants and animals to coat their spear tips before battle.[13] The modern world witnessed the first large-scale use of chemical weapons on the battlefields of World War I, where chlorine,[14] phosgene,[15,16] and sulfur mustard[17,18] were deployed, with devastating effects.[19] During World War II, the Nazi regime developed new and much more lethal nerve agents, such as sarin,[20] tabun,[21] and soman,[22] though they were never deployed on the battlefield against the Allied

Table 1. Classes of Chemical-Warfare Agents (CWAs) Likely to Be Used in a Civilian Attack.

Class	Representative Agents	Last Known Use or Attempted Use as a CWA*
Nerve agents (cholinesterase inhibitors)	G-series (sarin, soman, cyclosarin, tabun), V-series (VE, VG, VM, VX), organophosphates	Syria, 2017: sarin; Malaysia, 2017: VX
Asphyxiants (blood agents)	Hydrogen cyanide, cyanogen chloride	New York City subway, 2003: cyanide
Opioid agents	Fentanyl, carfentanil, remifentanil	Moscow theater, 2002: fentanyl or carfentanil (used to subdue terrorists)
Anesthetic agents	Chloroform, halothane, nitrous oxide	No known use as CWA
Anticholinergic (antimuscarinic) agents	3-Quinuclidinyl benzilate (BZ), Agent 15 (chemically the same as or related to BZ), atropine	Syria, 2012: Agent 15
Vesicant agents	Mustards (nitrogen and sulfur), lewisite, phosgene oxime	Syria and Iraq, 2016: mustard gas
Caustic agents (acids)	Hydrochloric acid, hydrofluoric acid, sulfuric acid	London, 2017: sulfuric acid
Riot-control agents	Chloroacetophenone (CN), chlorobenzylidenemalononitrile (CS), bromobenzylcyanide (CA)	Falkland Islands, 1982: "tear gas" used on British troops
Trichothecene mycotoxins	T-2 toxin	Possible use in Vietnam War, 1970: T-2
Pulmonary agents	Chlorine, phosgene, diphosgene	Syria, 2017: chlorine
Botulinum toxin	Botulinum toxin	Tokyo, 1995: botulinum toxin used by Aum Shinrikyo

* Information on previous use of CWAs is from the Global Terrorism Database, University of Maryland,[1] and other sources.[3,9,10]

troops.[23,24] The Nazis did, however, combine hydrogen cyanide with an absorbent to form Zyklon B, which was then used to kill millions of people in gas chambers.[25] Chemical weapons have also been used in the Iran–Iraq war and present-day Syria.[26-28] As a response to the development and use of such agents, the Chemical Weapons Convention, essentially an arms-control agreement put into effect on April 29, 1997, prohibits the development, stockpiling, transfer, and use of chemical weapons by state entities.[29]

Late in the 20th century, terrorist groups began to obtain chemical-warfare agents and use them on civilian targets. The most extensively documented case was the use of sarin in the subways of Tokyo by the Aum Shinrikyo group in 1995.[30,31] During the same period, a number of countries clandestinely developed more advanced and more lethal chemical weapons that were safer to handle and transport yet harder to detect.[32,33] Such agents include binary agents and lesser known, nontraditional agents. Binary formulations are two chemically stable and nonlethal precursors that are safe to carry separately; however, when combined, they become a lethal chemical agent. VX is an example of a chemical-warfare agent that has two nontoxic binary precursors, and there has been some speculation that the assassination of Kim Jong-nam may have involved the application of two such binary agents.[5] Nontraditional agents such as Novichok are next-generation chemical compounds with varying effects, levels of detection, and mechanisms of action. These newly developed chemicals are considered classified by the United States, so little is known about them outside of the government.

AGENTS OF CONCERN

Chemical weapons vary in their onset of action, toxicity, and symptomatology.[34-36] The characteristics most suitable for use in a terrorist attack include high volatility, fast and effective absorption through the respiratory tract or skin, and rapid onset of lethal or incapacitating effects.[37] Some toxins (i.e., poisons produced by living organisms) can behave like chemical weapons.

In World War II, botulinum toxin was produced and used by the Japanese; after the war, it was produced by some other countries, which maintained large stockpiles.[38] The two lethal toxins included in this review, botulinum toxin and T-2 toxin (a trichothecene mycotoxin), can be absorbed through the respiratory system or skin and are relatively fast-acting.[38,39]

The effects of nerve agents such as sarin and VX, asphyxiants such as cyanide, and opioids such as fentanyl and carfentanil, can be countered by the emergency administration of specific antidotes. Nerve agents inhibit cholinesterase at the synapse, leading to a build-up of acetylcholine and requiring atropine and pralidoxime as antidotes. Asphyxiants block cellular respiration, requiring urgent administration of hydroxocobalamin or sodium thiosulfate and sodium nitrite as antidotes, and opioids cause respiratory depression, requiring rapid administration of naloxone. All other agents are incapacitating and potentially lethal but have no specific lifesaving antidote, therefore requiring urgent decontamination and supportive care initially. Anesthetic agents may cause sedation and bradypnea, whereas pulmonary agents cause eye and throat irritation, coughing, chest pain, and shortness of breath. Riot-control agents and caustic agents cause eye and skin irritation, as do vesicants (which also cause skin burns and blistering) and T-2 toxin (which may also cause dyspnea and vomiting). Finally, anticholinergic agents cause confusion, mydriasis, and dry mouth and skin, whereas botulinum toxin causes diplopia and descending paralysis.

In the event of an attack, the classes of chemical-warfare agents that are most rapidly lethal (i.e., nerve and opioid agents and asphyxiants), but not necessarily the agents themselves, should be quickly identified with the use of a toxidrome-based system of rapid triage.[10] It is important to understand, however, that any victim may need emergency treatment at any time, and such care should be rendered as required. It must also be understood that in the case of exposure to a rapidly toxic agent, immediate on-the-scene cleansing of contaminated areas of the body (referred to as spot decontamination) may be part of lifesaving treatment, since it removes the offending agent and rescues the victim and caregiver from ongoing exposure.[20] Decontamination is a medical countermeasure that mitigates the conversion of an external dose to an internal dose.

THE PROBLEM

Chemical-weapons attacks occur without warning and create chaotic scenes, resulting in confusion on the part of emergency medical responders and hospital-based personnel, most of whom are unprepared[40,41] and have very little training in the recognition of a chemical attack[42] or in the donning and doffing of personal protective equipment.[43,44] In addition, the initial scene of a chemical attack may look very similar to other incidents involving mass casualties, particularly if release of the agent is combined with use of conventional weapons as part of a multimodal attack. The chaos of the early phase of such an event may lead to further delay in identifying the chemical agent, placing responders at risk while also delaying potentially lifesaving treatment for the victims. An understanding of the patterns of signs and symptoms (toxidromes) that characterize the classes of known agents, as well as familiarity with the patterns of injuries caused by conventional weapons, are required for a quick assessment of victims of both types of attack, leading to an efficient and safe response.[45,46] Nerve agents, opioid agents, and asphyxiants are lethal if the victims are not treated with antidotes quickly,[47] either in conjunction with or before spot decontamination.[48,49] In addition, most chemical-warfare agents pose a substantial risk for responding personnel, either through direct exposure to the agent or through secondary exposure to off-gassing (evaporation of the agent from a contaminated victim).[9,50,51] Without quick identification of the class of offending agent, it is not possible to administer appropriate antidotes and other treatment measures[52] or use the correct personal protective equipment.[53] Because classes of chemical agents have different clinical presentations, a comprehensive understanding of the toxidrome for each class of agent is imperative (Table 2).[54]

THE NEED

Mass-casualty triage systems in use around the world today are designed primarily to differenti-

Table 2. Class-Specific Toxidromes of Chemical-Warfare Agents.

Class	Initial Toxidromes in Order of Onset*			Subsequent Signs and Symptoms
	Primary	Secondary	Tertiary	
Nerve agents	Mental-status changes, fasciculations, muscle weakness, paralysis	Increased secretions, miosis	Shallow breaths	Convulsions, coma, respiratory arrest
Asphyxiants (metabolic poisons, including cyanide and other "knockdown" agents)†	Respiratory distress (including initial gasping)	Seizures	Coma	Cardiopulmonary arrest
Opioids	Confusion, miosis	Depression of respiratory depth and rate (bradypnea), sedation, apnea	Coma	Respiratory arrest, bradycardia, hypotension
Anesthetic agents	Confusion	Bradypnea	Sedation	Coma, respiratory arrest
Anticholinergic (antimuscarinic) agents	Confusion, disorientation, delusions, hallucinations, confabulation, phantom behaviors	Mydriasis	Fever, dry skin	Lethargy, stupor, coma
Vesicants (blister agents)	Eye, throat, skin irritation	Coughing	Skin burning, blistering rash	Tremors, convulsions, ataxia, coma
Caustic agents (acids)	Skin irritation and burning	Eye irritation	Throat irritation	Coughing
Riot-control agents	Eye irritation	Throat irritation	Respiratory noise (coughing, hoarseness, stridor, wheezing)	Nausea and vomiting with some agents
Trichothecene mycotoxins	Skin irritation, rash	Eye irritation	Vomiting, dyspnea	Bleeding
Centrally acting (large-airway) pulmonary agents	Eye, throat, skin irritation	Respiratory noise (coughing, hoarseness, stridor, wheezing)	Shortness of breath, collapse	Pulmonary edema, lung injury
Peripherally acting (small-airways-and-alveoli) pulmonary agents	Few or no initial symptoms except at high doses	Delayed-onset shortness of breath	Chest tightness	Pulmonary edema, lung injury
Botulinum toxin	Diplopia	Difficulty swallowing	Descending paralysis	Respiratory arrest

* Signs and symptoms may occur simultaneously in some cases, especially at higher doses.
† The knockdown syndrome involves rapid loss of consciousness, collapse, seizures, hypotension, and cardiac arrest.

ate victims with minor injuries from those with more serious injuries.[55] Few of these systems address the possibility of a chemical-weapons attack.[56] One of the systems that does, the CBRN (Chemical, Biological, Radiological, Nuclear) system, incorporates injuries related to chemical-warfare agents.[56,57] However, this system uses only the presence of a toxidrome, not identification of the class of agent, to determine treatment categories.[58] When tested in a drill setting, the CBRN system resulted in significant undertriage of victims.[57] Other attempts to include signs and symptoms associated with chemical-warfare agents in mass-casualty triage systems have classified victims on the basis of treatment categories (minimal, delayed, urgent, or emergency treatment), without necessarily confirming the presence of chemical weapons or providing rapid identification of the class of agent.[59,60] Triage systems that include symptoms either tend to be designed to isolate nerve agents from everything else[61] or are so rudimentary that it is difficult to differentiate among classes of agents.[62] The symptom-based triage system that perhaps comes closest to being both thorough and practical is the Madsen protocol.[63] However, this algorithm is very detailed, identifying individual agents in many cases. Therefore, the Madsen

protocol may be better suited for use after the acute phase of an attack.

A chemical-weapons triage algorithm is needed that can be rapidly deployed in the acute phase of an attack, is simple to use, and is based on identification of specific toxidromes. The goal would be to quickly identify victims who require emergency treatment with antidotes along with other therapeutic interventions.

SAFE AND EFFECTIVE RESPONSE

A chemical-warfare attack on a metropolitan target may not be immediately identified as such. The use of a chemical agent is likely to be combined with the use of other weapons, such as firearms and explosives, resulting in multiple victims who could be mistakenly identified as casualties of a conventional attack. The first responders must quickly analyze the scene for signs of chemical agents, including more victims than would be expected from a blast or gunfire, multiple victims with no obvious signs of trauma, and clusters of victims collapsing with similar symptoms. If a chemical agent is suspected, the responders must stay at a safe distance and thoroughly analyze the scene. Does the agent appear to be in a gas or a liquid state? Is it contained, or is the scene still active? What are the other safety issues: fire, collapsing buildings, active combatants? All factors must be taken into account as responders prepare to enter the scene and care for the victims. Historical precedent, such as the sarin gas attack in 1995 in the Tokyo subway system[31] and the more recent use of sarin and chlorine on civilians in Syria,[3,4] has also shown that, depending on the agent used, the venue, and the effectiveness of the attack, secondary exposure to these very dangerous chemicals can make responders susceptible to injury.[8] Therefore, safety at the scene of the attack, including proper use of personal protective equipment, must be the priority for all responders.

An attack involving a single release of a chemical agent is likely to result in a clustering of victims. Victims with the most severe injuries are generally closest to the site where the agent was released; the severity of the injuries decreases with increasing distance from the site of release.[64] A dispersed attack, such as a series of devices resulting in multiple releases over a wide area, will involve more varied patterns. The rule of severity will stand, however, with the most critically injured patients clustered around each site of release, unless exposure to the agent is characterized by a latent (asymptomatic) period before the onset of toxic effects. In this case, the most seriously affected victims may be scattered over a wider range. These patterns of severity will suggest the epicenter of the release, influencing safety concerns and decisions about where responders should initially stage and assess victims.

On arrival at the scene, first responders must rapidly identify the presence of a chemical agent and then determine hot, warm, and cold zones. The hot zone is the contaminated area, the cold zone is the uncontaminated area, and the warm zone (sometimes called the decontamination corridor), which is between the hot and cold zones, is where decontamination units can be staged.[65] In establishing these zones, the responders must identify the event as an isolated or dispersed release and must account for the physical state of the chemical (especially liquid vs. gas), wind patterns, and any other hazards.

After safe staging has been established, it is important to determine which class of agent is present and how best to approach the scene. Some agents carry a higher risk of primary or secondary exposure for the responders than other agents. In addition, a highly volatile liquid or gas poses an immediate risk until it is dissipated, and the presence of vapor or gas is one of the most important and urgent factors to determine once responders arrive at the scene. If either gas or substantial vapor (collectively referred to as a vapor hazard) is present, responders should remain upwind and at a safe distance (at least 150 ft [approximately 50 m] away) until personal protective equipment can be donned. The current Occupational Safety and Health Administration (OSHA) recommendation for an incident with an unknown agent is to use Level A protective equipment, which is the highest degree of protection available.[66] Level A suits include a self-contained breathing apparatus with positive pressure and totally encapsulating (head-to-toe and sealed), chemical protection. Donning Level A suits can be cumbersome and must be practiced before use to maximize efficiency. In light of the recent terrorist attacks on civilian targets, this OSHA policy may require modification to

take into account the need for rapid administration of antidotes or other treatment approaches while preserving safety at the scene.

The most definitive way to identify a chemical agent is to analyze environmental or biologic samples. Handheld devices are available for agent identification, although most have suboptimal sensitivity and specificity and require several hours for definitive classification, leading to false alarms and limiting their usefulness in the field.[11] Such devices are also not always readily available in the very early phase of an event and therefore may be more useful in a subsequent phase. During the initial encounters with casualties, clinical suspicion and toxidrome recognition, aided by a rapid-triage system, will be the primary means of determining treatment protocols.

An interactive graphic showing possible scenarios is available at NEJM.org

USING TOXIDROMES TO RAPIDLY IDENTIFY CLASSES OF CHEMICAL AGENTS

Most chemical weapons are deadly and pose a risk to responders who are tasked with providing care for those who are injured. If at any time a victim requires airway support or other emergency treatment, it should be rendered immediately, within the constraints of on-the-scene safety requirements and mass-casualty triage principles. Exposure to some chemical weapons requires immediate administration of antidotes, and rapid spot decontamination is required in all cases. For these reasons, a rapid-triage system based on the identification of class-specific toxidromes must be used for the acute phase of a chemical-weapons attack, enabling health care responders to both implement appropriate safety measures quickly and begin administering time-sensitive treatments early and rapidly (Fig. 1).

As with any strategy for making decisions in a crisis, the process should be easy to follow. The first step is to determine whether injury patterns can be accounted for by conventional mechanisms alone, such as blast, gunshot, fire, or crush. If so, responders should use traditional mass-casualty triage protocols, while remaining vigilant for the possibility of a delayed-onset chemical attack or the presence of radiation. If symptoms appear to be unrelated to conventional mechanisms of injury, responders should ensure that the scene is safe, don appropriate personal protective equipment, and move to the second step. This step entails rapid identification of toxidromes, with specific patterns matched to classes of chemical-warfare agents.

Responders should identify toxidromes sequentially, beginning with those that match the most rapidly lethal agents (for which exposed persons require emergency antidotes and treatment), followed by those that match agents for which exposed persons should undergo thorough decontamination before or concurrent with treatment (Fig. 2); three examples are provided in an interactive graphic, available with the full text of this article at NEJM.org. The possibility of the presence of nerve agents is considered first. Muscle twitching, weakness, or paralysis and increased secretions suggest that a nerve agent may have been used; atropine and pralidoxime should be administered immediately, and emergency supportive care and spot decontamination should be performed. Bradypnea or apnea, combined with gasping, collapse, and seizures, supports the presence of asphyxiants such as cyanide; hydroxocobalamin or sodium thiosulfate and sodium nitrite should be administered as antidotes, and emergency supportive care and spot decontamination should be performed. If bradypnea or apnea is combined with sedation, then the presence of miosis suggests a class of agents that includes opioids. In this case, naloxone should be administered immediately, and emergency supportive care and spot decontamination should be performed. If miosis is not present, the most likely agent is an anesthetic, which represents the first of the classes of agents for which there are no antidotes and for which decontamination, supportive care, and close monitoring are urgently required. If it is not certain whether the agent is an opioid or an anesthetic agent, administer naloxone. Any patient who has apnea will require emergency airway management.

After ruling out chemical-warfare agents for which antidotes must be administered on an emergency basis, this system identifies toxidromes associated with chemical-warfare agents for which decontamination, supportive care, and close monitoring are urgently required. Such classes include anesthetic agents; pulmonary agents (those that act both centrally and peripherally); vesicant, caustic, and riot-control agents; T-2 and botulinum toxin; and anticholinergic agents.

	Initial Toxidrome	Agent Class	Initial Treatment
Urgently Identify Agent	Increased secretions or muscle effects (fasciculations, weakness, paralysis), with or without miosis	Nerve agent	Administer atropine and pralidoxime, provide urgent care and spot decontamination at the site.
	Bradypnea or apnea, gasping, collapse, and seizures with or without cyanosis	Asphyxiant	Administer cyanide antidote, provide urgent care and spot decontamination at the site.
	Bradypnea or apnea, sedation, miosis	Opioid agent	Administer naloxone, provide urgent care and spot decontamination at the site.
Decontaminate Immediately after Identification of Agent	Sedation and bradypnea	Anesthetic agent	Decontaminate and provide supportive care, monitor airway closely. If uncertain, administer naloxone.
	Respiratory noise (coughing, hoarseness, stridor); eye, throat, skin irritation; shortness of breath	Central-compartment (large-airway) pulmonary agent	Decontaminate and provide supportive care, monitor airway closely, irrigate eyes. Reassess frequently.
	Respiratory noise (coughing, hoarseness, stridor); eye, throat, skin irritation; skin blistering	Vesicant, caustic, riot-control agent, or T-2 toxin	Decontaminate and provide supportive care, monitor airway closely, irrigate eyes. Reassess frequently.
	Delayed-onset shortness of breath or chest tightness	Peripheral-compartment (small-airways) pulmonary agent	Decontaminate and provide supportive care, monitor airway closely. Reassess frequently.
	Diplopia, descending paralysis, dysphagia, mydriasis	Botulinum toxin	Decontaminate and provide supportive care, monitor airway closely. Reassess frequently.
	Confusion, mydriasis, dry skin, elevated temperature	Anticholinergic agent	Decontaminate and provide supportive care, consider physostigmine. Reassess frequently.

Figure 1. Matching Initial Toxidrome with Chemical-Agent Class and Emergency Treatment.

Any patient may require emergency medical treatment at any time. Responders should provide lifesaving treatment when needed, adhering to safety constraints. This table is designed for the acute phase of a chemical-warfare attack and can be used for rapid identification of the class of agent used. Victims who require emergency antidote administration and spot decontamination, followed by supportive treatment, should be identified first (red section), followed by those who require initial spot decontamination and urgent treatment concurrently (tan section). Centrally acting and peripherally acting pulmonary agents are not mutually exclusive; certain agents (e.g., chlorine and lewisite) or high doses of any pulmonary agent can cause damage to large airways as well as small airways and alveoli.

SUMMARY

An effective rapid-triage system for chemical-warfare agents need not, and in fact should not, take into account every conceivable toxidrome, since the agent can be definitively identified after the acute phase of the attack. Instead, the triage system should identify those classes of agents that require rapid treatment with antidotes, emergency airway support, and spot decontamination, and then further delineate within that group the class of agent that is present so that the correct antidote can be given.

In the absence of high-quality data, the triage system outlined here is based primarily on expert opinion, with an understanding of mass-casualty triage combined with recognition of

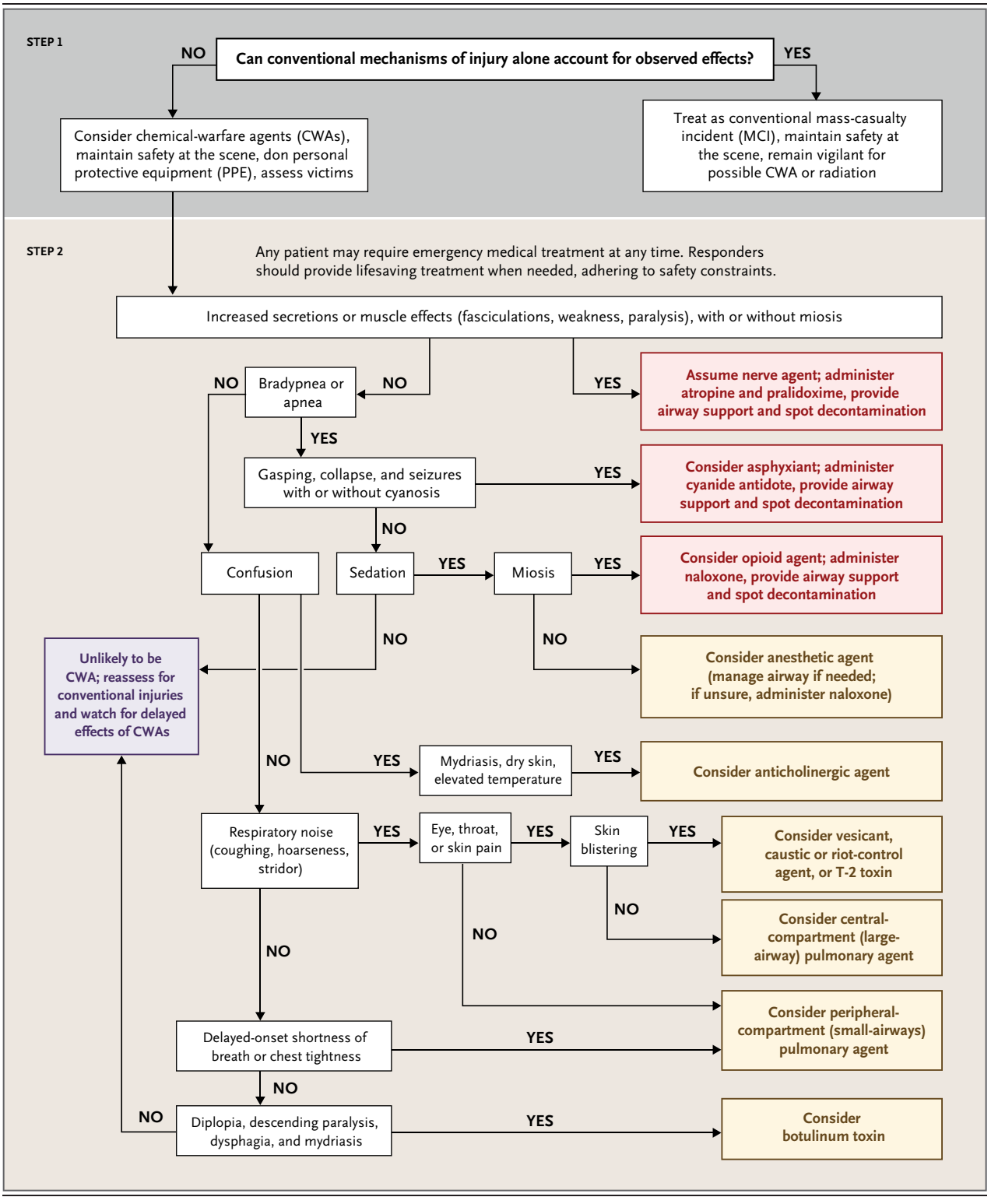

Figure 2 (facing page). Flowchart for Toxidrome-Based Rapid Identification of Chemical-Warfare Agent Classes.

A diagnostic algorithm to be used in the acute phase of a chemical-warfare attack allows responders to rapidly detect victims who require emergency antidote administration and treatment first, followed by those who require initial decontamination and urgent treatment concurrently. Centrally acting and peripherally acting pulmonary agents are not mutually exclusive; certain agents (e.g., chlorine and lewisite) or high doses of any pulmonary agent can cause damage to large airways as well as small airways and alveoli. The red boxes indicate that urgent action is required (i.e., administering antidotes, providing lifesaving supportive care, and performing rapid, initial spot decontamination at the site). The tan boxes indicate that it is important to decontaminate immediately and provide concurrent urgent supportive care, as well as reassess frequently.

the toxidromes associated with classes of chemical-warfare agents. This system uses experience to help address the glaring hole in our civilian-response models for chemical-warfare attacks: the inability to identify the class of agent deployed in time to successfully provide lifesaving treatment. As we witness an escalation in terrorist attacks involving unconventional methods, a toxidrome-based, rapid-triage system may become part of the armament used to prepare for and safely respond to these horrific events.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

I thank Amalia Voskanyan for her guidance and support, and Dr. Robert G. Darling for his technical assistance.

REFERENCES

1. National Consortium for the Study of Terrorism and Responses to Terrorism (START). Global terrorism database. College Park: University of Maryland, 2017 (https://www.start.umd.edu/gtd).

2. OPCW Technical Secretariat. Report of the OPCW fact-finding mission in Syria regarding an alleged incident in Khan Shaykhun, Syrian Arab Republic April 2017. The Hague, the Netherlands: Organisation for the Prohibition of Chemical Weapons, June 29, 2017 (https://www.opcw.org/fileadmin/OPCW/Fact_Finding_Mission/s-1510-2017_e_.pdf).

3. Zarocostas J. Syria chemical attacks: preparing for the unconscionable. Lancet 2017;389:1501.

4. United Nations Mission to Investigate Allegations of the Use of Chemical Weapons in the Syrian Arab Republic. Final report. New York: United Nations General Assembly Security Council, December 13, 2013 (https://undocs.org/A/68/663).

5. Thierren T, Roxby P. Russian spy: what are nerve agents and what do they do? BBC News, March 12, 2018 (http://www.bbc.com/news/health-43328976).

6. Sandler T. The analytical study of terrorism: taking stock. J Peace Res 2014;51:257-71.

7. Cagliuso N, Rabrich JS, Postel TM. Multimodality, layered attack. In: Ciottone GR, Biddinger PD, Darling, RG, et al., eds. Ciottone's disaster medicine. 2nd ed. Philadelphia: Elsevier, 2015:416-23.

8. Nozaki H, Hori S, Shinozawa Y, et al. Secondary exposure of medical staff to sarin vapor in the emergency room. Intensive Care Med 1995;21:1032-5.

9. Okumura S, Okumura T, Ishimatsu S, Miura K, Maekawa H, Naito T. Clinical review: Tokyo — protecting the health care worker during a chemical mass casualty event: an important issue of continuing relevance. Crit Care 2005;9:397-400.

10. Kales SN, Christiani DC. Acute chemical emergencies. N Engl J Med 2004;350:800-8.

11. Ganesan K, Raza SK, Vijayaraghavan R. Chemical warfare agents. J Pharm Bioallied Sci 2010;2:166-78.

12. Rosman Y, Eisenkraft A, Milk N, et al. Lessons learned from the Syrian sarin attack: evaluation of a clinical syndrome through social media. Ann Intern Med 2014;160:644-8.

13. Chaboo CS, Biesele M, Hitchcock RK, Weeks A. Beetle and plant arrow poisons of the Ju|'hoan and Hai||om San peoples of Namibia (Insecta, Coleoptera, Chrysomelidae; Plantae, Anacardiaceae, Apocynaceae, Burseraceae). Zookeys 2016;558:9-54.

14. Cevik Y, Onay M, Akmaz I, Sezigen S. Mass casualties from acute inhalation of chlorine gas. South Med J 2009;102:1209-13.

15. Tewari-Singh N, Inturi S, Jain AK, et al. Catalytic antioxidant AEOL 10150 treatment ameliorates sulfur mustard analog 2-chloroethyl ethyl sulfide-associated cutaneous toxic effects. Free Radic Biol Med 2014;72:285-95.

16. Lim SC, Yang JY, Jang AS, et al. Acute lung injury after phosgene inhalation. Korean J Intern Med 1996;11:87-92.

17. Ghabili K, Agutter PS, Ghanei M, Ansarin K, Shoja MM. Mustard gas toxicity: the acute and chronic pathological effects. J Appl Toxicol 2010;30:627-43.

18. Wattana M, Bey T. Mustard gas or sulfur mustard: an old chemical agent as a new terrorist threat. Prehosp Disaster Med 2009;24:19-29.

19. Fitzgerald GJ. Chemical warfare and medical response during World War I. Am J Public Health 2008;98:611-25.

20. Watermeyer MJ, Dippenaar N, Simo NCT, Buchanan S, Laher AE. Essential lessons in a potential sarin attack disaster plan for a resource-constrained environment. Disaster Med Public Health Prep 2017;18:1-8.

21. Vale A, Marrs TC, Rice P. Chemical terrorism and nerve agents. Medicine 2016;44:106-8.

22. Leadbeater L, Inns RH, Rylands JM. Treatment of poisoning by soman. Fundam Appl Toxicol 1985;5:S225-S231.

23. Munro NB, Ambrose KR, Watson AP. Toxicity of the organophosphate chemical warfare agents GA, GB, and VX: implications for public protection. Environ Health Perspect 1994;102:18-38.

24. Schmaltz F. Neurosciences and research on chemical weapons of mass destruction in Nazi Germany. J Hist Neurosci 2006;15:186-209.

25. Keim ME. Cyanide attack. In: Ciottone GR, Biddinger PD, Darling RG et al., eds. Ciottone's disaster medicine. 2nd ed. Philadelphia: Elsevier, 2015:664-70.

26. Haines DD, Fox SC. Acute and long-term impact of chemical weapons: lessons from the Iran-Iraq War. Forensic Sci Rev 2014;26:97-114.

27. Eisenkraft A, Gilburd D, Kassirer M,

Kreiss Y. What can we learn on medical preparedness from the use of chemical agents against civilians in Syria? Am J Emerg Med 2014;32:186.
28. Dolgin E. Syrian gas attack reinforces need for better anti-sarin drugs. Nat Med 2013;19:1194-5.
29. Convention on the prohibition of the development, production, stockpiling and use of chemical weapons and on their destruction. The Hague, the Netherlands: Organisation for the Prohibition of Chemical Weapons, 2005 (https://www.opcw.org/fileadmin/OPCW/CWC/CWC_en.pdf).
30. Okumura T, Hisaoka T, Yamada A, et al. The Tokyo subway sarin attack — lessons learned. Toxicol Appl Pharmacol 2005; 207:Suppl:471-6.
31. Okumura T, Suzuki K, Fukuda A, et al. The Tokyo subway sarin attack: disaster management, part 3: national and international responses. Acad Emerg Med 1998;5:625-8.
32. Carota A, Calabrese P, Bogousslavsky J. Neurotoxic weapons and syndromes. Front Neurol Neurosci 2016;38:214-27.
33. Pacsial-Ong EJ, Aguilar ZP. Chemical warfare agent detection: a review of current trends and future perspective. Front Biosci (Schol Ed) 2013;5:516-43.
34. Pitschmann V. Overall view of chemical and biochemical weapons. Toxins (Basel) 2014;6:1761-84.
35. Rodgers GC Jr, Condurache CT. Antidotes and treatments for chemical warfare/terrorism agents: an evidence-based review. Clin Pharmacol Ther 2010;88:318-27.
36. Lioy PJ, Laskin JD, Georgopoulos PG. Preparedness and response to chemical and biological threats: the role of exposure science. Ann N Y Acad Sci 2016;1378: 108-17.
37. Brennan RJ, Waeckerle JF, Sharp TW, Lillibridge SR. Chemical warfare agents: emergency medical and emergency public health issues. Ann Emerg Med 1999;34: 191-204.
38. Berger T, Eisenkraft A, Bar-Haim E, Kassirer M, Aran AA, Fogel I. Toxins as biological weapons for terror — characteristics, challenges and medical countermeasures: a mini-review. Disaster Mil Med 2016;2:7.
39. Emergency preparedness and response: bioterrorism agents/diseases. Atlanta: Centers for Disease Control and Prevention, 2017 (https://emergency.cdc.gov/agent/agentlist-category.asp).
40. Phelps S. Mission failure: emergency medical services response to chemical, biological, radiological, nuclear, and explosive events. Prehosp Disaster Med 2007;22:293-6.
41. Reilly MJ, Markenson D, DiMaggio C. Comfort level of emergency medical service providers in responding to weapons of mass destruction events: impact of training and equipment. Prehosp Disaster Med 2007;22:297-303.
42. Madsen JM, Greenberg MI. Preparedness for the evaluation and management of mass casualty incidents involving anticholinesterase compounds: a survey of emergency department directors in the 12 largest cities in the United States. Am J Disaster Med 2010;5:333-51.
43. Schumacher J, Bond AR, Woodham V, Buckingham A, Garnham F, Brinker A. Survey of UK health care first responders' knowledge of personal protective equipment requirements. Prehosp Disaster Med 2015;30:254-8.
44. Bentley MA, Levine R. A national assessment of the health and safety of emergency medical services professionals. Prehosp Disaster Med 2016;31:Suppl 1: S96-S104.
45. Kirk MA, Deaton ML. Bringing order out of chaos: effective strategies for medical response to mass chemical exposure. Emerg Med Clin North Am 2007;25:527-48.
46. Tomassoni AJ, French RN, Walter FG. Toxic industrial chemicals and chemical weapons: exposure, identification, and management by syndrome. Emerg Med Clin North Am 2015;33:13-36.
47. Chauhan S, Chauhan S, D'Cruz R, et al. Chemical warfare agents. Environ Toxicol Pharmacol 2008;26:113-22.
48. Baker D. Civilian exposure to toxic agents: emergency medical response. Prehosp Disaster Med 2004;19:174-8.
49. Joosen MJ, van den Berg RM, de Jong AL, van der Schans MJ, Noort D, Langenberg JP. The impact of skin decontamination on the time window for effective treatment of percutaneous VX exposure. Chem Biol Interact 2017;267:48-56.
50. Okumura T, Suzuki K, Fukuda A, et al. The Tokyo subway sarin attack: disaster management, part 2: hospital response. Acad Emerg Med 1998;5:618-24.
51. Melnikova N, Wu J, Yang A, Orr M. Acute chemical incidents with injured first responders, 2002-2012. Disaster Med Public Health Prep 2017;1:1-11.
52. Borron SW. Checklists for hazardous materials emergency preparedness. Emerg Med Clin North Am 2015;33:213-32.
53. Eyre AJ, Hick JL, Thome CD. Personal protective equipment. In: Ciottone GR, Biddinger PD, Darling RG, et al., eds. Ciottone's disaster medicine. 2nd ed. Philadelphia: Elsevier, 2015:294-301.
54. Tokuda Y, Kikuchi M, Takahashi O, Stein GH. Prehospital management of sarin nerve gas terrorism in urban settings: 10 years of progress after the Tokyo subway sarin attack. Resuscitation 2006;68: 193-202.
55. Turris SA, Lund A. Triage during mass gatherings. Prehosp Disaster Med 2012; 27:531-5.
56. Culley JM, Svendsen E. A review of the literature on the validity of mass casualty triage systems with a focus on chemical exposures. Am J Disaster Med 2014;9:137-50.
57. Cone DC, MacMillan DS, Parwani V, Van Gelder C. Pilot test of a proposed chemical/biological/radiation/nuclear-capable mass casualty triage system. Prehosp Emerg Care 2008;12:236-40.
58. Cone DC, Koenig KL. Mass casualty triage in the chemical, biological, radiological, or nuclear environment. Eur J Emerg Med 2005;12:287-302.
59. Khoshnevis MA, Panahi Y, Ghanei M, Borna H, Sahebkar A, Aslani J. A triage model for chemical warfare casualties. Trauma Mon 2015;20(3):e16211.
60. Ramesh AC, Kumar S. Triage, monitoring, and treatment of mass casualty events involving chemical, biological, radiological, or nuclear agents. J Pharm Bioallied Sci 2010;2:239-47.
61. Krivoy A, Layish I, Rotman E, Goldberg A, Yehezkelli Y. OP or not OP: the medical challenge at the chemical terrorism scene. Prehosp Disaster Med 2005;20: 155-8.
62. Subbarao I, Johnson C, Bond WF, et al. Symptom-based, algorithmic approach for handling the initial encounter with victims of a potential terrorist attack. Prehosp Disaster Med 2005;20:301-8.
63. Madsen JM. Chemical terrorism: rapid recognition and initial medical management. Waltham, MA: UpToDate, 2017 (https://www.uptodate.com/contents/chemical-terrorism-rapid-recognition-and-initial-medical-management).
64. Cieslak T. Ten steps in the management of potential biological casualties. In: Withers M, ed. USAMRIID's medical management of biological casualties handbook. 8th ed. Frederick, MD: U.S. Army Medical Research Institute of Infectious Diseases, September 2014:23-9.
65. Kenar L, Karayilanoglu T. Prehospital management and medical intervention after a chemical attack. Emerg Med J 2004; 21:84-8.
66. Best practices for protecting EMS responders during treatment and transport of victims of hazardous substance releases. Washington DC: Occupational Health and Safety Administration, 2009 (https://www.osha.gov/Publications/OSHA3370-protecting-EMS-respondersSM.pdf).