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The Impact of Medical Care on Casualty Estimates from Battlefield Exposure to Chemical, Biological and Radiological Agents and Nuclear Weapon Effects

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March 2012
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IDA Document D-4465
Log: H 12-000420

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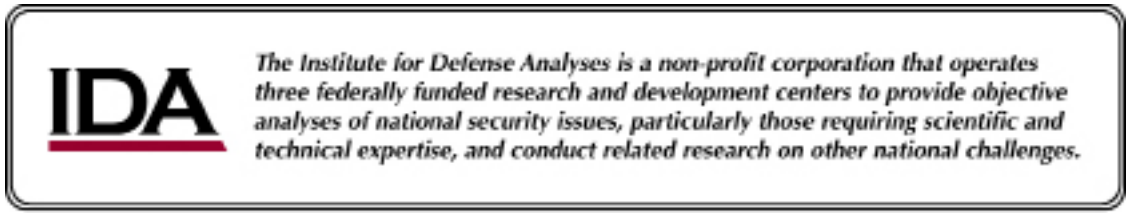

About This Publication

The work was conducted under contract DASW01 04 C 0003, Task CA-6-3079, "CBRN Casualty Estimation Work Effort of the Medical CBRN Defense Planning & Response Project," for the Joint Staff, Joint Requirements Office for CBRN Defense and the U.S. Army Office of the Surgeon General. The views, opinions, and findings should not be construed as representing the official position of either the Department of Defense or the sponsoring organization.

Acknowledgments

The authors wish to thank Dr. William Blakely, Dr. Charles G. Hurst, Dr. Anna Johnson-Winegar, Dr. Leonard Smith, and Dr. Thomas MacVittie for their careful review of this document and their constructive comments. We are also grateful to our editor, Dr. Elisse Wright Barnes, and Ms. Barbara Varvaglione, who produced this document.

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Executive Summary

The Institute for Defense Analyses (IDA) developed a symptom-based methodology, now promulgated as North Atlantic Treaty Organization (NATO) Standardization Agreement (STANAG) 2553, *Allied Medical Publication 8: NATO Planning Guide for the Estimation of CBRN Casualties* (*AMedP-8(C)*), to estimate the number, type, and timing of chemical, biological, radiological, and nuclear (CBRN) casualties. During the development of *AMedP-8(C)*, the NATO CBRN Medical Working Group placed restrictions on the conditions IDA was able to consider in the casualty estimation methodology. Specifically, neither the impact of medical treatment was estimated nor the casualty category of return to duty (RTD) was included in *AMedP-8(C)*.

This study extends the methodology to consider how medical intervention would influence the number of casualties in the died of wounds (DOW) and RTD categories, and the times at which personnel would move into these categories. Moreover, since medical management extends well beyond the immediate area of the battlefield, some characterization of extended therapy and long term convalescent care must also be considered. This document proposes incorporating patient estimation methodology (P8PEM) as an extension of the *AMedP-8(C)* casualty estimation methodology (P8CEM).

Within the P8CEM, the dose/dosage/insult of the CBRN agent or effect determines the human response and associated injury. Injury includes both wounds and disease. Only acute injuries that manifest within the time period that operational and medical estimates are made are considered in the casualty estimate.

The P8CEM estimates of the human response due to exposure to CBRN agents and effects are based on an injury profile. An injury profile is a description of the progression of injury and is expressed in step-wise symptom severity level changes over time. Five severity levels are used in this methodology to describe the progression of injury. The severity levels for chemical, radiological, and nuclear agents and effects are described solely in terms of observable symptoms, whereas the levels associated with exposure to biological agents are described in terms of both symptoms and clinical signs.

The P8PEM starts with the products of the P8CEM, specifically the estimate of the wounded in action (WIA) casualties that will enter the medical system and become patients. Within the P8PEM, casualties are characterized within parameters that allow the user to consider the effect of medical treatment. The P8PEM identifies the WIA casualties as patients within the medical system and estimates the time at which these patients progress to other casualty

categories including DOW, Convalescent, and RTD. The specific parameters for modeling the medical management of patients vary for the different CBRN agents and effects.

The parameters for modeling the medical management of sarin (GB) and O-Ethyl-S-(2-diisopropylaminoethyl) methyl phosphonothiolate (VX) casualties are derived from the existing *AMedP-8(C)* untreated injury profiles, RTD recommendations from *Medical Aspects of Chemical Warfare* (Sidell, Newmark, and McDonough), and the human and animal cases described in this document.

- Since pyridostigmine bromide (PB) pretreatment would not be used in anticipation of exposure with GB or VX, there is no reason to model it. Treatment is assumed to be as described in the doctrine: decontamination, artificial ventilation and cardiovascular support, if necessary, and antidote therapy with atropine, 2-PAM Cl, and diazepam, when required.
- For nonlethal exposures resulting in symptoms (0.2–30 mg-min/m^3 inhaled GB, 0.02–13 mg-min/m^3 inhaled VX, or 0.8–3.9 mg/man percutaneous VX), service members may relieve some symptoms with self-aid, but since atropine is ineffective against miosis, mild ocular symptoms will remain for some time. If the severity criterion is WIA (1), then mild ocular symptoms will still dictate that a service member is a casualty in any dose range.
- The treatment for an individual exposed to a degree that would result in casualty status at the WIA (2) ($\geq$ 1 mg-min/m^3 inhaled GB, $\geq$ 0.3 mg-min/m^3 inhaled VX, or $\geq$ 0.8 mg/man percutaneous VX) or WIA (3) level ($\geq$12 mg-min/m^3 inhaled GB, $\geq$ 4 mg-min/m^3 inhaled VX, or $\geq$ 1.6 mg/man percutaneous VX) is more than what would be given as self-aid. Therefore, self-aid will not prevent individuals from entering the medical system.
- Patients within the two lowest inhaled dosage ranges can be returned to duty within a few hours.
- Patients exposed to the next highest inhaled dosage ranges (6.5–12 mg-min/m^3 inhaled GB and 2–4 mg-min/m^3 inhaled VX) are modeled to RTD in two days.
- Patients exposed to the dose/dosage ranges of 12–25 mg-min/m^3 inhaled GB, 4–10 mg-min/m^3 inhaled VX, and 1.6–3.9 mg/man percutaneous VX are modeled to RTD in two to six days.
- The inhaled dosage ranges of 25–30 mg-min/m^3 for GB and 10–13 mg-min/m^3 for VX are the highest dosages that are non-lethal without treatment. With medical treatment, casualties in this group will be retained for convalescent care.
- The highest dose/dosage ranges ($\geq$ 30 mg-min/m^3 inhaled GB, $\geq$ 13 mg-min/m^3 inhaled VX, and $\geq$ 3.9 mg/man percutaneous VX) are modeled as 100% lethal without treatment. To model the increased survivability with treatment, a protection ratio (PR)

of 20 median lethal doses (LD_{50}) was applied to humans, effectively extending the range of non-lethal exposures, resulting in new dose/dosage range limits of 600 mg-min/m^3 inhaled GB, 260 mg-min/m^3 inhaled VX, and 78 mg/man percutaneous VX. Individuals exposed to a degree less than the new lethal threshold are modeled as survivors that require convalescent care and will not RTD. Individuals exposed to amounts above these values are modeled as fatalities, even with treatment. It is assumed that if medical care can be provided before a casualty in this highest range is declared dead (i.e., if the casualty is not killed in action (KIA)), then treatment will prolong, but not preserve, life. These individuals are modeled to die after two weeks.

Unlike nerve agent casualties, sulfur mustard (HD) casualties may not benefit from a shortened recovery time as a result of medical intervention, since treatment consists mainly of supportive care, which does little to accelerate the regeneration of damaged tissues. The parameters for modeling the treatment of HD are derived from the existing *AMedP-8(C)* untreated injury profiles, RTD recommendations from *Medical Aspects of Chemical Warfare*, and historical war casualties described in this document.

- The lowest level of exposure modeled to produce ocular symptoms is in the range of 4–26 mg-min/m^3. Because miosis is likely to be unresponsive to treatment, ocular symptoms from exposure to this dosage range will still be modeled to persist for two and a half days. Casualties with symptoms dominated by ocular effects in this range (i.e., those exposed to 4–12 mg-min/m^3) will not RTD until day three.
- At the low end of the first dosage range that produces skin symptoms (12–125 mg-min/m^3), local treatment for skin irritation would consist of antiseptic solutions, ointments, and creams, but skin symptoms will still be modeled to last four days.
- The second ocular range (26–50 mg-min/m^3) falls within the skin range described above. Treatment is modeled to offer little benefit in the reduction of recovery time and the duration of medical care is dominated by ocular, rather than skin, symptoms. Casualties are modeled to RTD on day five post-exposure.
- At the exposure range of 50–70 mg-min/m^3, treatment is modeled to reduce the RTD time to two weeks for casualties exhibiting these symptoms.
- Above 70 mg-min/m^3 ocular symptoms become severe, and above 125 mg-min/m^3 skin lesions become more significant. All treated casualties receiving dosages above 70 mg-min/m^3 are modeled according to the DOW, RTD, or convalescent casualty distributions in the data set studied.

This document describes the effects of medical management on the biological agent human response models. For many biological agent-induced diseases, no medical countermeasures or specific treatments exist, and treatment is limited to supportive care. In these cases, the submodels now used in *AMedP-8(C)* to describe human response to these agents would not

change with consideration of treatment. Patient management parameters for each agent are provided only for those submodels that change as a consequence of treatment.

- For inhalational anthrax, considering medical countermeasures and treatment alters submodels for infectivity, lethality, and duration of illness. In addition, the injury profile for anthrax has been modified to include a separate profile for survivors. The incubation period submodel for anthrax is unaffected and remains the same as described in *AMedP-8(C)*.
- For botulism, considering medical countermeasures and treatment alters submodels for effectivity, lethality, and duration of illness. In addition, the injury profile for botulism has been modified. The latent period submodel for botulism is unaffected and remains the same as described in *AMedP-8(C)*.
- For brucellosis, the only submodel affected by considering treatment is duration of illness.
- For glanders, considering treatment results in changes to submodels of lethality, injury profile, and duration of illness.
- For pneumonic plague, considering medical countermeasures and treatment alter submodels for infectivity, lethality, and duration of illness. In addition, the injury profile for pneumonic plague has been modified to include a survivor profile. The latent period submodel for pneumonic plague is unaffected and remains the same as described in *AMedP-8(C)*.
- For Q fever, considering medical countermeasures and treatment affects submodels of infectivity and duration of illness. The Q fever injury profile, consisting of a single stage of acute illness of Moderate severity, remains unchanged.
- Because there are no medical countermeasures or specific treatments for Staphylococcal enterotoxin B (SEB) that would change any of the component submodels of SEB human response, the P8PEM methodology uses the same parameters as *AMedP-8(C)* for SEB.
- The current *AMedP-8(C)* methodology now incorporates parameters for the efficacy of smallpox vaccination, administered both before and after exposure to the virus. Because there are no additional smallpox medical countermeasures or treatments that would alter the submodels characterizing the disease, the P8PEM methodology uses the same parameters as *AMedP-8(C)* for smallpox.
- For tularemia, considering medical countermeasures and treatment alter submodels for infectivity, lethality, injury profile, and duration of illness. The latent period submodel for tularemia is unaffected and remains the same as described in *AMedP-8(C)*.

- Because there are no medical countermeasures or specific treatments for Venezuelan equine encephalitis (VEE) that would change any of the component submodels of VEE human response, the P8PEM methodology uses the same parameters as *AMedP-8(C)* for VEE.

Prompt nuclear effects include the initial radiation, static blast overpressure, and thermal fluence (radiant thermal energy) resulting from the detonation of a nuclear weapon.

- For patients treated for whole-body radiation exposure, the recommendation is to use the dose reduction factor (DRF) for supportive care of 1.3, since in a mass-casualty scenario it is unlikely that cytokines will be available in sufficient supply to impact a significant number of patients. DOWs will still occur, but at a higher dose range than would normally be expected without treatment. With supportive medical treatment, it is expected that the LD_{50} would increase from 4.5 Gy to about 5.9 Gy. At doses above 6 Gy, death would be expected at the time modeled by the P8CEM *Radiation Time-to-Death* model. RTD was not modeled at doses above 3 Gy.
- Due to the prolonged symptomatology expected in a cutaneous radiation injury, and the symptomatic and supportive aspects of the recommended medical care, no changes to the injury profiles in *AMedP-8(C)* are recommended.
- Patients treated for flash burns are modeled as having a median lethal burn area (LA_{50}) of 45 percent body surface area (%BSA) (probit slope = 0.0539). With treatment, DOWs will still occur, but at higher BSAs than would normally be expected without treatment. RTD would occur in one to four weeks at 1–<15 %BSA, and half of those with 15–<30 %BSA would RTD in four to six weeks. Convalescent care would be required for some fraction of any survivor of flash burns 15 %BSA or greater.
- Primary blast injury (PBI) is most likely to occur during a conflict between opponents who have sophisticated weapons. The time to RTD can vary from almost immediate, in the case of tympanic membrane rupture, to months, in the case of more severe blast lung or abdominal injuries. DOWs are not expected to occur from PBI with treatment. At high burden levels (>290 kPa) most patients are expected to survive, but not RTD, remaining in a Convalescent status for a prolonged period of time.
- The significant impact of combined injuries is that lethality should be expected to result when any radiation dose above 2 Gy is combined with even moderate blast or burn trauma. At whole-body radiation doses greater than 1.25 Gy, DOW will occur at flash burns greater than 15 %BSA or primary blast levels greater than 140 kPa.

In conclusion, there is sufficient data to estimate the effect of treatment on CBRN casualty status. Some medical countermeasures can alter the dose response to CBRN agents and effects and, hence, change the number of expected casualties. Medical treatment, initiated after the onset

of symptoms, does not affect the time or rate of WIA. DOW is generally decreased with medical treatment. The number of patients who RTD or remain convalescent can also be estimated.

The results of this study should be considered for inclusion within the current medical planning and logistical tools and architecture to improve the medical planning process.

Contents

Appendices

1. Introduction

Since 1994, the Institute for Defense Analyses (IDA) has supported the United States (U.S.) Army Office of the Surgeon General (OTSG) in the Medical Chemical, Biological, Radiological, and Nuclear (CBRN) Defense Planning & Response Project in its planning, preparation, and exercises to respond to CBRN weapons use against U.S. military personnel. The objective of the project is to ensure that the U.S. military medical community can successfully fulfill its missions in a CBRN environment.

Over the past several years, the OTSG has been responsible for generating a North Atlantic Treaty Organization (NATO) standard for estimating the casualties that would result from battlefield attacks against Allied forces with CBRN weapons. To support this effort, IDA developed a symptom-based methodology for estimating the number, type, and timing of CBRN casualties, which was promulgated as NATO Standardization Agreement (STANAG) 2553, *Allied Medical Publication 8: NATO Planning Guide for the Estimation of CBRN Casualties* (*AMedP-8(C)*).[1]

In the development of *AMedP-8(C)*, the NATO CBRN Medical Working Group placed restrictions on the conditions to be considered in the casualty estimation methodology. Specifically, two aspects of casualty estimation were explicitly excluded:

- The impact of medical treatment was not estimated in *AMedP-8(C)* because there is no standardized or inter-operable model for medical treatment. Since medical treatment is not standardized within NATO, *AMedP-8(C)* does not assess the impact of medical treatment on CBRN casualty estimates.
- Although it was included in a prior version of *AMedP-8*, the casualty category of return to duty (RTD) is not included in *AMedP-8(C)*. This was due, to a large degree, to the cognitive dissonance of estimating when an individual would recover from an injury or illness without estimating the impact of medical treatment.

Since the promulgation of *AMedP-8(C)*, the OTSG has requested a study that addresses the impact of medical care on the *AMedP-8(C)* casualty estimation methodology (P8CEM). This study extends the methodology to consider how medical intervention would influence the number of casualties in the died of wounds (DOW) and RTD categories, and the times at which personnel would move into these categories. Moreover, medical management extends well beyond the immediate area of the battlefield, so some characterization of extended therapy and

[1] North Atlantic Treaty Organization (NATO), *AMedP-8(C): NATO Planning Guide for the Estimation of CBRN Casualties* (Brussels: NATO, 2011).

long term convalescent care must be considered as well. This document proposes the *AMedP-8(C)* patient estimation methodology (P8PEM) as an extension of the (P8CEM).

A. *AMedP-8(C)* Casualty Estimation Methodology

Within the P8CEM, the dose/dosage/insult of the CBRN agent or effect determines the human response and associated injury. Injury includes both wounds and disease. Only acute injuries that manifest within the time period when operational and medical estimates are made are considered in the casualty estimate.

Injury profiles form the basis for the P8CEM estimates of human response due to exposure to CBRN agents and effects. An injury profile is a description of the progression of injury and is expressed in terms of the step-wise symptom severity level changes that occur over time. Five severity levels are used in this methodology to describe the progression of injury. The severity levels for chemical, radiological, and nuclear (CRN) agents and effects are described solely in terms of observable symptoms, whereas the levels associated with exposure to biological agents are described in terms of both symptoms and clinical signs. The five severity levels are described in Table 1.

Table 1. *AMedP-8(C)* Injury Severity Level Definitions

	Degree	Description
0	No Observable Effect	Although some exposure to an agent or effect may have occurred, no observable injury (as would be indicated by manifested symptoms) has developed
1	Mild	Injury manifesting symptoms (and signs for biological agents) of such severity that individuals can care for themselves or be helped by untrained personnel; condition may not impact ability to conduct the assigned mission
2	Moderate	Injury manifesting symptoms (and signs for biological agents) of such severity that medical care may be required; general condition permits treatment as outpatient and some continuing care and relief of pain may be required before definitive care is given; condition may be expected to interrupt or preclude ability to conduct the assigned mission
3	Severe	Injury manifesting symptoms (and signs for biological agents) of such severity that there is cause for immediate concern but there is no imminent danger to life; individual is acutely ill and likely requires hospital care. Indicators are questionable – condition may or may not reverse without medical intervention; individual is unable to conduct the assigned mission due to severity of injury
4	Very Severe	Injury manifesting symptoms (and signs for biological agents) of such severity that life is imminently endangered. Indicators are unfavorable—condition may or may not reverse even with medical intervention; prognosis is death without medical intervention; individual is unable to conduct the assigned mission and is not expected to return to the mission due to severity of injury

Note: See NATO, *AMedP-8(C): NATO Planning Guide for the Estimation of CBRN Casualties* (Brussels: NATO, 2011), 1–5.

The injury profiles are used to determine the timing of the three types of casualties identified in the P8CEM:[2]

- Killed in action (KIA) is "a battle casualty who is killed outright or who dies as a result of wounds or other injuries before reaching a medical treatment facility."
- Wounded in action (WIA) is "a battle casualty other than "killed in action" who has incurred an injury due to an external agent or cause."
- Died of wounds (DOW) is "a battle casualty who dies of wounds or other injuries received in action, after having reached a medical treatment facility."

To be classified as a KIA, an individual's death must occur before reaching a medical treatment facility, so the injury profile is assessed to see whether an individual dies (determined by prolonged period (recommended as 15 minutes) with Severity Level 4 ("Very Severe") symptoms) before the medical treatment facility is established (recommended as 30 minutes post-exposure).

The first step in estimating WIA is defining the injury severity level at which individuals would be expected to become casualties—that is, the injury severity level that would result in the individual becoming a loss to the unit. The first onset of any severity level above "No Observable Effect" (Severity Level 0) indicates the presence of an observable injury, and operational availability decreases as the injury severity level increases.

- WIA (1): The casualty criterion defining a casualty at Severity Level 1 ("Mild") or greater
- WIA (2): The casualty criterion defining a casualty at Severity Level 2 ("Moderate") or greater
- WIA (3): The casualty criterion defining a casualty at Severity Level 3 ("Severe") or greater

Since Severe symptoms, by definition, preclude an individual's ability to conduct the assigned mission, a casualty criterion above WIA (3) is not defined, and a designation of WIA (4) is never assigned.

An individual not already classified as a KIA is considered to be a WIA at the first time t at which the individual's injury severity level is at or exceeds the user-defined severity level:

If (not KIA and Severity at time t ≥ User-Defined Severity Level),
then WIA at time t.

[2] NATO, *AAP-6, NATO Glossary of Terms and Definitions*, (Brussels: NATO, 2010), 2-K-1.

Lastly, individuals move from the WIA category to the DOW category if their symptoms progress to Very Severe and remain at that severity level for a prolonged period (recommended as 15 minutes) even after reaching a medical treatment facility.

B. *AMedP-8(C)* Patient Estimation Methodology

The P8PEM starts with the products of the P8CEM, specifically the estimate of the WIA casualties that will enter the medical system and become patients. The P8CEM characterizes casualties by the type of exposure (or agent/effect) and by the severity of symptoms at the time of becoming a casualty. Within the P8PEM, casualties are characterized by parameters that allow the user to consider the effect of medical treatment. To develop the P8PEM, IDA began by analyzing the recommended medical treatments for CBRN casualties. IDA then identified the additional information required to estimate a patient's status for specific agents, such as the magnitude of dose/dosage/insult or the specification of the disease stage.

The P8PEM both identifies the WIA casualties as patients within the medical system and estimates the time at which these patients progress to other casualty categories including DOW, Convalescent, and RTD. The specific parameters for modeling the medical management of patients, which vary for the different CBRN agents and effects, are presented in the subsequent chapters of this document.

2. Chemical Agents

Within *AMedP-8(C)*, injury profiles are presented for two nerve agents (sarin (GB) and O-Ethyl-S-(2-diisopropylaminoethyl) methyl phosphonothiolate (VX) and one blister agent (sulfur mustard (HD)). These injury profiles are used to model the human response to chemical agent exposure and to estimate the resulting casualties in the absence of treatment. To understand the effects of medical intervention on human response and the *AMedP-8(C)* casualty estimate, data were collected from accidental human exposures, intentional releases of chemical agents by states or terrorist groups, and controlled animal studies, as well as recommendations from U.S. military publications on anticipated patient recovery.

The untreated injury profiles were developed by describing the symptoms within distinct physiological systems, then combining them to represent the whole-body response. This level of detail is unnecessary to model the parameters relevant to a patient estimate, namely the number and timing of patients that recover, die, or enter convalescent care. As a result, the chemical agent medical management model describes the fractions of patients each day in these categories (RTD, DOW, and Convalescent) by dose/dosage range.

This chapter describes the effects of nerve and blister agents on the human body, the accepted medical management principles, and the expected result of applying these principles to chemical agent patients. At the end of the section for each type of agent, the specific parameters for *AMedP-8(C)* patient estimation are provided.

A. Nerve Agent Patients

1. The Effects of Nerve Agent Intoxication

Acetylcholine (ACh) is a neurotransmitter responsible for sending signals throughout the central and peripheral nervous systems. After transmission, these signals are terminated by the enzyme acetylcholinesterase (AChE), which hydrolyzes the ACh and allows the next nerve impulses to be transmitted. Nerve agents disrupt this process by inhibiting AChE and preventing the breakdown of ACh. Without an antidote, the resulting over-stimulation of the tissues by ACh may result in a combination of effects called a cholinergic crisis.[3] Symptoms of cholinergic crisis

[3] Chemical Casualty Care Division, U.S. Army Medical Research Institute of Chemical Defense, *Nerve Academy Featuring Simapse 2.0 Nerve Agent Laboratory* (2009); John H. McDonough and Tsung-Ming Shih, "Atropine and Other Anticholinergic Drugs," in *Chemical Warfare Agents: Toxicology and Treatment*, ed. Timothy C. Marrs, Robert L. Maynard, and Frederick R. Sidell (Chichester, UK: John Wiley & Sons, Ltd, 2007); Frederick R. Sidell, Jonathan Newmark, and John H. McDonough, "Nerve Agents," in *Medical Aspects of Chemical*

include excess ocular, nasal, and gastric secretions; sweating; muscle twitching; constricted pupils; airway constriction and secretions; and seizures. Death, if it occurs, is usually attributed to respiratory failure resulting from some combination of "bronchoconstriction, excessive respiratory secretion, failure of the muscles of respiration, and depression of the respiratory center."[4]

The level of AChE inhibited in the body following exposure can be approximated by the degree of red blood cell cholinesterase (RBC-ChE) inhibition, which is easier to measure.[5] Sidell and Groff[6] observed that VX-inhibited RBC-ChE undergoes spontaneous reactivation at a rate of approximately 1% per hour, but Grob and Harvey[7] reported no spontaneous reactivation of sarin-inhibited cholinesterase over the course of several weeks, indicating that these enzymes had been irreversibly inactivated. In contrast, another source reported that a small percentage of sarin-inhibited enzyme (5%) undergoes spontaneous reactivation.[8] In the absence of treatment, regeneration of the irreversibly inhibited enzyme depends on the synthesis of new enzyme molecules, which occurs at a rate of approximately 1% of normal per day.[9]

2. Nerve Agent Medical Management Principles

With appropriate medical care, the process of reactivating inhibited AChE is accelerated considerably. The principles of treatment for nerve agent casualties entering the medical system include eliminating the exposure, maintaining ventilation and circulation, and administering antidotes (atropine, 2-PAM Cl, and possibly diazepam).[10] While respiratory and cardiovascular symptoms must be managed in order to sustain life, only the antidote therapy directly counteracts the inhibition of AChE. A pre-treatment adjunct to the recommended therapy is also used for some nerve agents.

Warfare, *Textbooks of Military Medicine,* ed. Shirley D. Tuorinsky, (Washington, DC: Government Printing Office, 2008).

4 William F. Durham and Wayland J. Hayes, "Organic Phosphorus Poisoning and Its Therapy," *Archives of Environmental Health* 5(1962).

5 Sidell, Newmark, and McDonough, "Nerve Agents," 158.

6 Frederick R. Sidell and William A. Groff, "The Reactivatibility of Cholinesterase Inhibited by Vx and Sarin in Man," *Toxicology and Applied Pharmacology* 27(1974).

7 David Grob and John C. Harvey, "Effects in Man of the Anticholinesterase Compound Sarin (Isopropyl Methyl Phosphonofluoridate)," *Journal of Clinical Investigation* 37, no. 3 (March 1958).

8 Sidell, Newmark, and McDonough, "Nerve Agents," 186.

9 Durham and Hayes, "Organic Phosphorus Poisoning"; McDonough and Shih, "Atropine and Other Anticholinergic Drugs," 1; Sidell, Newmark, and McDonough, "Nerve Agents," 164.

10 Frederick R. Sidell, "Clinical Considerations in Nerve Agent Intoxication," in *Chemical Warfare Agents*, ed. Satu M. Somani (San Diego, CA: Academic Press, Inc., 1992), 175; Sidell, Newmark, and McDonough, "Nerve Agents," 180.

a. Pretreatment with Pyridostigmine Bromide

The U.S. military issues a pretreatment adjunct called pyridostigmine bromide (PB) to service members serving in a location where a nerve agent attack is likely. One 30-mg tablet of PB taken every eight hours[11] protects individuals from some nerve agents by bonding with a small portion (approximately 20–40%)[12] of their bodies' AChE, preventing nerve agent from later bonding with the enzyme during an exposure. An important difference between PB and nerve agents is that PB is a reversible inhibitor of AChE; in other words, the bond between PB and AChE is spontaneously broken, allowing the enzyme to resume its function of hydrolyzing ACh.

The benefit of PB pretreatment is only realized if the aging time of the nerve agent-AChE complex is shorter than the time at which nerve agent antidotes are administered. Aging is the biochemical reaction between a nerve agent and AChE that leaves the complex permanently resistant to treatment via oxime reactivation. For GB and VX, the two nerve agents modeled in *AMedP-8(C)*, the aging time is 3–5 hours and 48 hours, respectively.[13] Due to this long aging time, PB provides no additional benefit in the treatment of poisoning with GB or VX, and service members would not be directed to use PB in anticipation of an attack with either nerve agent.[14] Therefore, PB will not be considered as part of the course of medical treatment for patients exposed to GB or VX.

b. Eliminate Exposure/Decontaminate Patient

Decontaminating the patient is perhaps the most important step in treating acute nerve agent cases. This is vital both to eliminate further exposure to the casualty and to prevent medical personnel from becoming exposed. Except in cases where delaying treatment in order to decontaminate would result in a patient's immediate death, eliminating exposure should precede other treatment steps.

c. Administer Antidotes

1) Battlefield Administration of Nerve Agent Antidotes

To treat the harmful effects of nerve agents, NATO member countries issue nerve agent antidote kits to military service members operating in an area where these agents pose a potential

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11 Sidell, Newmark, and McDonough, "Nerve Agents," 202; Chemical Casualty Care Division, U.S. Army Medical Research Institute of Chemical Defense, *Medical Management of Chemical Casualties Handbook*, ed. Gary Hurst, et al., Fourth ed. (Aberdeen Proving Ground, MD: USAMRICD, 2007), 149.

12 Michael A. Dunn and Frederick R. Sidell, "Progress in Medical Defense against Nerve Agents," *Journal of the American Medical Association* 262(1989): 651.

13 Sidell, Newmark, and McDonough, "Nerve Agents," 198, Table 5-8.

14 Ibid., 199; I. Koplovitz et al., "Reduction by Pyridostigmine Pretreatment of the Efficacy of Atropine and 2-Pam Treatment of Sarin and Vx Poisoning in Rodents," *Fundamental and Applied Toxicology* 18(1992): 104.

hazard.[15] Three types of drugs are typically used to treat nerve agent poisoning: an anticholinergic, an oxime reactivator, and an anti-convulsant.[16] The most commonly administered anticholinergic is atropine, which counteracts nerve agent poisoning by making nerve tissues less receptive to ACh. By binding to certain muscarinic ACh receptors found on nerves, smooth muscle, glands, and the brain, atropine essentially blocks the excess ACh from transmitting its signal in these parts of the body. Oximes break the bonds between nerve agents and AChE, freeing up the enzyme to resume hydrolyzing ACh. Lastly, the anti-convulsant is used to treat seizures that may result from severe nerve agent exposure.[17] There is some evidence that atropine also plays a role in reducing nerve agent-induced seizures.[18]

The nerve agent antidotes issued to individual U.S. service members consist of three Antidote Treatment Nerve Agent Auto-Injectors (ATNAAs) that each include 2.1 mg of atropine and 600 mg of pralidoxime chloride (2-PAM Cl), the only oxime approved by the U.S. Food and Drug Administration (FDA) for use in the United States,[19] and one auto-injector containing 10 mg of the anti-convulsant diazepam. The recent switch to the single-needle ATNAAs resulted in a 50% reduction in time to administer both the atropine and 2-PAM Cl over the formerly fielded Mark I kits, which contained two separate auto-injectors for the two antidotes.[20]

The *Medical Management of Chemical Casualties Handbook* describes the procedures for self- and buddy aid on the battlefield. The instructions in the following extract are still current, although the next edition of the handbook will replace all references to the Mark I kits with the currently-fielded ATNAAs.

> The doctrine for self-aid for nerve agent intoxication states that if an individual has effects from the agent, he/she should self-administer one Mark I kit. If there is no improvement within 10 minutes, he/she should seek out a buddy to assist in the evaluation of his/her condition before further Mark I kits are given. If a buddy finds an individual severely intoxicated (e.g., gasping respirations, twitching, etc.)

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15 North Atlantic Treaty Organization (NATO), *AMedP-6(C): NATO Handbook on the Medical Aspects of NBC Defensive—Vol III—Chemical*, (Brussels: NATO, 2006), 2–21.

16 McDonough and Shih, "Atropine and Other Anticholinergic Drugs."

17 Chemical Casualty Care Division, *Nerve Academy*; McDonough and Shih, "Atropine and Other Anticholinergic Drugs"; Sidell, Newmark, and McDonough, "Nerve Agents."

18 Tsung-Ming Shih, Tami C. Rowland, and John H. McDonough, "Anticonvulsants for Nerve Agent-Induced Seizures: The Influence of the Therapeutic Dose of Atropine," *Journal of Pharmacology and Experimental Therapeutics* 320, no. 1 (2007); Tsung-Ming Shih and John H. McDonough, "Efficacy of Biperiden and Atropine as Anticonvulsant Treatment for Organophosphorus Nerve Agent Intoxication," *Archives of Toxicology* 74(2000); Tsung-Ming Shih and John H. McDonough, "Organophosphorus Nerve Agent-Induced Seizures and Efficacy of Atropine Sulfate as Anticonvulsant Treatment," *Pharmacology Biochemistry and Behavior* 64, no. 1 (1999); Michael Murphy et al., "Diazepam as a Treatment for Nerve Agent Poisoning in Primates," *Aviation, Space, and Environmental Medicine* 64 (1993).

19 Sidell, Newmark, and McDonough, "Nerve Agents," 187.

20 Ibid., 183. Personal correspondence with the U.S. Army Office of the Surgeon General confirmed that the ATNAAs have been fielded as the replacement for the Mark I kits.

> so that the individual cannot self-administer a Mark I kit, the buddy should administer three Mark I kits and diazepam immediately.[21]

Medics responding to a severe casualty in the field without intravenous (IV) access may administer additional atropine intramuscular (IM) in intervals of three to five minutes until secretions are minimized and breathing is easy.[22]

2) Hospital Administration of Nerve Agent Antidotes

The antidotes used for definitive care of nerve agent casualties are the same as those carried by service members in their nerve agent antidote kits, namely atropine, 2-PAM Cl, and diazepam. According to *Medical Aspects of Chemical Warfare*, the amount of each antidote administered depends on the severity of exposure and the response to treatment.

> In a conscious casualty with mild-to-moderate effects who is not in severe distress, 2 mg of atropine should be given intramuscularly at 5-minute to 10-minute intervals until dyspnea and secretions are minimized. Usually no more than a total dose of 2 to 4 mg is needed. In an unconscious casualty, atropine should be given until secretions are minimized (those in the mouth can be seen and those in the lungs can be heard by auscultation), and until resistance to ventilatory efforts is minimized (atropine decreases constriction of the bronchial musculature and airway secretions).[23]

Administration of atropine to a severely exposed patient consists of "a 6-mg IM loading dose followed by 2-mg increments until IV access is established."[24]

As highlighted in the excerpt above, drier respiratory secretions and easier respiration are the recommended endpoints of administering atropine. Several references[25] expressly pointed out that since local ocular symptoms are not responsive to systemic administration of atropine unless given in very large doses, miosis alone should not be the basis for continuing to administer atropine.

Since 2-PAM Cl and atropine are administered together via the ATNAA, the appropriate dose of 2-PAM Cl is somewhat tied to the dose of atropine. However, "because of the hypertensive effect of 2-PAM Cl, U.S. military doctrine states that no more than 2000 mg IV or three autoinjectors (600 mg each) should be given in 1 hour. If patients require additional

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21 Chemical Casualty Care Division, *Medical Management of Chemical Casualties Handbook*, 141.

22 Dr. Charles G. Hurst, U.S. Army Medical Research Institute for Chemical Defense (USAMRICD), personal communication, 15 November 2011.

23 Sidell, Newmark, and McDonough, "Nerve Agents," 184.

24 Ibid.

25 Durham and Hayes, "Organic Phosphorus Poisoning"; Sidell, Newmark, and McDonough, "Nerve Agents"; U.S. Department of the Army, "Multiservice Tactics, Techniques and Procedures for Treatment of Chemical Agent Casualties and Conventional Military Chemical Injuries," (Washington, DC: Government Printing Office, 2007).

treatment in the interim, atropine alone is used."[26] Although the therapeutic dosage of 2-PAM Cl is still undetermined, *Medical Aspects of Chemical Warfare* indicates that it is likely 15–25 mg/kg,[27] which is roughly equivalent to the amount from two to three ATNAAs administered to a 70 kg individual.

U.S. doctrine states that if a nerve agent casualty requires three ATNAAs, one 10 mg autoinjector of diazepam is to be administered following the third ATNAA.[28] For a convulsing casualty, 30–40 mg of diazepam should be given to treat the seizures and prevent their return. A casualty with flaccid paralysis should be assumed to be seizing and treated the same way.[29]

d. Maintain Ventilation and Circulation

Maintaining ventilatory and cardiovascular function is important both for long-term survival and for the success of short-term antidote therapy. Oberst et al.[30] noted that "atropine will not bring about resuscitation in the absence of adequate ventilation. In fact, atropine delivered to an anoxic heart may even be deleterious, in that ventricular fibrillation may be precipitated."[31] Durham and Hayes reiterated the risks of administering atropine to a patient with severe anoxia. "Atropine should not be given to an anoxic patient because of the danger of producing ventricular fibrillation. In the cyanotic patient, artificial respiration, oxygen, or other indicated measures should be carried out first to correct the anoxia, and then atropine should be given."[32]

Several studies on animals have demonstrated the benefit of artificial respiration in addition to treating nerve agent poisoning with atropine. Wills[33] reported the unpublished findings of Muir and Clements that artificial ventilation of sarin-exposed monkeys as a supplement to atropine therapy increased the protection ratio (PR) more than 25 times over that of treatment with atropine alone. In their study of dogs exposed to sarin gas, Oberst et al.[34] found that artificial respiration, in addition to atropine, saved a majority of dogs when treatment was initiated within four minutes post-exposure.

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26 Sidell, Newmark, and McDonough, "Nerve Agents," 189.

27 Ibid., 187.

28 Ibid., 190.

29 Dr. Charles G. Hurst, USAMRICD, personal communication, 15 November 2011.

30 Fred W. Oberst et al., "Resuscitation of Dogs Poisoned by Inhalation of the Nerve Gas Gb," *Military Medicine* 119 (1956).

31 Ibid., 384.

32 Durham and Hayes, "Organic Phosphorus Poisoning," 32.

33 J.H. Wills, "Pharmachological Antagonists of the Anticholinesterase Agents," in *Cholinesterases and Anticholinesterase Agents*, ed. George B. Koelle (Berlin; Göttingen; Heidelberg: Springer-Verlag, 1963).

34 Oberst et al., "Resuscitation of Dogs."

Sustaining circulation is also essential to successful treatment of nerve agent casualties, as the absorption of intramuscularly injected antidotes relies on adequate blood flow through the muscles. "Atropine injected after [the precipitous fall in blood pressure] into a muscle no longer perfused with blood will be increasingly ineffective. Therefore, an important limiting factor in resuscitation is circulatory, in that the specific antagonist is dependent on the circulation for distribution."[35] As previously mentioned, there is a risk of cardiac arrhythmia with atropine administration to a severely hypoxic patient, so heart complications will need to be treated if they occur.

3. Nerve Agent Medical Countermeasures

The literature on the treatment of nerve agent poisoning is quite extensive. It includes experiments on a variety of animal models, using various nerve agents through different routes of exposure and with different treatment regiments. Information on the effects of nerve agents and their treatment can be gleaned from in vitro and in vivo human experiments, as well as multiple reported laboratory exposures. The Iran-Iraq War produced thousands of Iranian battlefield nerve agent casualties,[36] and the terrorist attacks with sarin in Tokyo resulted in thousands of civilians seeking medical care. In addition, the treatment of other organophosphorus compounds, used as pesticides, has been reported in the literature.[37]

a. Human Cases

A summary of articles reporting pertinent human exposures is provided in Table 2. Although the doses are unknown, based on the symptom descriptions many of these cases were compared to the nerve agent casualty descriptions in *Medical Aspects of Chemical Warfare* and the injury profile maps in *AMedP-8(C)* to approximate the severity of exposure and inform the duration of treatment and the expected time until patients RTD.

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35 Ibid., 384.

36 Sidell, Newmark, and McDonough, "Nerve Agents," 157; Jonathan Newmark, "The Birth of Nerve Agent Warfare: Lessons from Syed Abbas Foroutan," *Neurology* 62, no. 9 (2004); Ulrich Helm, "Treatment of Nerve Agent Poisoning by the Iranian Medical Services in the First Gulf War," (University of Bonn, 1999).

37 Durham and Hayes, "Organic Phosphorus Poisoning"; Tatusji Namba and Kiyoshi Hiraki, "Pam (Pyridine-2-Aldoxime Methiodide) Therapy for Alkylphosphate Poisoning," *Journal of the American Medical Association* 166, no. 15 (1958); M. Balali-Mood and M. Shariat, "Treatment of Organophosphate Poisoning. Experience of Nerve Agents and Acute Pesticide Poisoning on the Effects of Oximes," *Journal of Physiology (Paris)* 92, no. 5–6 (1998).

Table 2. Reported Human Exposures to Nerve Agents or Organophosphorus (OP) Pesticides

Exposure type	Agent	Exposure route(s)	Source
Accident	GB	Inhalational	Clanton and Ward, 1952
Accident	GB	Inhalational	Gaon and Werne, 1955
Accident	GB	Inhalational, percutaneous, oral	Grob, 1956
Experiment	GB	Oral, intra-arterial, conjunctival	Grob and Harvey, 1958
Accident	Parathion	Inhalational, oral	Durham and Hayes, 1962
Accident	GB, GD	Inhalational, oral/dermal	Sidell, 1974
Accident	VX, GB	Oral, IV	Sidell and Groff, 1974
Terrorism	VX	Percutaneous	Nozaki et al., 1995a
Terrorism	GB	Inhalational	Nozaki et al., 1995b
Terrorism	GB	Inhalational	Okumura et al., 1996
Terrorism	GB	Inhalational	Nakajima et al., 1997
Terrorism	GB	Inhalational	Ohbu et al., 1997
Terrorism	GB	Inhalational	Okudera et al., 1997
Accident	OP pesticides	Oral	Balali-Mood and Shariat, 1998
War	GA, GB	Inhalational	Helm, 1999
Terrorism	GB	Inhalational	Okudera, 2002
War	GA, GB	Inhalational	Newmark, 2004

Note: Some cases are reported in more than one of the above sources.

b. Animal Studies

Although the human cases described above indicate that there is a history of success treating even severe nerve agent casualties, it is anticipated that there is some dose above which treatment will cease to be effective. One measure of this upper boundary is the protection ratio (PR), defined as the median lethal dose (LD_{50}) for a treated population divided by the LD_{50} for an untreated population exposed to the same challenge agent. Since human studies cannot be used to determine this value, animal studies are a logical surrogate.

The most appropriate animal model to use for human inhalation of nerve agent poisoning continues to be a matter of debate within the scientific community. It is generally accepted that non-human primates are an acceptable model,[38] although there may be a difference among

[38] Paul M. Lundy et al., "Comparative Protective Effects of Hi-6 and Mmb-4 against Organophosphorus Nerve Agent Poisoning," *Toxicology* 285, no. 3 (2011); Chunyuan Luo et al., "Comparison of Oxime Reactivation and Aging of Nerve Agent-Inhibited Monkey and Human Acetylcholinesterases," *Chemico-Biological Interactions* 175, no. 1–3 (2008); Timothy C. Marrs, Paul Rice, and J. Allister Vale, "The Role of Oximes in the Treatment of Nerve Agent Poisoning in Civilian Casualties," *Toxicological Review* 25, no. 4 (2006); UK Department of

various species of non-human primates. At the same time, variation in response to treatment between such closely related species as mice and rats has led some to conclude that humans and monkeys may differ significantly as well.[39] Some have purported that guinea pigs are also acceptable models,[40] but others have disputed this.[41]

Even the route of exposure in animal models is not without debate. Some believe that the intravenous route is an acceptable model for inhalation since the degree of protection and signs of poisoning obtained with the drug treatment are similar for both routes. More recently, however, Che et al.[42] reported that, due to differences in the toxicokinetics of nerve agents, "parenteral administration cannot be substituted for inhalation exposure."

The most relevant study would, theoretically, provide a PR from inhalation exposures to non-human primates subsequently treated with human equivalent doses of atropine, 2-PAM Cl, and diazepam, along with artificial respiration if necessary. PRs were cited or calculated from more than 20 sources.[43] While none of these values are derived from studies that exactly match

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Health, P.G. Blain, "Treatment of Poisoning by Selected Chemical Compounds. First Report. Expert Group on the Management of Chemical Casualties Caused by Terrorist Activity," (UK Department of Health, October 2003).

39 E.M. Cohen and H. Wiersinga, "Oximes in the Treatment of Nerve Gas Poisoning," *Acta Physiologica et Pharmacologica Neerlandica* 8, no. 1 (1959).

40 UK Department of Health, "Treatment of Poisoning by Selected Chemical Compounds"; Robert H. Inns and Levence Leadbeater, "The Efficacy of Bispyridinium Derivatives in the Treatment of Organophosphonate Poisoning in the Guinea-Pig," *Journal of Pharmacy and Pharmacology* 35, no. 7 (1983).

41 Lundy et al., "Protective Effects of Hi-6 and Mmb-4"; Luo et al., "Oxime Reactivation and Aging"; Marrs, Rice, and Vale, "Role of Oximes."

42 Magnus M. Che et al., "Post-Exposure Treatment with Nasal Atropine Methyl Bromide Protects against Microinstillation Inhalation Exposure to Sarin in Guinea Pigs," *Toxicology and Applied Pharmacology* 239, no. 3 (2009).

43 Dana R. Anderson et al., "The Effect of Pyridostigmine Pretreatment on Oxime Efficacy against Intoxication by Soman or Vx in Rats," *Drug and Chemical Toxicology* 15, no. 4 (1992); Beryl M. Askew, "Oximes and Atropine in Sarin Poisoning," *British Journal of Pharmacology* 12, no. 3 (1957); Cohen and Wiersinga, "Oximes in the Treatment of Nerve Gas Poisoning"; D.R. Davies, A.L. Green, and G.L. Willey, "2-Hydroxyiminomethyl-N-Methylpyridinium Methanesulphonate and Atropine in the Treatment of Severe Organophosphate Poisoning," *British Journal of Pharmacology* 14, no. 1 (1959); R.M. Dawson, "Review of Oximes Available for Treatment of Nerve Agent Poisoning," *Journal of Applied Toxicology* 14, no. 5 (1994); P. Dirnhuber et al., "Effectiveness of Pretreatment with Pyridostigmine in Protecting Rhesus Monkeys against Nerve Agent Poisoning," (Chemical Defense Establishment, 1977); J.J. Gordon and L. Leadbeater, "The Prophylactic Use of 1-Methyl, 2-Hydroxyiminomethyl-Pyridinium Methanesulfonate (P2s) in the Treatment of Organophosphate Poisoning," *Toxicology and Applied Pharmacology* 40, no. 1 (1977); Milan Jokanović and Milica Prostran, "Pyridinium Oximes as Cholinesterase Reactivators. Structure-Activity Relationship and Efficacy in the Treatment of Poisoning with Organophosphorus Compounds," *Current Medicinal Chemistry* 16, no. 17 (2009); D.E. Jones, W.H. Carter, and R.A. Carchman, "Assessing Pyridostigmine Efficacy by Response Surface Modeling," *Fundamental and Applied Toxicology* 5, no. 6 (1985); D.E. Jones et al., "Models for Assessing Efficacy of Therapy Compounds against Organophosphates (Op)," *Proceedings of the Fourth Annual Chemical Defense Bioscience Review* (1984); J. Kassa, "Review of Oximes in the Antidotal Treatment of Poisoning by Organophosphorus Nerve Agents," *Journal of Toxicology Clinical Toxicology* 40, no. 6 (2002); Irwin Koplovitz et al., "Evaluation of the Toxicity, Pathology, and Treatment of Cyclohexylmethylphosphonofluoridate (Cmpf) Poisoning in Rhesus Monkeys," *Archives of Toxicology* 66, no.

the ideal animal model experiment described above, one UK laboratory published a set of experiments that nearly meet these conditions.

The human dose of atropine (for a 70 kg person) is approximately 0.1 mg/kg, but humans are approximately four times more sensitive to atropine than rhesus monkeys.[44] The oxime P2S (pralidoxime mesylate) is closely related to 2-PAM Cl, which is the chloride salt of the same parent compound. According to Durham and Hayes,[45] "there appears to be no essential difference in the effects of the different salts of 2-PAM." Finally, the dose of diazepam administered to humans is approximately 0.14 mg/kg, but the rhesus monkey is likely to be less sensitive to diazepam than humans.[46]

Unpublished data by Muir and Clements and referenced by Wills[47] indicate that atropine (0.0285 mg/kg) and artificial ventilation alone afforded monkeys exposed to GB via inhalation a PR of greater than 80. Similarly, data from Oberst et al.[48] indicate that the PR for dogs exposed to GB via inhalation and then treated with atropine (5 mg/kg) and artificial ventilation is greater than 35.

Non-human primate studies in which the route of exposure was parenteral rather than inhalation provide some insight into the PR as well. Dirnhuber et al.[49] reported the results of subcutaneous exposures of GB and VX to rhesus monkeys that were treated with the same regimen as in the 1978 study described above. For both nerve agents, the PR was shown to be greater than 20; all six monkeys exposed to 20 LD_{50} survived. These findings were supported by a 1997 study by Olson et al.[50] in which three of three GB-exposed rhesus monkeys survived more than 2 LD_{50} and four of four VX-exposed monkeys survived more than 15 LD_{50} when treated with atropine (0.4 mg free base/kg) and 2-PAM (25.7 mg/kg).

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9 (1992); Koplovitz et al., "Efficacy of Atropine and 2-Pam."; Irwin Koplovitz and James R. Stewart, "A Comparison of the Efficacy of Hi6 and 2-Pam against Soman, Tabun, Sarin, and Vx in the Rabbit," *Toxicology Letters* 70, no. 3 (1994); Marrs, Rice, and Vale, "Role of Oximes"; Oberst et al., "Resuscitation of Dogs"; John F. O'Leary, Anne M. Kunkel, and Aili H. Jones, "Efficacy and Limitations of Oxime-Atropine Treatment of Organophosphorus Anticholinesterase Poisoning," *Journal of Pharmacology and Experimental Therapeutics* 132, no. 1 (1961); C.T. Olson et al., "Efficacies of Atropine/2-Pam and Atropine/Hi-6 in Treating Monkeys Intoxicated with Organophosphonate Nerve Agents," *International Journal of Toxicology* 16, no. 1 (1997); V. Simeon et al., "1,3-Bispyridinium-Dimethylether Mono- and Dioximes: Synthesis, Reactivating Potency and Therapeutic Effect in Experimental Poisoning by Organophosphorus Compounds," *Archives of Toxicology* 41, no. 4 (1979); Jacob W. Skovira et al., "Reactivation of Brain Acetylcholinesterase by Monoisonitrosoacetone Increases the Therapeutic Efficacy against Nerve Agents in Guinea Pigs," *Chemico-Biological Interactions* 187, no. 1–3 (2010); Wills, "Pharmachological Antagonists."

44 Dirnhuber et al., "Pretreatment with Pyridostigmine," 495.

45 Durham and Hayes, "Organic Phosphorus Poisoning."

46 Dirnhuber et al., "Pretreatment with Pyridostigmine," 495–96.

47 Wills, "Pharmachological Antagonists."

48 Oberst et al., "Resuscitation of Dogs."

49 Dirnhuber et al., "Pretreatment with Pyridostigmine."

50 Olson et al., "Atropine/2-Pam and Atropine/Hi-6."

Askew[51] reported a PR of three for a subcutaneous exposure of GB to monkeys (unspecified species) treated one minute after exposure with atropine (0.029 mg/kg). Wills[52] reported a similar study performed by Muir and Clements (1953, unpublished) in which a PR of three was also observed when monkeys (unspecified species) were exposed to GB via inhalation and shortly thereafter treated with atropine (0.0285 mg/kg). Based on the similar response to treatment for the two routes of exposure, it is reasonable to assume that monkeys exposed via inhalation and treated according to the protocols in the Dirnhuber reports would also survive exposures of 20 LD_{50}.

4. Nerve Agent Patient Management Parameters

The parameters for modeling the medical management of GB and VX casualties are shown in Table 3. They are derived from the existing *AMedP-8(C)* untreated injury profiles, RTD recommendations from *Medical Aspects of Chemical Warfare*, and the human and animal cases described in the previous chapter of this document.

Table 3. Patient Management Modeling Parameters for Nerve Agents GB and VX

Inhaled GB Dosage Range (mg-min/m^3)	Inhaled VX Dosage Range (mg-min/m^3)	Percutaneous VX Dose Range (mg/man)	Casualty Criteria			
			WIA	DOW	RTD	Convales-cent
0–0.2	0–0.02	0–0.8	0%	0%	0%	0%
0.2–6.5	0.02–2		If criterion met: 100%	0%	Day 1: 100%	0%
6.5–12	2–4	0.8–1.6	If criterion met: 100%	0%	Day 2: 100%	0%
12–25	4–10	1.6–3.9	100%	0%	For WIA (2) or WIA (3): Day 2: 33.3% Day 3: 33.3% Day 4: 33.3% For WIA (1): Day 4: 33.3% Day 5: 33.3% Day 6: 33.3%	0%
25–600	10–260	3.9–78	100%	0%	0%	100%
>600	>260	>78	100%	Day 14:100%	0%	0%

Since PB pretreatment would not be used in anticipation of exposure with GB or VX, there is no reason to model it. Treatment will be assumed to be as described in the doctrine:

[51] Askew, "Oximes and Atropine."

[52] Wills, "Pharmachological Antagonists."

decontamination, artificial ventilation and cardiovascular support if necessary, and antidote therapy with atropine, 2-PAM Cl, and diazepam when required.

AMedP-8(C) defines the nerve agent No Observable Effects exposure levels as 0–0.2 mg-min/m^3 inhaled GB, 0–0.02 mg-min/m^3 inhaled VX, and 0–0.8 mg/man percutaneous VX.[53] For nonlethal exposures resulting in symptoms (0.2–30 mg-min/m^3 inhaled GB, 0.02–13 mg-min/m^3 inhaled VX, or 0.8–3.9 mg/man percutaneous VX), service members may relieve some symptoms with self-aid, but since atropine is ineffective against miosis, mild ocular symptoms will remain for some time. If the severity criterion is WIA (1), then mild ocular symptoms will still dictate that a service member is a casualty in any dose range. The treatment for an individual exposed to a degree that would result in casualty status at the WIA (2) ($\geq$ 1 mg-min/m^3 inhaled GB, $\geq$ 0.3 mg-min/m^3 inhaled VX, or $\geq$ 0.8 mg/man percutaneous VX) or WIA (3) level ($\geq$12 mg-min/m^3 inhaled GB, $\geq$ 4 mg-min/m^3 inhaled VX, or $\geq$ 1.6 mg/man percutaneous VX) is more than what would be given as self-aid. Therefore, self-aid will not prevent an individual from entering the medical system.

The two lowest inhaled dosage ranges produce symptoms consistent with the *Medical Aspects of Chemical Warfare* descriptions of Minimal and Mild exposures.[54] For Minimal exposures, "if liquid exposure can be excluded, there is no reason for prolonged observation,"[55] and patients can be returned to duty within a few hours. Even without treatment, the symptoms of Minimal or Mild exposures would dissipate within a day.[56] This is confirmed by Sidell[57] who described three mild cases of accidental sarin inhalation that all healed without therapy. After six hours of observation, the three patients were discharged with only slight eye irritation and decreased vision in dim light. Nozaki et al.[58] reported Mild symptoms among 13 emergency room doctors treating victims of the Tokyo subway sarin attacks. Fewer than half were treated with atropine (and one additionally received 2-PAM iodide), but all were able to continue working through their symptoms. The last symptom to resolve, dim vision, lasted from two to twelve hours in most patients, but did persist for two days in two patients. A summary of the treatment of 640 victims from the same attack was reported by Okumura et al.[59] Most (528) of

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53 Carl A. Curling et al., *Technical Reference Manual: NATO Planning Guide for the Estimation of Chemical, Biological, Radiological, and Nuclear (CBRN) Casualties, Allied Medical Publication-8(C)*, IDA Document D-4082 (Alexandria, VA: Institute for Defense Analyses, August 2010).

54 Sidell, Newmark, and McDonough, "Nerve Agents," 191–92.

55 Ibid., 192.

56 Curling et al., *Technical Reference Manual*, 76–77, 82–83.

57 Frederick R. Sidell, "Soman and Sarin: Clinical Manifestations and Treatment of Accidental Poisoning by Organophosphates," *Clinical Toxicology* 7, no. 1 (1974).

58 H. Nozaki et al., "Secondary Exposure of Medical Staff to Sarin Vapor in the Emergency Room," *Intensive Care Medicine* 21, no. 12 (1995).

59 Tetsu Okumura et al., "Report on 640 Victims of the Tokyo Subway Sarin Attack," *Annals of Emergency Medicine* 28, no. 2 (1996).

these patients exhibited only Mild symptoms and were released after a maximum of 12 hours of observation.

The next highest inhaled dosage ranges (6.5–12 mg-min/m^3 inhaled GB and 2–4 mg-min/m^3 inhaled VX) and the percutaneous VX dose range (0.8–1.6 mg/man) result in symptoms that generally match those of Moderate exposures described by *Medical Aspects of Chemical Warfare*.[60] This reference recommends that "casualties with this degree of exposure should be observed closely for at least 18 hours after the onset of signs and symptoms." Grob and Harvey's 1958 article[61] describes experimental administration of sarin to volunteers via oral, intra-arterial, or conjunctival exposure and comments generally that "the effects of sarin were very prolonged, lasting from several hours after the smallest effective doses to several days after doses which produced Moderate symptoms."[62] These volunteers were treated only with atropine, and it is probable that the use of 2-PAM would have expedited their recovery times. In a later experiment,[63] all volunteers, including those that experienced vomiting (a Moderate symptom in *AMedP-8(C)*), had apparently recovered within the 48-hour timeframe of the experiment. Patients exposed to doses/dosages in these Moderate exposure ranges will be modeled to RTD in two days, reflecting the minimum waiting period of 18 hours recommended in *Medical Aspects of Chemical Warfare* and the multiple recovery days reported in the human experiments.

There are fewer human cases from which to model the next highest dose/dosage ranges (12–25 mg-min/m^3 inhaled GB, 4–10 mg-min/m^3 inhaled VX, and 1.6–3.9 mg/man percutaneous VX), and RTD recommendations for this exposure level are not given. The best indication for the duration of recovery comes from a second group of patients described by Okumura et al.[64] consisting of those with symptoms in addition to the mild ocular symptoms previously discussed, but not severe enough to require intubation or result in loss of consciousness. The 107 patients in this group likely contained those exposed to the dose/dosage ranges of interest as well as the ranges for Moderate exposure. After treatment with atropine and 2-PAM (and in some cases diazepam), all but two patients were discharged within two to four days, although at the time of discharge, approximately 60% of patients still complained of eye symptoms and approximately 25% complained of headache. The mean duration in the hospital for this group was 2.4 days.[65] The time to RTD for exposures in the dose/dosage ranges discussed in this paragraph will be modeled as two to four days (equal probability for days two, three, and four) if the *AMedP-8(C)* WIA criterion was above Severity Level 1, Mild. If WIA (1) (Mild symptoms or greater) was chosen as the criterion for casualty status, then mild ocular symptoms will delay the RTD by a

60 Sidell, Newmark, and McDonough, "Nerve Agents," 192.

61 Grob and Harvey, "Effects in Man."

62 Ibid., 367.

63 Sidell and Groff, "Reactivatibility of Cholinesterase."

64 Okumura et al., "Report on 640 Victims."

65 Ibid., 131.

few days. Assuming the resolution of miosis will be slightly faster than the seven and nine day durations reported in two of the most severely exposed cases,[66] this delay will be modeled as two days, resulting in the RTD on days four, five, and six after exposure.

The next highest inhaled dosage ranges (25–30 mg-min/m^3 for GB and 10–13 mg-min/m^3 for VX) are the highest dosages that are non-lethal without treatment. They are characterized by *AMedP-8(C)* Severity Level 3, i.e., Severe; respiratory; muscular and ocular symptoms; as well as brief lapses of consciousness. *Medical Aspects of Chemical Warfare* states that

> a soldier who has had signs of severe exposure with loss of consciousness, apnea, and convulsions, may have milder CNS [central nervous system] effects for many weeks after recovery from the acute phase of intoxication. Except in dire circumstances, return to duty during this time period should not be considered for such casualties.[67]

Casualties in this group will instead be retained for convalescent care.

The highest dose/dosage ranges (≥ 30 mg-min/m^3 inhaled GB, ≥ 13 mg-min/m^3 inhaled VX, and ≥ 3.9 mg/man percutaneous VX) are modeled as 100% lethal without treatment since the casualty remains at Severity Level 4, Very Severe, for more than 15 minutes.[68] Yet, it is reasonable to assume that with treatment, many of these casualties would recover. In fact, of 10 individuals reported in the literature that lost consciousness and required artificial respiration after nerve agent exposure, 8 were effectively treated.[69] One of the two fatalities was neither conscious nor breathing and was pronounced dead at the emergency room after no response to 30 minutes of CPR; the second died of "severe hypoxic brain damage" 28 days post-exposure.[70]

To model the increased survivability with treatment, a PR, like those derived from animal studies, will be applied to humans, effectively extending the range of non-lethal exposures. The new threshold for lethality will be the previous upper boundary times the PR. As discussed in the previous section on animal studies, it is sensible to assume that monkeys would survive exposures of 20 LD_{50}. This same PR will be assumed to apply to humans for both GB and VX exposure, resulting in new dose/dosage range limits of 600 mg-min/m^3 inhaled GB, 260 mg-min/m^3 inhaled VX, and 78 mg/man percutaneous VX. Everyone exposed to a degree less than the new lethal threshold will be modeled to survive but require convalescent care and will not

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66 Nozaki et al., "Secondary Exposure of Medical Staff"; B.R. Clanton and J.R. Ward, "Case Report of a Severe Human Poisoning by Gb," (Dugway Proving Ground, MD: Chemical Corps Medical Laboratories, 1952).

67 Sidell, Newmark, and McDonough, "Nerve Agents," 194.

68 NATO, *AMedP-8(C): NATO Planning Guide for the Estimation of CBRN Casualties*, (Brussels: NATO, 2011), 4-4.

69 Clanton and Ward, "Severe Human Poisoning by Gb"; David Grob, "The Manifestations and Treatment of Poisoning Due to Nerve Gas and Other Organic Phosphate Anticholinesterase Compounds," *Archives of Internal Medicine* 98, no. 2 (1956); Nozaki et al., "Secondary Exposure of Medical Staff"; Okumura et al., "Report on 640 Victims"; Sidell, "Soman and Sarin"; Sidell, Newmark, and McDonough, "Nerve Agents."

70 Okumura et al., "Report on 640 Victims," 132–33.

RTD. Everyone exposed to amounts above these values will be modeled to die, even with treatment. Given only two data points on the time to death (1 day and 28 days), it will be assumed that if medical care can be provided before a casualty in this highest range is declared dead (i.e., if the casualty is not KIA), then treatment will prolong, but not preserve, life. These individuals will be modeled to die after two weeks. The choice of two weeks is somewhat arbitrary and may result in an overestimate (if individuals die sooner) or underestimate (if individuals die later) of the burden on the medical system.

B. Blister Agent Patients

1. The Effects of Blister Agents

Under normal conditions, approximately 80% of sulfur mustard, or HD, applied to the skin evaporates, and the remaining 20% penetrates the skin,[71] of which approximately 90% is carried away in the blood stream.[72] Some sources[73] suggest that the 10% remaining in the skin rapidly becomes "fixed" (reacted) through interaction with the antioxidant glutathione,[74] and poses no threat to medical personnel. Others have concerns that a reservoir of unbound HD remains in the skin for some time and could potentially expose medical personnel even after patient decontamination through off-gassing.[75]

Not only does HD harm the directly exposed skin, eyes, and respiratory tract, but the rapid uptake of HD circulating in the blood stream by tissues throughout the body results in damage to the lymphatic system, bone marrow, and intestinal tract.[76] At least two hypotheses exist to explain the injury-causing biochemical processes induced by HD exposure. One contends that, as a DNA alkylating agent, HD causes tissue damage by directly breaking DNA strands in rapidly dividing cells. This triggers apoptosis (programmed cell death), an inflammatory response, and the separation of the dermis and epidermis causing blisters. A second hypothesis attributes these effects to the severe depletion of glutathione (due to its interaction with HD); a shortage of this

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71 Bruno Papirmeister et al., eds., *Medical Defense against Mustard Gas: Toxic Mechanisms and Pharmacological Implications* (Boca Raton, FL: CRC Press,1991), 80.

72 Chemical Casualty Care Division, *Medical Management of Chemical Casualties Handbook*, 69; H. Cullumbine, "Mustard Gas: Its Mode of Action and the Treatment of Its Local and General Effects," (Porton, Wilts: Chemical Defense Experimental Station, 1944), 262.

73 Chemical Casualty Care Division, *Medical Management of Chemical Casualties Handbook*, 69; Cullumbine, "Mustard Gas," 262.

74 Andrew J. Bobb, Darryl P. Arfsten, and Warren W. Jederberg, "N-Acetyl-L-Cysteine as Prophylaxis against Sulfur Mustard," *Military Medicine* 170, no. 1 (2005).

75 John S. Graham et al. "Wound Healing of Cutaneous Sulfur Mustard Injuries: Strategies for the Development of Improved Therapies," *Journal of Burns and Wounds* 4 (2005): 16.

76 Cullumbine, "Mustard Gas"; Dana R. Anderson et al., "Sulfur Mustard-Induced Neutropenia: Treatment with Granulocyte Colony-Stimulating Factor," *Military Medicine* 171, no. 5 (2006); Jan L. Willems, Clinical Management of Mustard Gas Casualties," *Annales Mediciniae Militaris Belgicae* 3, no. suppl 1 (1989).

antioxidant means the body cannot sufficiently inhibit naturally-produced reactive oxygen species to prevent cell damage and death.[77]

While the mortality rate is low (a rate of less than 5% can be expected[78]), most of the casualties that die from HD exposure succumb to "pulmonary damage complicated by infection bronchopneumonia, immunosuppression, and sepsis."[79]

2. Blister Agent Medical Management Principles

Although researchers around the world are developing concepts for medical countermeasures aimed at "elimination of body contact, improved decontamination, pharmacological intervention, and chemical casualty management,"[80] no antidote exists for HD exposure and no uniform standards of care have been developed.[81] Treatment consists mainly of symptomatic and supportive care. Describing the management of 65 Iranian patients evaluated in European hospitals after medical evacuation from the Iran-Iraq War, Willems wrote, "Treatment of these casualties was based on the following principles: avoidance of secondary infection, treatment of secondary infections when they occurred, general support, and the application of detoxification procedures."[82] These principles differ little from the policy of non-specific treatment of World War Two (WWII) mustard casualties 40 years earlier.[83]

Decontamination (by the service member) immediately after exposure is the only way to prevent or minimize symptoms from HD exposure.[84] By the time a patient presents to the medical system, decontamination will do little to counteract tissue damage at the site of exposure, but as "clothing, hair, and skin surfaces may still be contaminated hours [after exposure],"[85] decontamination may prevent further spreading to other areas on the body and exposure to medical personnel.

Following decontamination, the treatment of mustard burns on the skin is very similar to the treatment of thermal burns, although healing may take longer.[86] Lesions on the skin should

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77 Chemical Casualty Care Division, *Medical Management of Chemical Casualties Handbook*, 71–72; Charles G. Hurst et al., "Vesicants," in *Medical Aspects of Chemical Warfare*, *Textbooks of Military Medicine,* ed. Shirley D. Tuorinsky, (Washington, DC: Government Printing Office, 2008), 263–65; Bobb, Arfsten, and Jederberg, "N-Acetyl-L-Cysteine as Prophylaxis," 52.

78 Hurst et al., "Vesicants," 266.

79 Ibid., 276.

80 Graham et al., "Cutaneous Sulfur Mustard Injuries," 10.

81 Hurst et al., "Vesicants," 278.

82 Willems, "Clinical Management," 53.

83 Cullumbine, "Mustard Gas."

84 Hurst et al., "Vesicants," 277.

85 Ibid., 265.

86 Cullumbine, "Mustard Gas," 266.

be disinfected to avoid secondary infection and protected using sterile dressings.[87] Blister aspiration and debridement may reduce pain, infection, and healing time.[88] In addition, antiseptic solutions, ointments, and creams may be applied to both the skin and eyes of patients exposed to mustard.[89] Graham et al. advocate a more aggressive approach to optimize the healing time and cosmetic and functional outcome following severe HD cutaneous injuries, including full-thickness debridement of deep dermal burns followed by autologous split-thickness skin grafting.[90]

Willems noted a variety of general treatments applied to the Iranian casualties he reviewed:

> Systemic treatment included bronchodilators, corticosteroids, mucolytics, expectorants and antibiotics. When necessary, oxygen was given or artificial ventilation was applied. Further treatment was symptomatic, maintaining water and electrolyte balance, giving a calorie-rich diet, and sometimes white cell transfusions to counteract leucopenia.[91]

Many of these same procedures were reported by Cullumbine, who reiterated electrolyte replacement as a key factor in reducing mortality.[92] Cullumbine also cautioned that shock, toxemia, and secondary infection need to be prevented or treated.[93] Although antibiotics are sometimes required to combat secondary infections, *Medical Aspects of Chemical Warfare* specifies that "there is no indication for the routine administration of systemic antibiotics to patients with HD injury."[94]

3. Blister Agent Medical Countermeasures

There has been no systematic evaluation of the efficacies of various treatments, but the effect of treatment on mortality and the duration of hospitalization can be gleaned from historical reports such as Willems' description of the 65 Iranian patients treated in Europe.[95] This data set provides information on the cause of death for those casualties that did not survive as well as the time until discharge from the hospital for those that survived. "Most patients returned to Iran in a fairly good condition after 2 to 10 weeks of treatment. Their lesions were nearly completely

87 Willems, "Clinical Management," 55.

88 Cullumbine, "Mustard Gas," 266; Hurst et al., "Vesicants," 278.

89 Willems, "Clinical Management," 27, 54.

90 Graham et al., "Cutaneous Sulfur Mustard Injuries," 13; John S. Graham et al., "Efficacy of Laser Debridement with Autologous Split-Thickness Skin Grafting in Promoting Improved Healing of Deep Cutaneous Sulfur Mustard Burns," *Burns* 28, no. 8 (2002); John S. Graham et al., "Medical Management of Cutaneous Sulfur Mustard Injuries," *Toxicology* 263, no. 1 (2009).

91 Willems, "Clinical Management," 54.

92 Cullumbine, "Mustard Gas," 269.

93 Ibid., 267.

94 Hurst et al., "Vesicants," 281.

95 Willems, "Clinical Management."

healed, although some lesions remained."[96] Additionally, at the time of their discharge from the hospital, several patients still complained of expectorations and coughing[97] and some still experienced photophobia.[98]

The total duration of hospitalization for each of the 65 patients is shown in Table 4 (reproduced from Willems' Table II-1)[99] and was determined mainly by the time needed for the deeper skin lesions to heal, which typically occurred within five to seven (although sometimes more than nine) weeks.[100] Superficial skin lesions normally healed within two to three weeks.[101] Treatment of ocular symptoms in this group lasted between 3 and 28 days, which Willems notes is "in agreement with previous observations: healing times of 2 weeks for mild conjunctivitis, 4–5 weeks for severe conjunctivitis, and 2–3 months for corneal lesions."[102]

96 Ibid., 56.

97 Ibid., 39.

98 Ibid., 40.

99 Ibid., 4–5.

100 Ibid., 40, Table IV-1.

101 Ibid.

102 Ibid., 40.

Table 4. Time Post-Exposure until Discharge from European Hospital or Death for 65 Iranian Mustard Casualties

Index	Days to discharge	Days to death	Index	Days to discharge	Days to death	Index	Days to discharge	Days to death
1	27		23	71		45	17	
2		12	24	41		46	25	
3		16	25	26		47	34	
4	21		26	76		48	69	
5		13	27	26		49	54	
6	22		28	48		50	69	
7	33		29	34		51	51	
8	33		30	43		52	40	
9	28		31	42		53	45	
10		185	32	38		54	50	
11	28		33	38		55	45	
12	21		34	41		56	50	
13	41		35	39		57	66	
14	42		36	27		58		7
15		15	37	34		59	52	
16	47		38	27		60	Unknown	
17	36		39	39		61		Unknown
18	47		40		12	62	Unknown	
19	36		41	50		63	Unknown	
20	26		42	50		64	28	
21	26		43	43		65	28	
22		6	44	26				

Table 4 also shows the time to death for the nine patients that did not survive. "Eight patients died between 6 and [16] days after exposure. One patient died 185 days after exposure; he had been ventilated for an extended period because of severe bronchiolitis complicated by a series of more or less localized pneumothoraxes."[103] This is in general agreement with the results of historical mustard casualties, most of whom died four or more days after exposure.[104] The distribution of time to death for World War One (WWI) mustard casualties is recreated in Table 5.[105] Since the Iranian casualties reported by Willems arrived no earlier than four days after exposure, this data set cannot be compared to the early end of the WWI casualty distribution.

[103] Ibid., 55–56.

[104] Hurst et al., "Vesicants," 266.

[105] Ibid., 266, Table 8-4.

Table 5. Day of Death after Exposure in World War I Fatal Mustard Casualties

Day of death (after exposure)	Percentage of deaths
≤1	1
2	2
3	5
4	8
5	22
≥6	62

The rate of mortality (approximately 14%) seen among the 65 Iranian casualties is greater than the 3% figure cited by *Medical Aspects of Chemical Warfare*[106] due to the fact that all the casualties evacuated from Iran had Moderate to Severe injuries.[107]

4. Blister Agent Patient Management Parameters

Unlike nerve agent casualties, HD casualties may not benefit from a shortened recovery time as a result of medical intervention, since treatment consists mainly of supportive care, which does little to accelerate the regeneration of damaged tissues. The parameters for modeling the treatment of HD are shown in Table 6. They are derived from the existing *AMedP-8(C)* untreated injury profiles, RTD recommendations from *Medical Aspects of Chemical Warfare*, and historical war casualties described in the previous chapter of this document.

Table 6. Patient Management Modeling Parameters for Blister Agent HD

HD Dosage Range (mg-min/m^3)	Casualty Criteria			
	WIA	DOW	RTD	Convalescent
0–4	0%	0%	0%	0%
4–12	If criterion met: 100%	0%	Day 3: 100%	0%
12–26	If criterion met: 100%	0%	Day 4: 100%	0%
26–50	If criterion met: 100%	0%	Day 5: 100%	0%
50–70	If criterion met: 100%	0%	Day 14: 100%	0%
>70	100%	Day 1: 0.1% Day 2: 0.3% Day 3: 0.7% Day 4: 1.1% Day 5: 3.0% Days 6–16: 0.8% each	Week 3: 7.5% Week 4: 9.6% Week 5: 14.7% Week 6: 17.5%	36.7%

106 Ibid., 266.

107 Willems, "Clinical Management," 26.

Medical Aspects of Chemical Warfare provides guidelines on how the major physiological systems affected by HD determine which casualties should RTD and when. In general, "because of the slow healing properties of sulfur mustard injuries, any casualty with significant injury to the eyes, respiratory tract, skin, gastrointestinal tract, or CNS should not RTD for weeks to months."[108]

The lowest level of exposure modeled to produce ocular symptoms is in the range of 4–26 mg-min/m^3. Untreated, these symptoms are expected to resolve within 60 hours.[109] Although ointments and creams applied to the eyes may reduce the pain, they may not restore vision, and miosis is likely to be unresponsive to treatment. Consequently, ocular symptoms from exposure to this dosage range will still be modeled to persist for two and a half days. Casualties with symptoms dominated by ocular effects in this range (i.e., those exposed to 4–12 mg-min/m^3) will not RTD until day three.

At the low end of the first dosage range that produces skin symptoms (12–125 mg-min/m^3), sensitivity of the skin in the crotch, armpits, and on the insides of the elbows and knees is more prolonged than the ocular symptoms just described. In this range, no blisters are expected to form, and healing requires four days without treatment.[110] As with ocular symptoms, local treatment for skin irritation would consist of antiseptic solutions, ointments, and creams, but skin symptoms will still be modeled to last four days.

The second ocular range (26–50 mg-min/m^3) falls within the skin range just described, and untreated symptoms resolve in four and a half days.[111] As before, treatment will be modeled to offer little benefit in the reduction of recovery time and the duration of medical care will be dominated by ocular, rather than skin, symptoms. Casualties will be modeled to RTD on day five post-exposure.

According to *Medical Aspects of Chemical Warfare*, "even the mildest form of conjunctivitis causes a functional blindness from pain, photophobia, and spasm of the eyelid muscles; this conjunctivitis resolves in an average of 2 weeks."[112] At the exposure range of 50–70 mg-min/m^3, untreated ocular symptoms are estimated to last four weeks.[113] Since this is the lowest dosage range in which untreated symptoms exceed two weeks, it is assumed that the two week duration of treated symptoms applies to exposures in this range. Thus treatment will be modeled to reduce the RTD time to two weeks for casualties exhibiting these symptoms.

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[108] Hurst et al., "Vesicants," 290.

[109] Curling et al., *Technical Reference Manual*, 116.

[110] Ibid., 112, 117.

[111] Ibid., 116.

[112] Hurst et al., "Vesicants," 290.

[113] Curling et al., *Technical Reference Manual*, 116.

Above 70 mg-min/m^3 ocular symptoms become severe, and above 125 mg-min/m^3 skin lesions become more significant. Although the inhaled dosages cannot be known precisely for the 65 Iranian casualties treated in European hospitals described by Willems,[114] it is assumed that all were exposed to dosages greater than 70 mg-min/m^3, since all patients were hospitalized for more than two weeks. Moreover, the majority of patients reported conjunctivitis (85%), corneal damage (54%), and airway lesions (71%). In addition, all 65 patients experienced skin lesions, although not all developed blisters. Without additional knowledge of the dosage-dependence of these exposures, all treated casualties receiving dosages above 70 mg-min/m^3 will be modeled according to the DOW, RTD, or convalescent casualty distributions in the Willems data set.

The time to death for HD fatalities will reflect the distribution shown in Table 5 from WWI mustard casualties as well as the more recent Iranian casualties detailed in Table 4. Since there were more than 4,000 data points to define the WWI distribution,[115] the percentages are fairly precise. With comparably few fatal cases from the Iranian casualties, fleshing out the distribution beyond five days is likely to introduce a higher level of uncertainty. Therefore since the nine fatalities (with the exception of the death at day 185) were distributed more or less uniformly across the span of days 6 through 16 after exposure (days 6, 7, 12, 12, 13, 15, 16, 185, and unspecified),[116] the 62% of fatalities after day 5 will be split evenly among days 6 through 16 as shown in Table 7 below.

[114] Willems, "Clinical Management."

[115] Hurst et al., "Vesicants," 266.

[116] Willems, "Clinical Management," 4–5.

Table 7. DOW Casualty Distribution for Blister Agent HD

Day of death (after exposure)	Percentage of deaths		Percentage of all casualties
1	1	*9/65=	0.1
2	2	*9/65=	0.3
3	5	*9/65=	0.7
4	8	*9/65=	1.1
5	22	*9/65=	3.0
6	62/11	*9/65=	0.8
7	62/11	*9/65=	0.8
8	62/11	*9/65=	0.8
9	62/11	*9/65=	0.8
10	62/11	*9/65=	0.8
11	62/11	*9/65=	0.8
12	62/11	*9/65=	0.8
13	62/11	*9/65=	0.8
14	62/11	*9/65=	0.8
15	62/11	*9/65=	0.8
16	62/11	*9/65=	0.8
Total DOWs as a percentage of all casualties:			14.0

The remaining 86% of HD casualties will be split among the RTD and convalescent casualty categories, with patients discharged within the first six weeks post-exposure designated as RTD casualties and those discharged later than six weeks assigned to the convalescent casualty category. The specific time to discharge was reported for 53 of the 56 surviving patients in the Willems report and ranged from 17 to 76 days, as shown in Figure 1 below. The distribution that best fits these data is a normal distribution with a mean of 39.5 days and a standard deviation of 13.6 days, which is overlaid on the data in Figure 1. This distribution was used to model the percentage of individuals that RTD in weeks three through six or require convalescent care, as shown in Table 8.

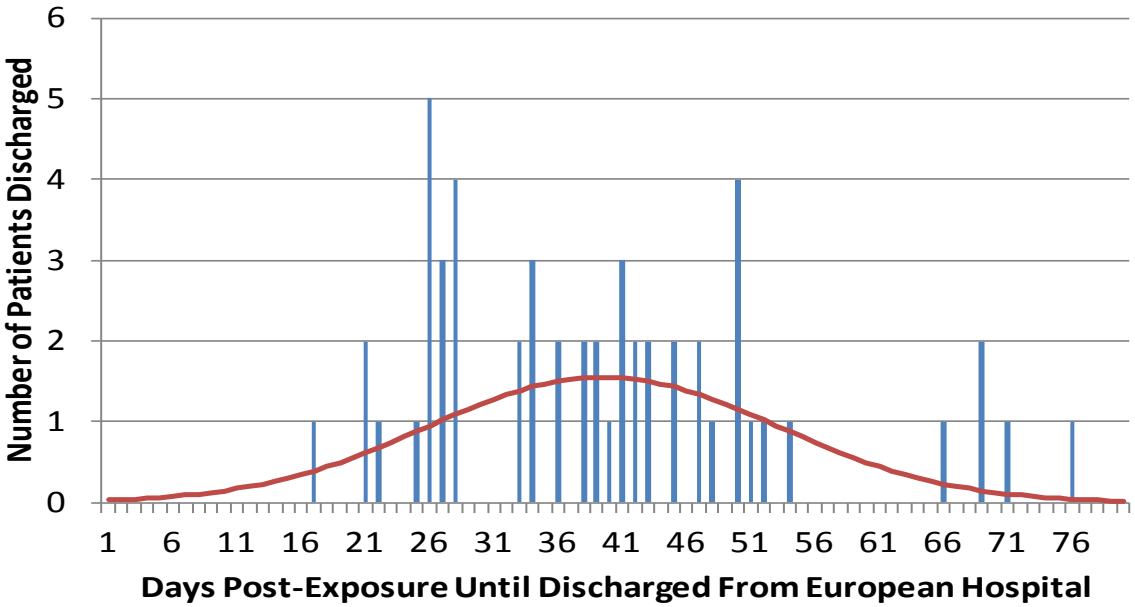

Figure 1. Time to Discharge for 53 Blister Agent Patients Reported by Willems

Table 8. RTD and Convalescent Casualty Distribution for Blister Agent HD

Day of discharge (after exposure)	Percentage of survivors		Percentage of all casualties	Modeled as
0–21	8.7	*0.86=	7.5	RTD Week 3
22–28	11.2	*0.86=	9.6	RTD Week 4
29–35	17.1	*0.86=	14.7	RTD Week 5
36–42	20.3	*0.86=	17.5	RTD Week 6
>42	42.7	*0.86=	36.7	Convalescent

3. Biological Agents

The *AMedP-8(C)* model of human response to biological agents is derived from a set of five underlying submodels characterizing various aspects of the disease. An infectivity submodel estimates the number of individuals who become ill, given their dose of agent. An incubation or latency period submodel estimates when those individuals develop signs and symptoms. A lethality submodel estimates the number of ill individuals who die. A duration of illness submodel estimates the length of time between onset of symptoms and death or recovery. Finally, an injury profile submodel describes clinically differentiable stages of the disease and the severity of the associated signs and symptoms over time.

For non-contagious biological agents, the current outputs of *AMedP-8(C)*—numbers of WIA and DOW over time—are derived directly from these five submodels. For contagious biological agents, these submodels are incorporated into the framework of an epidemic model that includes additional factors, such as disease transmission rate, to account for the spread of contagious disease within a population. *AMedP-8(C)* human response models have been developed for eight non-contagious agents (anthrax, tularemia, brucellosis, glanders, Q fever, Venezuelan equine encephalitis (VEE), botulism, and Staphylococcal enterotoxin B (SEB)) and two contagious agents (pneumonic plague and smallpox).

Consideration of medical management can change some or all of the parameters associated with specific biological agent human response submodels, and, hence, change the outputs of the *AMedP-8(C)* casualty estimation methodology. Medical countermeasures such as vaccines, pre-exposure prophylaxis, and post-exposure prophylaxis can reduce or eliminate the probability that an individual will become ill, or reduce mortality among those who develop disease. For some agents, medical countermeasures can also reduce the severity or duration of illness in the event it does occur. Treatment provided after onset of symptoms will not change infectivity or time to onset, but can alter the probability of mortality, the duration of illness, and the severity of illness over time. The individual agent sections that follow focus on the nature and extent of the effects of medical countermeasures and treatment on those aspects of illness caused by biological agents considered in *AMedP-8(C)* and their associated submodels.

The biological agent casualty estimation methodology in *AMedP-8(C)* differs from the CRN methodology in a number of ways that affect associated data requirements. For example, unlike CRN agent human response models, biological agent human response models consider disease as manifest in the whole body. For biological agents, injury profiles that consider medical management can be derived from top-down measures of severity, such as time spent in intensive care. This contrasts with the CRN methodology, where injuries are characterized as a

collection of separable signs/symptoms observed in individual physiological systems. For CRN agents and effects, therefore, injury profiles that consider medical management have to be built from the bottom up, starting with the effects of medical countermeasures and treatment on specific signs/symptoms over time.

In addition, the *AMedP-8(C)* biological agent models account for the variation in human response typically seen among individuals by characterizing the five submodels as probability distributions of various types. To the extent that it is supported by the literature, the variability in biological agent human response is retained when considering medical countermeasures and treatment. However, for some agents there are very few, if any, human cases of the disease from which the required data can be taken. Thus, consideration of treatment may result in more deterministic models for some biological agents.

Medical management of biological agent casualties follows several general principles:

- Minimize individual susceptibility to disease. Vaccination and chemoprophylaxis are designed to counter specific biological agent threats by boosting an individual's immune system and preventing infection.
- Counter specific pathogens. Once infection has occurred, antibiotic and antiviral drugs may be available to target and destroy many organisms within the body and arrest the progression of the disease. For many viral biological warfare agents, however, these drugs are not available, and for bacterial agents, natural or engineered resistance may limit their effectiveness.
- Reverse or repair damage caused by pathogens. Recovery from biological agent illness often requires extended periods of convalescence, when treatment focuses on repairing bodily systems and functions damaged during the course of illness.
- Provide supportive care. During periods of active infection and convalescence, treatment is often targeted towards mitigating the effects of the disease, to both limit damage to bodily systems and to alleviate pain and suffering. Ventilation, fluid replacement, and pain management are examples of supportive care.

This section describes medical management for biological agent-induced illnesses, to include medical countermeasures and treatment. It also discusses the effects of medical management on the aspects of the disease used to model human response, and describes the corresponding changes to the biological agent human response models resulting from consideration of medical management.

For many biological agent-induced diseases, no medical countermeasures or specific treatments exist, and treatment is limited to supportive care. In these cases, the submodels now used in *AMedP-8(C)* to describe human response to these agents would not change with consideration of treatment. In other cases, the effects of treatment may be limited to some but not all submodels for a given agent. In the sections below, patient management parameters for each

agent are provided only for those submodels that change as a consequence of treatment. Where submodel parameters remain unchanged, note is made that they are the same as those in *AMedP-8(C)*, but the values and derivation thereof are not given.

A. Anthrax Patients

1. The Effects of Inhalational Anthrax

Anthrax is a zoonosis caused by the bacteria *Bacillus anthracis*. It occurs world-wide in wild and domesticated animals, primarily herbivores. In humans the disease is acquired primarily through contact with infected animals, usually via the cutaneous route. However, anthrax can also be acquired through ingesting or inhaling anthrax spores. The presentation and severity of the disease varies by route of entry: cutaneous anthrax, the most common naturally occurring form of the disease, has a mortality rate of less than 1%, while inhalation anthrax has a mortality rate approaching 100% in the absence of treatment, and, historically, even with treatment, mortality rates have been between 45% and 70%.[117]

Anthrax acquired via inhalation begins with non-specific symptoms of febrile illness, including malaise, fatigue, myalgia, and fever; this early phase of the disease continues for a few days. During this period of active infection, anthrax bacteria produce copious amounts of toxin, which circulates in the body and builds up in pleural fluid around the lungs, severely inhibiting respiration. The second, fulminate stage of the disease begins abruptly, with the patient experiencing sudden respiratory distress. In the absence of treatment, there is rapid progression to shock and death, typically within one to two days.[118]

2. Anthrax Medical Management Principles

Medical management of inhalation anthrax has two primary objectives: preventing onset of the disease through vaccination or chemoprophylaxis and, if that fails, administering antibiotics as quickly as possible after the onset of symptoms. Supportive care typically focuses on reducing toxin load in the body and assisting respiration as needed.

3. Anthrax Medical Countermeasures

In 2009, the U.S. Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) issued revised recommendations for the use of anthrax

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117 Bret K. Purcell, Patricia L. Worsham, and Arthur M. Friedlander, "Anthrax," in *Medical Aspects of Biological Warfare*, *Textbooks of Military Medicine,* ed. Zygmunt F. Dembek (Washington, DC:Government Printing Office, 2007), 75–76.

118 Ibid., 76. The mortality rate in the 1979 accidental aerosol release of anthrax at Sverdlovsk is estimated to be about 70%, while in the 2001 U.S. anthrax letters cases, five of 11 individuals with inhalation anthrax died, for a mortality rate of 45%. Many of the patients in the latter series of cases received intensive and heroic medical care, which likely contributed to a lower mortality rate than that seen in Sverdlovsk.

vaccine in both pre- and post-exposure scenarios, and for antimicrobial drugs in post-exposure scenarios.[119] This report updates and expands upon guidelines initially issued in 2002.

Individuals at risk of occupational exposure to inhalation anthrax, including military personnel as determined by the Department of Defense (DOD), should be vaccinated against anthrax with the FDA-licensed vaccine, BioThrax, formerly known as Anthrax Vaccine Adsorbed (AVA). The approved vaccination schedule consists of five 0.5 ml injections at 0 and 4 weeks and 6, 12, and 18 months, with annual boosters.[120]

Post-exposure prophylaxis combining vaccination with BioThrax and antimicrobial therapy can effectively prevent illness in individuals who have not previously been vaccinated, or have begun but not completed, the recommended BioThrax vaccination series. In the event of exposure to anthrax via inhalation, the ACIP recommends that unvaccinated individuals be administered 500 mg ciprofloxacin or 100 mg doxycycline orally, twice daily for 60 days; this therapy should begin as soon as possible after exposure. In addition, individuals should receive injections of BioThrax vaccine at 0, 2, and 4 weeks post-exposure, preferably beginning within 10 days of exposure. ACIP also recommends that individuals who completed the full BioThrax vaccination schedule prior to exposure consider a 30-day course of post-exposure antibiotics.[121]

4. Anthrax Treatment

Current guidelines for treatment of inhalation anthrax, derived primarily from experience in the 2001 U.S. anthrax letters cases, recommend administration of two or more antibiotics in combination, to preclude variations in strain susceptibility to different classes of antibiotics.[122] Until antibiotic susceptibility is known, administered antibiotics should include ciprofloxacin or doxycycline, plus one or two additional antibiotics known to be effective against anthrax. This treatment should be administered intravenously until the patient is clinically stable enough to take oral medication.

Case histories of 10 of the 11 inhalation anthrax patients in the 2001 U.S. cases show that all patients followed the pattern of an early period of nonspecific febrile illness followed by sudden onset of respiratory distress and Very Severe illness. As shown in Table 9, the average duration of the initial phase was four days for survivors and five days for non-survivors; to some extent this difference can be attributed to delays in hospitalization for two of the non-survivors (Cases 5 and 6) who were initially misdiagnosed. All non-survivors, despite being treated

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119 Jennifer Gordon Wright et al., "Use of Anthrax Vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices (Acip), 2009," *Morbidity and Mortality Weekly Report* 59, no. rr06 (2010).

120 Ibid., 20.

121 Ibid., 20–21.

122 Thomas V. Inglesby et al., "Anthrax as a Biological Weapon, 2002: Updated Recommendations for Management," *Journal of the American Medical Association* 287, no. 17 (2002).

aggressively in an intensive care unit (ICU) setting, died, on average, two days after admission to the hospital. Survivors, on average, remained hospitalized in an ICU setting for approximately 18 days; upon release they typically continued oral antibiotic therapy for several weeks.[123]

All six survivors of the 2001 anthrax letters cases were near the end of the first phase of illness when they first sought medical care. All six were promptly hospitalized and administered appropriate antibiotics on that same day. All four non-survivors were in the second, Very Severe, stage of illness when they were hospitalized and appropriate antibiotics were administered.[124]

In addition, pleural effusions were present in all 10 patients. Seven patients required drainage of pleural fluid as part of their supportive care, and 6 of those 7 patients survived.

Table 9. Duration of Illness for 10 U.S. Inhalational Anthrax Cases

Case	Time from Onset to Hospitalization (days)	Time from Hospitalization to Death or Discharge (days)	Outcome
Case 1	5	3	Death
Case 2	7	22	Recovery
Case 3	3	24+	Recovery
Case 4	4	20	Recovery
Case 5	5	<1	Death
Case 6	6	1	Death
Case 7	2	16	Recovery
Case 8	5	17	Recovery
Case 9	3	8	Recovery
Case 10	3	4	Death
Average (Survivors)	**4**	**18**	
Average (Non-survivors)	**5**	**2**	

A recent case of naturally occurring inhalational anthrax in Minnesota involved a 61-year-old man who was treated according to these guidelines and survived. The patient's case history closely mirrored that observed in the 2001 cases.[125] The man had been suffering fatigue at the end of a lengthy vacation and became seriously ill while visiting friends in Minnesota in early August, 2011. He was hospitalized with a preliminary diagnosis of pneumonia on August 4, and

123 John A. Jernigan et al., "Bioterrorism-Related Inhalational Anthrax: The First 10 Cases Reported in the United States," *Emerging Infectious Diseases* 7, no. 6 (2001).

124 Ibid., 940.

125 Robert Roos, "Early Diagnosis and Treatment Helped Florida Man Beat Anthrax," *Center For Infectious Disease Research and Policy (CIDRAP) News*(30 August 2011), http://www.cidrap.umn.edu/cidrap/content/bt/anthrax/news/aug3011anthrax.html; ProMED-mail, "Anthrax—USA (09): (Minnesota)," (International Society for Infectious Diseases, 31 August 2011).

subsequently diagnosed with inhalational anthrax the next day, after which he was treated with intravenous ciprofloxacin and clindamycin. Like the survivors in the 2001 anthrax cases, the man had pleural fluid drained from around his lungs; in this case, however, they were drained as part of a deliberate attempt to reduce the load of anthrax toxin in his body rather than maintain ventilation. The man was also treated with anthrax immune globulin derived from the serum of vaccinated individuals.[126] The man was released after 25 days of hospitalization, most of it in intensive care, with instructions to continue taking oral ciprofloxacin for 60 days per CDC recommendations.

5. Anthrax Patient Management Parameters

For inhalational anthrax, consideration of the medical countermeasures and treatment described above alter submodels for infectivity, lethality, and duration of illness. In addition, the injury profile for anthrax has been modified to include a separate profile for survivors. The incubation period submodel for anthrax is unaffected and remains the same as the one described in *AMedP-8(C)*.

a. Infectivity

Both pre-exposure vaccination and post-exposure prophylaxis can prevent development of disease in the vast majority of exposed individuals. The efficacy of the BioThrax vaccine appears to be very high, although not necessarily uniform against all strains of anthrax. Based on a review of a number of vaccine challenge studies involving rhesus monkeys, *AMedP-8(C)* recommends the (conservative) use of a vaccine efficacy factor of 90%.[127] The P8PEM model incorporates this same value.

In a study of the efficacy of post-exposure prophylaxis against inhalational anthrax in rhesus monkeys, Friedlander et al. found that a combination of vaccination and antibiotic therapy was completely effective in preventing the onset of the disease.[128] The basic premise, demonstrated in the study, is that antibiotic therapy staves off infection long enough to allow a vaccine-generated immune response to develop. This study and its findings continue to provide the basis for the ACIP post-exposure prophylaxis recommendations.

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126 Anthrax immune globulin is an experimental product currently available only through the U.S. CDC. According to Roos, "Early Diagnosis and Treatment Helped Florida Man Beat Anthrax," the Minnesota patient was the 19th to receive this drug, which the CDC also provided to Health Protection Scotland in 2010 to treat cases of anthrax among intravenous drug users. See Nicki Pesik, "Helping Scotland Investigate, Treat Anthrax among Heroin Users," *Public Health Matters Blog* (11 February 2010), http://blogs.cdc.gov/publichealthmatters/2010/02/helping-scotland-investigate-treat-anthrax-among-heroin-users. The safety and efficacy of this product is the subject of ongoing research.

127 Curling et al., *Technical Reference Manual*, 198.

128 Arthur M. Friedlander et al., "Postexposure Prophylaxis against Experimental Inhalation Anthrax," *Journal of Infectious Diseases* 167, no. 5 (1993).

In the Friedlander study, 8 of 10 animals treated with vaccine alone died; clinical presentation and time to death did not differ from that observed in control animals. Three groups of 10 animals each were treated with antibiotics alone for 30 days: one with penicillin, one with doxycycline, and one with ciprofloxacin. One animal in the ciprofloxacin group died during the period of therapy for reasons determined to be unrelated to the experiment and was eliminated from consideration; all other animals survived the period of therapy and none developed symptoms of disease during this time. However, some animals developed anthrax and died after the period of therapy ended, including three in the penicillin group and one each in the doxycycline and ciprofloxacin groups. A fifth group of 10 animals was both vaccinated and given doxycycline. One of these animals died during the period of study from undetermined causes and was eliminated from further consideration. All others survived both an initial inhaled challenge dose of $4.0 \pm 1.6 \times 10^5$ spores and a re-challenge 131 to 142 days later with $2.6 \pm 1.6 \times 10^6$ spores, and all remained disease-free at the time of study publication.[129]

The findings of the Friedlander study regarding the efficacy of post-exposure prophylaxis combining antibiotics and vaccination were confirmed in a subsequent study by Vietri et al., which sought to demonstrate efficacy in a shortened course of antibiotics.[130] In the Vietri study, all 10 rhesus monkeys that were vaccinated and given ciprofloxacin survived challenges of approximately 1,600 LD_{50} of aerosolized anthrax spores.

Studies have found that anthrax spores can remain dormant in the lungs for weeks or months; this accounts for cases where disease develops after cessation of antibiotic treatment and thus underlies the ACIP recommendations for a lengthy course of antibiotic therapy in the aftermath of exposure. Thus despite the complete protection offered by combined antibiotics and vaccination in the rhesus monkey studies, it is possible that disease could eventually develop in individuals despite post-exposure prophylaxis. However, given the efficacies of pre-exposure vaccination (90%) and long-course post-exposure antibiotic prophylaxis (90%) observed independently in the studies cited above, it would be expected that the combination would have an overall efficacy of at least 99%. For the purposes of the P8PEM methodology, therefore, post-exposure prophylaxis is assumed to have an efficacy of 100%.

b. Lethality

Treatment can significantly reduce the lethality rate for inhalational anthrax. The P8PEM model incorporates a lethality model from Holty et al.'s review of identified cases of inhalational

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129 Ibid., 1240–41.

130 Nicholas J. Vietri et al., "Short-Course Postexposure Antibiotic Prophylaxis Combined with Vaccination Protectst against Experimental Inhalational Anthrax," *Proceedings of the National Academy of Sciences* 103, no. 20 (2006).

anthrax occurring between 1900 and 2005.[131] This review used data from the 2001 anthrax letters cases to derive a conditional probability of mortality given time to initiation of antibiotics:

Probability of mortality = (0.012 * (time to antibiotic treatment measured in days)) + 0.1, if initiated during initial, prodromal stage;

Probability of mortality = 1, if antibiotics initiated during the second, fulminant stage.

c. Injury Profile

Because it does not include the effects of treatment, *AMedP-8(C)* considered anthrax to have a lethality rate of 100%, and included a single injury profile, for non-survivors. The P8PEM methodology, by contrast, includes injury profiles for both survivors and non-survivors.

The review of inhalational anthrax cases by Holty et al.[132] and the case histories of the 2001 anthrax letters cases published by Jernigan et al.[133] suggest that while the duration of illness varies for survivors and non-survivors, treated or untreated, the basic presentation of illness remains generally the same. Thus in the P8PEM model, the signs and symptoms experienced in Stage 1 (prodromal stage) and Stage 2 (fulminate stage) and their associated severities are common for both survivors and non-survivors, and are the same as those described in *AMedP-8(C)*. Non-survivors are assumed to die at the end of Stage 2. Survivors recover gradually, with Stage 3 recovery taking place in a hospital setting and Stage 4 recovery taking place over an extended convalescent period at home. The inhalation anthrax injury profile with treatment is shown in Table 10.

131 Jon-Erik C. Holty et al., "Systematic Review: A Century of Inhalational Anthrax Cases from 1990 to 2005," *Annals of Internal Medicine* 144, no. 4 (2006): 272.

132 Ibid., 270–80.

133 Jernigan et al., "Bioterrorism-Related Inhalational Anthrax."

Table 10. Inhalational Anthrax Injury Profile with Treatment

	Stage 1 (all)	Stage 2 (all)	Stage 3 (survivors)	Stage 4 (survivors)
Signs and Symptoms (S/S)	Flu-like symptoms including malaise, fatigue, drenching sweats, fever, headache, and chills; nausea and vomiting; nonproductive cough; mild chest discomfort and dyspnea; myalgia.	Fever; sudden onset of increasing respiratory distress; tachycardia, tachypnea, hypotension,; altered neurological status (confusion, syncope, or coma) meningoencephalitis; pleural effusion and likely widening and edemas of the mediastinum.	Resolution of fever, gradual cessation of acute symptoms	Malaise, weakness
S/S Severity	Severity Level 3 (Severe)	Severity Level 4 (Very Severe)	Severity Level 3 (Severe)	Severity Level 2 (Moderate)
Outlook	Individual will progress to Stage 2	Death or progression to Stage 3	Individual will progress to Stage 4	Return to Duty

d. Duration of Illness

The Holty review identified 36 cases from 1900 to 2005 where inhalational anthrax was treated with either antibiotics, anthrax antiserum, or both. Overall, these treatments prolonged both the prodromal and fulminant stages of disease beyond what was typically observed in untreated cases. Holty et al. used a maximum likelihood estimator[134] to derive both Weibull and lognormal distributions of duration of both the prodromal and fulminant stages of disease. Because *AMedP-8(C)* uses the lognormal distribution derived by Holty et al. to characterize duration of illness stages in untreated cases,[135] the present authors selected the same functional form to model treated cases.

In cases where antibiotic treatment was initiated in the prodromal phase, Holty et al., estimated the mean duration of prodromal and fulminant stages of anthrax to be 5.8 (std. dev. = 2.0) and 1.4 (std. dev. = 1.8) days, respectively. Where antibiotic treatment was delayed until the fulminant stage of illness, that stage was still prolonged: the mean duration of the prodromal stage was 4.2 days (std. dev. = 2.3)—the same as for untreated cases—and the mean duration of

[134] Holty et al., "Century of Inhalational Anthrax Cases," W-44–W-45.

[135] Curling et al., *Technical Reference Manual*, 200–01.

the fulminant stage was 1.5 days (std. dev. = 1.3)—some 0.3 days longer than for untreated cases.[136]

The Holty et al. review did not characterize the time between the end of the fulminant stage of the disease and recovery for survivors, all of whom would have initiated antibiotic treatment during the prodromal phase of illness. As noted above, in the 2001 anthrax cases survivors spent an average of 18 days in the hospital. For purposes of the P8PEM methodology, the duration of the hospital recovery period is estimated to be a fixed 11 days. This represents the difference between the mean hospital stay for survivors of the 2001 anthrax cases—18 days—and the combined mean duration of prodromal and fulminant stages of illness—7.2 days—derived from the Holty et al. review for individuals with early antibiotic intervention.

Finally, individuals who survive inhalational anthrax require an extensive period of convalescence, during which they continue to receive antibiotic treatment for several weeks to counter delayed germination of anthrax spores. Although limited data exist, at present, regarding the overall extent and nature of the convalescent period and long-term consequences of the disease, the P8PEM methodology assumes patients can RTD 60 days after their hospital release.

B. Botulism Patients

1. The Effects of Botulism

Botulinum toxins are a set of neurotoxins, serotypes A through G, produced by the *Clostridium botulinum* bacteria. Exposure to the toxin via various pathways—ingestion, intramuscular injection or inhalation—will cause the neuroparalytic disease botulism in humans. The symptoms of botulism are largely independent of route of entry. The disease presents as an acute, symmetrical, descending, flaccid paralysis beginning with the muscles involved in head control and extending through the upper extremities, respiratory muscles, and lower extremities. Time to onset, severity of illness, and probability of death vary by serotype. The discussion below focuses on serotype A because it has been responsible for the plurality of human botulism cases reported in the United States and, among those cases, has typically been associated with the most severe disease.

2. Botulism Medical Management Principles

Medical management of botulism patients has two primary objectives: to arrest progression of the disease through the body as quickly as possible, and to maintain life through supportive care until the patient recovers. Supportive care would initially focus on maintenance of ventilation, but would also include infection control and physical therapy during recovery.

[136] Holty et al., "Century of Inhalational Anthrax Cases," Appendix Table 4: W-52.

3. Botulism Medical Countermeasures

At present there are no FDA-approved vaccines for the prevention of botulism. A formalin-inactivated pentavalent toxoid vaccine, which protected against botulinum toxin serotypes A through E, was administered to laboratory personnel and other at-risk individuals from 1959 through 2011; the CDC recently stopped providing this vaccine, due to declining immunogenicity—possibly due to the age of the drug—and increased occurrence of moderate local reactions.[137]

The U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) recently developed a new bivalent recombinant vaccine, protective against botulinum toxin serotypes A and B. This vaccine promises to be both more immunogenic and less reactive than the toxoid vaccine and is now in clinical trials.[138]

Botulinum antitoxin—both despeciated equine antitoxin and human botulism immune globulin—can effectively prevent botulism if administered immediately prior to or immediately after exposure.[139] However, antitoxin has limited availability, requires refrigeration, offers short-lived protection, and carries significant risk of anaphylaxis. It is not, therefore, generally recommended for use in asymptomatic individuals. In those with known exposure to botulinum toxin, the risks from administration of antitoxin must be weighed against the risk of disease.[140] The American Medical Association (AMA) recommends that asymptomatic individuals who are believed to have been exposed should remain under close medical observation and, if feasible, near critical care services.[141]

4. Botulism Treatment

While often fatal if untreated, the case fatality rate for treated serotype A botulism patients in the United States was 6.7% between 1990–1996[142]; most deaths were the result of respiratory failure or secondary infection resulting from prolonged mechanical ventilation. While treatment

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137 Zygmunt F. Dembek, Leonard A. Smith, and Janice M. Rusnak, "Botulinum Toxin," in *Medical Aspects of Biological Warfare*, *Textbooks of Military Medicine,* ed. Zygmunt F. Dembek (Washington, DC: Government Printing Office, 2007), 345.

138 Ibid., 346.

139 David R. Franz et al., "Efficacy of Prophylactic and Therapeutic Administration of Antitoxin for Inhalation Botulism," in *Botulinum and Tetanus Neurotoxins: Neurotransmission and Biomedical Aspects*, ed. Bibhuti R. Das-Gupta (New York: Plenum Press, 1993).

140 Dembek, Smith, and Rusnak, "Botulinum Toxin," 344.

141 Stephen S. Arnon et al., "Botulinum Toxin as a Biological Weapon: Medical and Public Health Management," *Journal of the American Medical Association* 285, no. 8 (2001): 1068.

142 Centers for Disease Control and Prevention, "Botulism in the United States, 1899–1996: Handbook for Epidemiologists, Clinicians, and Laboratory Workers," (Atlanta, GA: Centers for Disease Control and Prevention, 1998), Table 2.

for botulism can be very effective, it is both extensive and enduring, including the administration of botulism antitoxin, assisted ventilation, and extensive supportive care.[143]

Until recently, botulinum antitoxin was available in various forms and limited quantities from the CDC. As of March 2010, a new heptavalent botulinum antitoxin, known as HBAT, became the only botulinum antitoxin available in the United States to treat non-infant botulism.[144] HBAT contains despeciated, equine-derived antibodies to botulinum toxin serotypes A through G.

Although antitoxin will effectively prevent further paralysis within hours of its administration, the progression of paralysis in botulism patients is so rapid that antitoxin cannot typically be administered quickly enough to avoid respiratory paralysis. Thus, most botulism patients will require assisted ventilation: in a study of all reported botulism patients in the United States from 1975 through 1988, 60% of those with serotype A botulism required intubation and assisted ventilation, and the average time from onset to intubation was one day.[145]

While antitoxin can prevent the further progression of paralysis, it does not reverse it. Recovery from botulism is slow, with mechanical ventilation required for several weeks and paralysis persisting for months.[146]

Because despeciated animal products carry a risk of hypersensitivity reactions, research is underway to develop human-compatible monoclonal antibodies (hMabs) for the treatment of botulism. For example, a combination of three hMabs, highly efficacious against all known subtypes of serotype A toxin, are now in Phase 1 clinical trials, while hMabs for other serotypes are in earlier stages of development.[147]

5. Botulism Patient Management Parameters

For botulism, consideration of the medical countermeasures and treatment described above alter submodels for effectivity, lethality, and duration of illness. In addition, the injury profile for botulism has been modified. The latent period submodel for botulism is unaffected and remains the same as that described in *AMedP-8(C)*.

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143 Arnon et al., "Botulinum Toxin as a Biological Weapon," 1066–67.

144 Centers for Disease Control and Prevention, "Investigational Heptavalent Botulinum Antitoxin (Hbat) to Replace Licensed Botulinum Antitoxin Ab and Investigational Botulinum Antitoxin E," *Morbidity and Mortality Weekly Report* 59, no. 10 (2010).

145 Bradley A. Woodruff et al., "Clinical and Laboratory Comparison of Botulism from Toxin Types a, B, and E in the United States, 1975–1988," *Journal of Infectious Diseases* 166, no. 6 (1992): 1283.

146 Dembek, Smith, and Rusnak, "Botulinum Toxin," 343–44.

147 Dr. Leonard Smith, USAMRIID, personal communication, November 2011.

a. Effectivity

Experience with the pentavalent toxoid vaccine suggests that countermeasures could be very effective in preventing the disease. For example, between 1945 and 1969, 50 accidental exposures to botulinum toxins occurred at Fort Detrick among vaccinated laboratory workers; none developed botulism.[148] Tests with early formulations of recombinant vaccines against serotypes A and B demonstrated that when vaccinated three times, mice were fully protected against intraperitoneal challenge doses of 10^5 mouse LD_{50}.[149]

Although, at present, there are no FDA-licensed medical countermeasures against botulism available, should vaccinated individuals be included in a population at risk for purposes of casualty estimation, they should be considered fully protected against the development of botulism.

b. Lethality

The overall case fatality rate for treated cases of naturally occurring type A botulism in the United States is 7%. Death was the result of respiratory failure or secondary infection resulting from prolonged mechanical ventilation.[150] Since some 60% of type A botulism overall required mechanical ventilation, the fatality rate for ventilated patients was 12%.

With treatment, a sizeable fraction of all botulism patients never require ventilation, either because the administration of antitoxin effectively arrests progression of the disease, or because the dose of toxin was insufficient to cause respiratory failure. The P8PEM model assumes that 40% of botulism patients fall into this category; all are expected to survive. The remaining 60% are assumed to become sufficiently ill to require mechanical ventilation; of these ventilated patients, 12% are expected to die.

c. Injury Profile

As noted, the P8PEM methodology assumes that all these patients who do not require mechanical ventilation will survive, and that deaths from botulism are restricted to those patients who do require mechanical ventilation. Consequently, the methodology includes three separate injury profiles for botulism with treatment: survivors without ventilation, survivors with ventilation, and non-survivors.

Because death may occur at any time after the onset of respiratory paralysis, survivors who require mechanical ventilation and non-survivors are assumed to experience the same injury

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148 Dembek, Smith, and Rusnak, "Botulinum Toxin," 345.

149 Michael P. Byrne and Leonard A. Smith, "Development of Vaccines for the Prevention of Botulism," *Biochimie* 83, no. 9–10 (2000): 962.

150 James M. Hughes et al., "Clinical Features of Types a and B Food-Borne Botulism," *Annals of Internal Medicine* 95, no. 4 (1981): 444.

profile through the first three stages of illness. The injury profiles for botulism with treatment are shown in Table 11 and Table 12.

Table 11. Botulism Injury Profile with Treatment, Unventilated Survivors

	Stage 1	Stage 2	Stage 3
Signs and Symptoms (S/S)	Fatigue; dry mouth; ptosis; diplopia; photophobia; dysphagia; facial paralysis.	Acute symmetrical descending flaccid paralysis; progressive muscle weakness in the head and neck, followed by upper extremities and lower extremities; dysphagia and loss of gag reflex; diplopia; dysarthria; dysphonia; fatigue.	Gradual reversal of muscle paralysis.
S/S Severity	Severity Level 2 (Moderate)	Severity Level 3 (Severe)	Severity Level 2 (Moderate)
Outlook	Individual will progress to Stage 2	Progression to Stage 3	Convalescence and RTD

Table 12. Botulism Injury Profile with Treatment, Ventilated Survivors and Non-Survivors

	Stage 1 (all)	Stage 2 (all)	Stage 3 (all)	Stage 4 (survivors)
Signs and Symptoms (S/S)	Fatigue; dry mouth; ptosis; diplopia; photophobia; dysphagia; facial paralysis.	Acute symmetrical descending flaccid paralysis; progressive muscle weakness in the head and neck, followed by upper extremities and lower extremities; dysphagia and loss of gag reflex; diplopia; dysarthria; dysphonia; fatigue.	Acute symmetrical descending flaccid paralysis; paralysis in respiratory muscles and upper and lower extremities; respiratory failure.	Gradual reversal of muscle paralysis.
S/S Severity	Severity Level 2 (Moderate)	Severity Level 3 (Severe)	Severity Level 4 (Very Severe)	Severity Level 2 (Moderate)
Outlook	Individual will progress to Stage 2	Progression to Stage 3	Death or Progression to Stage 4	Convalescence

The division of botulism patients into *unventilated* and *ventilated* categories is determined by assumptions about both the overall dose of toxin and the time at which the antitoxin is administered. Given the distribution of doses among the exposed population, the existing *AMedP-8(C)* model for lethality in the absence of treatment, is used to determine that fraction of patients that received a dose that is a priori insufficient to cause respiratory failure and death. These patients are automatically assigned to the unventilated category.

The remaining patients can be assigned to the unventilated category if the progression of the disease is halted by treatment—i.e., by the administration of antitoxin—before the point at which mechanical ventilation is required. The existing *AMedP-8(C)* methodology for duration of illness in the absence of treatment is used to determine the time at which these patients are expected to enter Stage 3 of the illness, as shown in Table 12 above. If that time is greater than the assumed time at which antitoxin is administered, patients are assigned to the unventilated category.

Finally, if the time at which patients enter Stage 3 is less than the assumed time of antitoxin administration, patients are assigned to the ventilated category. Of these patients, some 12% are expected non-survivors, while the remaining 88% are expected survivors.

d. Duration of Illness

Botulism is a disease with a rapid onset and protracted clinical course. A study of all botulism cases occurring in the United States over a 14-year period found that in cases where mechanical ventilation was required, it was implemented within a day of symptom onset. Once initiated, mechanical ventilation may be required for several weeks, and paralysis can persist for months. Some symptoms, such as cranial nerve dysfunction and mild autonomic dysfunction, can last for more than a year.[151] In one case study comparing the clinical features of type A and type B botulism, Type A patients requiring mechanical ventilation were ventilated for a mean duration of 58 days, and were hospitalized for a mean of 63 days.[152] In this study, no information was provided regarding duration of hospitalization for cases where ventilation was not required.

Another case study specifically assessed the course of clinical recovery from Type A botulism in the second largest outbreak of the disease recorded in the US, involving 34 people who ingested toxin at a restaurant in Clovis, New Mexico in April 1978.[153] All patients in this outbreak were hospitalized, all but one received antitoxin, and two died. The authors of the study interviewed 27 survivors at either 9 or 13 months after the outbreak, and provided them with a written questionnaire 24 months afterward. This study found that those who required mechanical ventilation had a mean duration of hospitalization of 76.4 days, with a range of 19 to 164 days.

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151 Dembek, Smith, and Rusnak, "Botulinum Toxin," 341.

152 Hughes et al., "Clinical Features of Types a and B Food-Borne Botulism," 444.

153 J.M. Mann et al., "Patient Recovery from Type a Botulism: Morbidity Assessment Following a Large Outbreak," *American Journal of Public Health* 71, no. 3 (1981).

Those who did not require ventilation had a mean duration of hospitalization of 7.3 days, with a range of 4 to 17 days.[154]

The study also found that symptoms persisted for longer periods of time and in greater numbers among patients requiring ventilation. At 24 months, those cases reported a mean of five persistent symptoms, while the unventilated cases reported a mean of two persistent symptoms. Data on return to work showed that virtually all of the unventilated patients had resumed a full work schedule within nine months of the outbreak, while only 25% of ventilated patients had done so.[155]

Using data from the Clovis outbreak, the P8PEM model assumes that unventilated patients spend an average of one day in Stage 1 of illness, seven days in Stage 2 of illness, and nine months in Stage 3 of illness, after which they are expected to RTD.

For ventilated patients, the duration of illness for Stages 1 and 2 of illness were derived from the *AMedP-8(C)* model of untreated duration for the purposes of assigning these patients to the ventilated category. Stage 3 for these patients is characterized by the need for mechanical ventilation: ventilation is assumed to be initiated at the start of Stage 3, and to continue for 10 weeks. Stage 4 begins with hospital discharge and lasts for months or years; these patients are assumed to be permanently convalescent and never RTD.

C. Brucellosis Patients

1. The Effects of Brucellosis

Brucellosis, also known as undulant fever, is a prevalent zoonotic infection of large animals, especially cattle, camels, sheep, and goats. Most naturally occurring cases of brucellosis in humans are caused by ingestion of animal food products or direct contact with infected animals. However, brucellosis is also highly infectious in aerosol form. Clinical manifestations of brucellosis are highly diverse, and are independent of route of entry; symptoms of patients infected by aerosol are indistinguishable from those of patients infected via other routes of entry.[156]

Patients with brucellosis may present with an acute febrile illness, a chronic infection, and/or localized inflammation. Most patients experience nonspecific symptoms such as fever and malaise, which makes the disease difficult to diagnose, particularly early in the course of illness. Brucellosis is notable among potential biological warfare agents for the duration of illness: in the absence of treatment, acute infection typically lasts several weeks, while chronic infection can

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154 Ibid., 266.

155 Ibid., 268.

156 Bret K. Purcell, David L. Hoover, and Arthur M. Friedlander, "Brucellosis," in *Medical Aspects of Biological Warfare*, *Textbooks of Military Medicine,* ed. Zygmunt F. Dembek (Washington, DC: Government Printing Office, 2007).

last for a year or more. Both acute and chronic forms are often associated with an undulating fever pattern, where individuals exhibit fluctuations in fever during the course of a day, or have afebrile periods lasting several days followed by renewed periods of fever. Brucellosis often localizes in a specific area of the body, causing pain in that area. This most frequently occurs in the bones, central nervous system, heart, liver, or spleen.[157]

Although brucellosis patients are extremely ill, the disease is very rarely fatal: generally, death only occurs when the infection resides in the central nervous system or the heart. Relapse is common, occurring in between 5% and 40% of patients, depending on antibiotic use, duration of treatment, and drug combination. Relapse infections are typically, but not always, less severe than initial infections.[158]

2. Brucellosis Medical Management Principles

Medical management of brucellosis focuses on reducing the duration of illness and preventing relapse through the administration of antibiotics.

3. Brucellosis Medical Countermeasures

There is no commercially available vaccine for humans against brucellosis. Neither are there formal or consensus recommendations for antibiotic prophylaxis, although anecdotal evidence indicates that it may effectively prevent disease. In one incident of accidental laboratory exposure,[159] five out of six technicians who may have been exposed to brucellosis underwent antibiotic prophylaxis and never developed symptoms; the sixth technician refused antibiotics and developed symptomatic disease. Thus antibiotic prophylaxis should be considered in the event of confirmed exposure to brucellosis.

4. Brucellosis Treatment

Treatment for brucellosis involves the administration of antibiotics and supportive care. Because therapy with a single antibiotic has resulted in a high relapse rate, combined regimens are generally recommended.[160] Although there is no standardized treatment regiment for brucellosis, a six-week oral regimen of the drugs rifampin at 900 mg per day and doxycycline at 200 mg per day for 45 days has been shown to be nearly 100% effective in treating most clinical

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157 Carl A. Curling et al., *Parameters for the Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia*, IDA Document D-4132 (Alexandria, VA: Institute for Defense Analyses, November 2010), 36–40.

158 Turan Buzgan et al., "Clinical Manifestations and Complications in 1028 Cases of Brucellosis: A Retrospective Evaluation and Review of the Literature," *International Journal of Infectious Diseases* 14, no. 6 (2010): e477.

159 Sophie Robichaud et al., "Prevention of Laboratory-Acquired Brucellosis," *Clinical Infectious Diseases* 38, no. 12 (2004).

160 Purcell, Hoover, and Friedlander, "Brucellosis," 191.

manifestations of brucellosis, with a relapse rate of less than 10%.[161] Other drug combinations may provide equal or better outcomes for patients with certain specific manifestations of illness, such as those with spondylitis or osteoarticular involvement.[162] Some studies have also suggested that adding a third antibiotic may provide an even higher cure rate and reduce relapse rates to near zero.[163]

5. Brucellosis Patient Management Parameters

For brucellosis, the only submodel affected by consideration of treatment is duration of illness.

a. Duration of Illness

The disease has an extended course, even with treatment, and typically is severe enough to require a period of routine hospitalization. In one study of 379 brucellosis patients in Kuwait, the mean hospital stay was 9 days, with a range of 3 to 90.[164] Among these patients, different symptoms resolved at different times: arthralgia, myalgia, and sweats resolved within seven days of the start of treatment, arthritis generally within two weeks, pulmonary signs and symptoms between one and two weeks, and the pain and muscle spasms associated with spondylitis within about two weeks, although patients with the latter manifestation did not see significant radiologic improvement for months. The resolution of fever was highly variable, with 19% of cases becoming afebrile before the initiation of treatment, 43% within 5 days of the start of treatment, 29% within 6 and 10 days, and 9% at periods longer than 10 days.

Although not a fatal disease, brucellosis patients are considered severely ill and are assumed to require routine hospitalization for two weeks. After discharge, they will require outpatient care and the continued administration of antibiotics for an additional four weeks.

The P8PEM methodology assumes that the antibiotic therapy administered is an effective drug combination and for an effective duration, and, hence, the probability of relapse is minimized. Because relapse in such circumstances would be expected in fewer than 10% of cases, it is not considered here.

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161 Recommendation of the Joint FAO/WHO Expert Committee on Brucellosis, *World Health Organization Technical Report Service* 740 (1986): 1–132. Cited in Purcell, Hoover, and Friedlander, "Brucellosis."

162 Buzgan et al., "1028 Cases of Brucellosis," e477.

163 See for example, Abdul Rabman M. Mousa et al., "The Nature of Human Brucellosis in Kuwait: Study of 379 Cases," *Reviews of Infectious Diseases* 10, no. 1 (1988); Mile Bosilkovski et al., "Human Brucellosis in Macedonia—10 Years of Clinical Experience in Endemic Region," *Croation Medical Journal* 51, no. 4 (2010).

164 Abdul Rahman M. Mousa et al., "The Nature of Human Brucellosis in Kuwait: Study of 379 Cases," *Reviews of Infectious Diseases* 10, no. 1 (1988).

D. Glanders Patients[165]

1. The Effects of Glanders

Glanders is a highly contagious and often fatal zoonotic disease of solipeds, including horses, mules, and donkeys caused by the bacteria *Burkholderia mallei*. Equids aerosolize nasal efflux through snorting, which is then transmitted to other animals in the vicinity via respiration or contact with mucous membranes in the eyes. Humans can be naturally infected by handling infected animals, through bacterial invasion of mucous membranes or via abraded or lacerated skin. Although highly contagious among solipeds, transmission from animals to humans is rare even with close and frequent contact, perhaps because of species-specific differences in susceptibility. Human-to-human transmission is rare but has occurred. Naturally occurring glanders has been eradicated in most countries, including the United States.

The vast majority of human glanders cases occurred before antibiotics were developed, and over 90% of recorded cases resulted in death. In the United States, eight cases of human glanders have been reported since the discovery of antibiotics, all among laboratory workers. All eight patients eventually recovered after a generally protracted and severe illness.

The clinical manifestation of glanders in humans varies over time and with route of infection. At least six forms of infection have been described, including nasal, localized, pulmonary, septicemic, disseminated, and chronic infection. As the disease progresses, any and all of these forms may present. Generalized symptoms include fever, myalgia, headache, fatigue, diarrhea, and weight loss. The organism travels through lymph channels and may enter the bloodstream. Dissemination within the body produces abscesses in organs, and typically results in septic shock and death. Disseminated infections that do not become septicemic can produce a chronic course of infection.

Of the eight U.S. cases of laboratory-acquired glanders infection since 1940, seven were likely caused by inhalation and one via percutaneous exposure. Six of these cases occurred in the 1940s, one in 1953, and the percutaneous case in 2000. The clinical features of these cases varied greatly. The percutaneous case was confirmed to have disseminated to the liver and spleen; in three of the seven inhalation cases dissemination was not confirmed but considered possible or likely. Chest x-rays showed pneumonia or abscesses in the lungs in six of the seven inhalation cases. Possibly because of the difficulty of diagnosis, the administration of antibiotics was generally delayed in all of these cases for days or even weeks after the onset of illness; the average time at which a successful course of antibiotics were started was 48 days. In one case, the patient received two unsuccessful courses of antibiotics, starting 2 and 15 days after onset, before a successful course was finally initiated on day 115 of illness. In three cases, recovery

[165] All information in this section is taken from Bridget Carr Gregory and David M. Waag, "Glanders," in *Medical Aspects of Biological Warfare*, *Textbooks of Military Medicine,* ed. Zygmunt F. Dembek (Washington, DC: Government Printing Office, 2007).

after initiation of antibiotic therapy was immediate, in other cases the infection persisted, lasting anywhere from two or three weeks to six months.

2. Glanders Medical Management Principles

Medical management of glanders focuses on preventing mortality and reducing the duration of acute illness through the administration of antibiotics.

3. Glanders Medical Countermeasures

There are no vaccines or other medical countermeasures available for glanders.

4. Glanders Treatment

Because human cases of glanders are rare, there is limited information on which to base recommendations for antibiotic treatment. Glanders infections are intractable and require sustained antibiotic therapy, the specifics of which may need to be tailored to the individual based on susceptibility testing of the organism. In the absence of susceptibility test results and for mild disease, oral doxycycline and trimethoprim-sulfamethoxazole are recommended for at least 20 weeks, plus oral chloramphenicol for the first 8 weeks. For severe disease, parenteral administration of antibiotics is recommended for at least 14 days or until the patient is clinically improved, followed by oral administration for an additional two to six months. Patients should be followed at regular intervals for at least five years after recovery, with diagnostic imaging to monitor the reduction and recurrence of abscesses, serology to monitor the clearing of antibodies, and testing with inflammatory markers to monitor recurrence of latent infection.

5. Glanders Patient Management Parameters

For glanders, consideration of treatment results in changes to submodels of lethality, injury profile, and duration of illness.

a. Lethality

With treatment, P8PEM considers glanders to be nonfatal.

b. Injury Profile

In the eight cases of laboratory-acquired glanders described above, patients generally experienced an initial wave of disease symptoms including low-grade fever, malaise, headache, myalgia, swollen lymph nodes, and chest pain. In at least half of the cases, patients showed a period of clinical improvement after this first phase, lasting from a few days to two months. The generally mild nature of these early symptoms and apparent clinical improvement typically led to a delay in the initiation of antibiotic treatment. Eventually all but one of the suspected inhalation cases developed significant pulmonary disease, including pneumonia, pulmonary abscesses,

pleuritis, and pleural effusion. The injury profile for glanders with treatment is shown in Table 13.

Table 13. Glanders Injury Profile with Treatment

	Stage 1	Stage 2	Stage 3
Signs and Symptoms (S/S)	Low-grade fever, malaise, headache, myalgia, swollen lymph nodes, chest pain.	High fever, headache, myalgia; development of pulmonary symptoms, including pneumonia, pulmonary abscesses, pleuritis, and pleural effusion.	Resolution of fever and gradual clearing of pulmonary infection.
S/S Severity	Severity Level 2 (Moderate)	Severity Level 4 (Very Severe)	Severity Level 2 (Moderate)
Outlook	Individual will progress to Stage 2	Progression to Stage 3	Convalescence and RTD

c. Duration of Illness

Glanders patients are assumed to experience an initial phase of moderate febrile illness, lasting for seven days, ending with a brief period of clinical recovery. They are subsequently assumed to develop very severe pulmonary disease and require ICU care for 14 days. After release, patients are assumed to enter a period of extended recovery lasting an additional 10 weeks.

E. Pneumonic Plague Patients

1. The Effects of Pneumonic Plague

Plague is a zoonosis caused by the *Yersinia pestis* bacteria, and has been responsible for some of the greatest disease pandemics in human history. Primarily a disease of rodents, it is typically transmitted to humans via the bites of fleas. The disease presents in various forms, the most severe of which is pneumonic. Pneumonic plague can develop secondarily through the course of illness, or primarily through the inhalation of infectious aerosols.[166] Unless antibiotic therapy is initiated within 24 hours of the onset of illness, pneumonic plague is almost invariably fatal.[167]

[166] Patricia L. Worsham et al., "Plague," in *Medical Aspects of Biological Warfare*, *Textbooks of Military Medicine,* ed. Zygmunt F. Dembek (Washington, DC: Government Printing Office, 2007).

[167] Raymond Gani and Steve Leach, "Epidemiologic Determinants for Modeling Pneumonic Plague Outbreaks," *Emerging Infectious Diseases* 10, no. 4 (2004).

Pneumonic plague is a biphasic illness. The first phase, which lasts about a day, is characterized by a sudden and rapid onset febrile illness, with severe headache, increases in body temperature, nausea, and vomiting; the second phase begins with the onset of cough and quickly progresses to severe pneumonia, with high fever, cough, chest pain, and hemotypsis. The second phase typically lasts about a day and half and results in death.[168]

2. Pneumonic Plague Medical Management Principles

Medical management of pneumonic plague has two main objectives: avoiding mortality via early antibiotic intervention—prior to symptom onset if possible or as soon as possible thereafter if not—and controlling the risk of contagion. Any patients who survive will likely need extensive supportive care, including respiratory assistance.

3. Pneumonic Plague Medical Countermeasures

Although research in pursuit of a vaccine effective against pneumonic plague in both the United States and the United Kingdom continues, at the present time, none is available.[169] Thus the P8PEM methodology does not consider vaccination for plague.

In the course of a plague outbreak, antibiotic prophylaxis is generally recommended for anyone who has had close physical contact—within two meters—with a pneumonic plague patient.[170] Prophylaxis is also recommended for laboratory workers who may have been accidentally exposed.[171] Presumably, should biological warfare attacks with plague be suspected, anyone within the population at risk should receive antibiotic prophylaxis. Orally administered doxycycline (100 mg twice daily) or ciprofloxacin (500 mg twice daily), continued for seven days, are the preferred antibiotic, with chloramphenicol as an alternative.[172]

4. Pneumonic Plague Treatment

Over the past 50 years, four of seven reported primary pneumonic plague patients in the United States died,[173] for a case fatality rate of 57%. Factors contributing to survival are the early administration of antibiotics and the availability of intensive supportive care. Streptomycin, administered parenterally, is the FDA-approved therapy for plague infection; because streptomycin is rarely used in the United States and is only available in limited quantities,

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168 Ibid.

169 Worsham et al., "Plague," 113.

170 Thomas V. Inglesby et al., "Plague as a Biological Weapon: Medical and Public Health Management," *Journal of the American Medical Association* 283, no. 17 (2000): 2288.

171 Worsham et al., "Plague," 112.

172 Inglesby et al., "Plague as a Biological Weapon," 2287–88.

173 Centers for Disease Control and Prevention, "Fatal Human Plague—Arizona and Colorado, 1996," *Morbidity and Mortality Weekly Report* 46, no. 27 (1997): 619.

gentamicin—although not FDA-approved for the treatment of plague—is considered an acceptable alternative.[174] Although the duration of antibiotic administration may vary given the clinical status of the patient, the standard treatment course for human plague infection of other types is 10 days.[175]

5. Pneumonic Plague Patient Management Parameters

For pneumonic plague, consideration of the medical countermeasures and treatment described above alter submodels for infectivity, lethality, and duration of illness. In addition, the injury profile for pneumonic plague includes a survivor profile. The latent period submodel for pneumonic plague is unaffected and remains the same as that described in *AMedP-8(C)*.

a. Infectivity

The current *AMedP-8(C)* methodology incorporates an efficacy factor for post-exposure antibiotic prophylaxis of 95%. Multiple mouse studies have shown ciprofloxacin to be 100% effective in preventing death from pneumonic plague, with other antibiotics having similar or slightly reduced efficacy.[176] The factor of 95% is derived from these studies and accounts for the possible use of drugs other than ciprofloxacin that are less efficacious.[177]

b. Lethality

The P8PEM methodology assumes that the only patients that survive pneumonic plague are those that receive antibiotics within the timeframe required to avoid progression of illness to the severe pneumonic phase. Typically, this timeframe is described in the literature as approximately 24 hours.[178] Similarly, the current *AMedP-8(C)* methodology considers the onset of the pneumonic phase of the disease to begin one day after symptom onset.

The time at which antibiotics are administered is an assumption made by the user of the methodology. All patients for whom this time is less than one day after symptom onset are expected to survive. All patients for whom this time is greater than one day after symptom onset are expected to die.

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174 Inglesby et al., "Plague as a Biological Weapon," 2286.

175 William R. Byrne et al., "Antibiotic Treatment of Experimental Pneumonic Plague in Mice," *Antimicrobial Agents and Chemotherapy* 42, no. 3 (1998): 676.

176 For a discussion of the derivation of this value and supporting references, see Curling et al., "Technical Reference Manual," 236.

177 John N. Bombardt, Jr., "Primary Pneumonic Plague Transmission and Bw Casualty Assessments," IDA Paper P-3657, (Alexandria, VA: Institute for Defense Analyses, 2001).

178 Inglesby et al., "Plague as a Biological Weapon," 2283–85.

c. Injury Profile

The injury profile for pneumonic plague is shown in Table 14. The profile for non-survivors is the same as the untreated injury profile now incorporated into *AMedP-8(C)*. Survivors experience the same initial stage as non-survivors, but via treatment they recover in Stage 2 and never progress to the Very Severe and invariably fatal pneumonic stage of illness.

Table 14. Pneumonic Plague Injury Profile with Treatment

	Stage 1	Stage 2 (non-survivors)	Stage 2 (survivors)
Signs and Symptoms (S/S)	Severe headache, chills, nausea and vomiting, vertigo and general malaise, increased respiration and heart rates; steady rise in temperature; dry cough.	Progressively more productive cough, eventually producing copious amounts of bloody sputum; increased respiratory rate; dyspnea; high fever; exhaustion; weak pulse; cyanosis; frequent ataxia; confusion and disorientation; delirium; coma; eventual circulatory collapse or respiratory failure.	Cessation of symptoms and return to normal body temperature.
S/S Severity	Severity Level 2 (Moderate)	Severity Level 4 (Very Severe)	Severity Level 2 (Moderate)
Outlook	Individual will progress to Stage 2, if treated in Stage 1 will survive, otherwise will not survive	Death	RTD

d. Duration of Illness

For non-survivors, treatment is ineffective and does not alter the duration of illness. The P8PEM methodology assumes that in such cases, the duration of illness will remain the same as that now considered in *AMedP-8(C)*, wherein the total length of illness is represented as a lognormal distribution with a mean of 2.5 days and standard deviation of 1.2 days.

Survivors are assumed to spend 1 day in Stage 1 and 10 days in Stage 2. During Stage 2, although the overall severity of illness would be consistent with at home care, these patients are assumed to require routine hospitalization to support parenteral administration of antibiotics.

F. Q Fever Patients

1. The Effects of Q Fever

Q fever is a zoonosis caused by the *Coxiella burnetii* bacteria, which is present worldwide due to a broad range of animal hosts.[179] The primary natural reservoirs for Q fever are cattle, sheep, goats, and, in an urban environment, cats. *C. burnetii* is highly survivable in the environment, capable of surviving for weeks, and presents a persistent hazard at any location where infected animals have been present. The disease is most commonly acquired through the inhalation of dried, infectious particles in barnyards, pastures and stalls. Infection can also occur via ingestion of contaminated milk or through tick bites.

Eradicating Q fever infection in animal populations is very difficult. The disease itself is asymptomatic in animals, but is associated with an increased rate of spontaneous abortion, which, in turn, results in vast numbers of organisms being released into the environment and further spread of infection.[180]

Humans are the only species to develop symptomatic disease from Q fever infection. Approximately 60% of infections are asymptomatic; among the 40% of infections that result in symptoms, the disease typically presents as a mild febrile illness, one that very rarely requires hospitalization and even more rarely results in death. A study of clinical cases of Q fever reported in the literature found that approximately 2% of symptomatic cases required hospitalization and 1–2% were fatal.[181] Because Q fever is generally mild and self-limiting, it is generally assumed to be widely underreported; hence the actual rates of hospitalization and death associated with Q fever are likely much lower than that observed among reported cases.

Q fever has two clinical manifestations: acute and chronic. Acute cases account for the overwhelming majority; only about one in 500 cases are chronic.[182] While chronic Q fever is more likely to be fatal—generally the result of endocarditis, which occurs in the majority of chronic cases—this form is so rare that it is excluded from further consideration in this document.[183]

Acute Q fever is associated with the sudden onset of severe fever, fatigue, chills and headaches. Cough is common and atypical pneumonia is frequently seen; this pneumonia can be asymptomatic, diagnosed via chest X-rays, or in the most severe cases of Q fever, can be

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179 David M. Waag, "Q Fever," in *Medical Aspects of Biological Warfare*, *Textbooks of Military Medicine*, ed. Zygmunt F. Dembek (Washington, DC: Government Printing Office, 2007).

180 Ibid.

181 M. Maurin and D. Raoult, "Q Fever," *Clinical Microbiology Reviews* 12, no. 4 (1999).

182 Ibid.

183 Most chronic Q fever patients have a history of heart disease or are immune-compromised due to disease or therapy; see Waag, "Q Fever."

associated with respiratory distress. Hepatitis is also common in acute Q fever, usually discovered through laboratory testing; jaundice is rare. [184]

In acute cases, fever peaks two to four days after onset and in the majority of cases, returns to normal within five to 14 days. One study of 138 untreated cases of acute Q fever found that approximately one-third of cases were associated with persistent fever, lasting as long as 57 days; duration of fever tended to increase with age.[185]

2. Q Fever Medical Management Principles

Because Q fever is a typically mild, self-limiting disease, medical management focuses on identifying and treating those rare cases of chronic infection that can have severe, long-term consequences.

3. Q Fever Medical Countermeasures

The Q-Vax vaccine is licensed for use in Australia; studies have shown it to be 100% efficacious in protecting individuals in occupational settings in that country.[186] The CDC can provide the vaccine to at-risk individuals as an investigational new drug (IND). Q fever vaccination is contraindicated for individuals with prior exposure to Q fever, as severe local reactions can occur at the injection site. A skin test is available to determine a history of previous exposure.[187]

4. Q Fever Treatment

Acute Q fever resolves spontaneously, without the intervention of antibiotic therapy. Uncertainty regarding the development of chronic infection makes treatment advisable. The currently recommended treatment for Q fever is 100 mg of doxycycline, taken orally twice daily for 14 days.[188]

5. Q Fever Patient Management Parameters

For Q fever, consideration of the medical countermeasures and treatment described above affects submodels of infectivity and duration of illness. The Q fever injury profile, consisting of a single stage of acute illness of Moderate severity, remains unchanged.

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184 Maurin and Raoult, "Q Fever."

185 E.H. Derrick, "The Course of Infection with *Coxiella Burneti*," *Medical Journal of Australia* 1, no. 21 (1973).

186 Waag, "Q Fever," 206.

187 Centers for Disease Control and Prevention, "Q Fever Prevention," accessed November 2011, http://www.cdc.gov/qfever/prevention/index.html.

188 Maurin and Raoult, "Q Fever"; Waag, "Q Fever."

a. Infectivity

Although at present there are no Q fever vaccines available for general use, should immunized individuals be included in a population at risk for purposes of casualty estimation, they should be considered fully protected against the development of Q fever.

b. Duration of Illness

While comparative studies of the efficacy of antibiotics are scarce, there is some evidence that a course of antibiotics begun within a few days of onset can reduce the duration of fever. Other symptoms, such as lethargy, sweats, and headache, have been found to persist despite antibiotic treatment, and the relationship between antibiotic use and the overall duration of illness is not described in the literature.

In a study of 111 cases of Q fever in Australia, the average duration of fever in untreated cases was 3.3 days, while the average duration for patients treated with tetracycline was 2 days, and average duration for patients treated with doxycycline was 1.7 days.[189]

In a series of controlled human experiments with Q fever, involving aerosol exposure of Military Research Volunteers (MRVs), individuals who developed symptomatic disease were given oral tetracycline within 24 hours of the onset of persistent fever. In these experiments, infection responded promptly to treatment with antibiotics, with a cessation of symptoms within 24 to 48 hours.[190]

Unfortunately, IDA researchers have not yet been able to access the MRV clinical records, which provide a controlled source of data describing the amelioration of fever and other symptoms over time in treated Q fever infection. While that access is pending, the P8PEM methodology assumes that the duration of Q fever with treatment is a total of five days, with a return to normal body temperature within three days of symptom onset, and a cessation of other symptoms within the following two days. Even so, antibiotic therapy is assumed to continue for the recommended 14 days.

G. Staphylococcal Enterotoxin B (SEB) Patients

1. The Effects of Inhalational SEB

SEB is secreted by the gram-positive bacteria *Streptococcus pyogenes* and *Staphylococcus aureus*. SEB is one of a class of bacterial products called "superantigens" because of their profound effects upon the immune system. It is the prototype enterotoxin and potential biological

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189 Denis W. Spelman, "Q Fever: A Study of 111 Consecutive Cases," *Medical Journal of Australia* 1, no. 13 (1982): 551.

190 William D. Tigertt, "Studies on Q Fever in Man," in *Symposium on Q Fever. Army Medical Services Graduate School, Walter Reed Medical Center Medical Science Publication No 6*, ed. J. E. Smadel (Washington, DC: U.S. Government Printing Office, 1959), 100.

threat agent—and hence, the focus of research efforts—because of its historical significance in past biowarfare efforts; however, it represents a large number of biologically related superantigens, all of which are presumed to have a similar mode of biological action.[191]

While the staphylococcal enterotoxins are most frequently associated with gastroenteritis resulting from food poisoning, more severe illness may result from a route of exposure other than ingestion.[192] Inhaling aerosolized SEB results in a pulmonary illness with a markedly different clinical syndrome than one resulting from ingestion.

As with the botulinum toxin, the only known cases of human exposure to aerosolized SEB occurred as a consequence of three separate laboratory accidents, none of which resulted in death. The clinical course of illness for inhalational SEB is derived from documentation of these cases, in which a total of 24 individuals may have been exposed, of whom 17 developed signs and symptoms of intoxication and 15 were hospitalized.[193]

In the laboratory accident cases, inhalation of SEB resulted in a severely incapacitating illness of rapid onset and modestly acute duration. Common signs and symptoms included cough, fever, chills, headache, nausea, myalgia, malaise, chest pain, vomiting, anorexia, and dyspnea.[194] All symptoms presented rapidly, within a few hours of exposure, and persisted for several days.[195] Among the nine individuals hospitalized in the largest of the laboratory accidents, their length of hospital stay averaged six days, and ranged from four to eight days.[196] Most patients were discharged with a residual cough, which resolved within the following week.

2. SEB Medical Management Principles

Medical management of inhalational cases of SEB focuses on providing supportive care.

3. SEB Medical Countermeasures

At present there are no vaccines or other drugs available to prevent SEB intoxication.

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191 Robert G. Ulrich, Catherine L. Wilhelmsen, and Teresa Krakauer, "Staphylococcal Enterotoxin B and Related Toxins," in *Medical Aspects of Biological Warfare*, *Textbooks of Military Medicine*, ed. Zygmunt F. Dembek (Washington, DC: Government Printing Office, 2007).

192 Ibid.

193 Sheldon Sidell, "Human Clinical Syndrome Associated with Accidental Exposure to Aerosolized Staphylococcal Enterotoxin B," in *Special Report to Commission on Epidemiological Survey*, ed. Harry G. Dangerfield (Fort Detrick, MD: Walter Reed Army Medical Center, 1965), 25, 27.

194 Janice M. Rusnak et al., "Laboratory Exposure to Staphylococcal Enterotoxin B," *Emerging Infectious Diseases* 10, no. 9 (2004).

195 Ulrich, Wilhelmsen, and Krakauer, "Staphylococcal Enterotoxin B and Related Toxins," 317.

196 Sidell, "Human Clinical Syndrome," 27–44.

4. SEB Treatment

There is no specific treatment for inhalational SEB intoxication; treatment is symptomatic and supportive. For inhalation exposure, general supportive treatment is intended to alleviate symptoms of febrile illness and control nausea and cough. In more severe cases, fluid replacement or assisted ventilation may be required.[197]

5. SEB Patient Management Parameters

Because there are no medical countermeasures or specific treatments for SEB that would change any of the component submodels of SEB human response, the P8PEM methodology uses the same parameters as *AMedP-8(C)* for SEB.

H. Smallpox Patients

1. The Effects of Smallpox

Smallpox is a highly contagious disease caused by the orthopox virus, *variola*. It has been one of history's most devastating diseases, estimated to be responsible for over 500 million deaths in the twentieth century alone.[198] The World Health Organization (WHO) successfully eradiated the disease by 1980, through a program involving ring vaccination surrounding every known or suspected case of smallpox; the last recorded case of smallpox occurred in 1977. Because the disease is unique to humans, there are no animal reservoirs to reintroduce the virus into the human population. Today, declared stocks of smallpox virus exist at only two WHO repositories, the CDC and at the State Research Center of Virology and Biotechnology in Russia.[199]

Smallpox presents in a variety of clinical forms, the prevalence and prognosis of each depending on the vaccination status of the individual.[200] Classic or ordinary type occurs in nearly 90% of unvaccinated cases and 70% of vaccinated cases. This presentation of the disease begins with a two- to three-day prodromal period, characterized by sudden onset of high fever and severe headache, followed by development of the maculopapular rash and finally, approximately two to three weeks after onset of illness, the formation of scabs. The fatality rate for this type of smallpox is 30% for unvaccinated cases and 3% in vaccinated cases, with death resulting from systemic toxemia and eventual multiple organ failure about two weeks after onset.

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197 Ulrich, Wilhelmsen, and Krakauer, "Staphylococcal Enterotoxin B and Related Toxins," 318.

198 Peter B. Jahrling et al., "Smallpox and Related Orthopoxviruses," in *Medical Aspects of Biological Warfare*, *Textbooks of Military Medicine*, ed. Zygmunt F. Dembek (Washington, DC: Government Printing Office, 2007), 216.

199 Ibid., 220.

200 The standard clinical classification of smallpox types was initially delineated in A.R. Rao, *Smallpox* (Bombay: The Kothari Book Depot, 1972), 8. Rao also describes the distribution by type for almost 7,000 personally observed cases and gives associated case fatality rates for both vaccinated and unvaccinated individuals.

Flat-type and hemorrhagic types of smallpox occur less frequently, and generally in individuals with an underlying immune deficiency; for example, hemorrhagic smallpox is seen disproportionately in pregnant women and flat-type in children. Both forms are associated with a severe toxemia that typically causes death 6 to 10 days after onset.[201] Together these types account for 10% of unvaccinated cases and have nearly 100% case fatality rates; among vaccinated cases the combined frequency is approximately 5% but case fatality rates remain very high, from 67% to 94% depending on type.

Modified type smallpox occurs in only 2% of unvaccinated cases but 25% of vaccinated cases; this type of smallpox resembles the classic or ordinary form but is milder in all respects and is nonfatal.

2. Smallpox Medical Management Principles

Because smallpox is highly contagious, the objective of medical management is to limit the spread of the disease by isolating patients and vaccinating at-risk individuals.

3. Smallpox Medical Countermeasures

Before 1972, smallpox vaccination was recommended in the United States for all children at the age of one year. Vaccination was a requirement for school entry in most states, as well as for military recruits and tourists visiting other countries. With the eradication of the disease, routine immunization ceased, and today less than half of the nation's population has ever received a smallpox vaccination.[202]

The smallpox vaccine used in the United States was Dryvax, a live-virus preparation of the New York Board of Health vaccinia strain prepared from calf lymph, manufactured by Wyeth laboratory. A small stockpile of the vaccine, manufactured in the 1970s, continued to exist under the control of the CDC and was initially used when vaccination of selected U.S. military personnel resumed in late 2002.[203]

To ensure adequate stockpiles of vaccine in the event of a bioterrorist event involving smallpox, the United States pursued development of a new smallpox vaccine, ACAM2000. Manufactured by Acambis, Inc., the vaccine is derived from a clone of Dryvax, purified, and produced using modern cell culture technology. It was approved by the FDA in 2007, and is now incorporated into the National Pharmaceutical Stockpile.[204] By agreement with the CDC, Wyeth

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201 Ibid., 17–21.

202 Donald A. Henderson et al., "Smallpox as a Biological Weapon: Medical and Public Health Management," *Journal of the American Medical Association* 281, no. 22 (1999): 2130–31.

203 John D. Grabenstein and William Winkenwerder, Jr., "U.S. Military Smallpox Vaccination Program Experience," *Journal of the American Medical Association* 289, no. 24 (2003): 3278.

204 U.S. Food and Drug Administration, "ACAM2000 (Smallpox Vaccine) Questions and Answers," last modified 23 February 2010, accessed 3 November 2011, http://www.fda.gov/BiologicsBloodVaccines/Vaccines/QuestionsaboutVaccines/ucm078041.htm.

Laboratory withdrew its DryVax license in 2008 and requested quarantine and destruction of any remaining quantities of the product. As a result, ACAM2000 has now supplanted DryVax as the only licensed vaccine against smallpox in the United States.[205]

The smallpox vaccination is administered via bifurcated needle, requiring multiple intradermal jabs. In successful vaccinations, a red blister appears at the vaccination site and turns white within five to six days. A scab will then form and eventually come off, 14 to 21 days after vaccination.[206] Mild system reactions to vaccination are fairly common: in the first 450,000 military personnel vaccinated beginning in 2002, these reactions included itching at the vaccination site (60%), muscle aches and "feeling lousy" (20%), headache (18%), and swollen lymph nodes (14%).[207]

Because live vaccinia virus remains at the vaccination site until it has healed, the virus can be spread to other areas of the body by scratching or touching the site, and transmitted to other people by close contact. In a small number of cases, this can result in the spread of the virus, the development of an associated rash, and systemic illness of a severe or even life-threatening nature. In general, smallpox vaccination is contraindicated for individuals considered at risk for these side effects, including those with a history of eczema, those with active acute, chronic, or exfoliative skin conditions, pregnant women, and persons who are immunocompromised.[208] In addition, otherwise healthy adults can develop inflammation and swelling of the heart and surrounding tissue, a very serious condition. Among the first 450,000 vaccinated military personnel, there were 37 such cases, for a rate of approximately 82 per million.[209]

At present, the DOD vaccinates military personnel who have related occupational responsibilities, including smallpox epidemic response teams and hospital workers, as well as other forces designated for deployment to specific geographic areas, primarily the Middle East. Under the DOD Smallpox Vaccination Program, over 2.1 million U.S. military personnel have been vaccinated since 2002.[210]

4. Smallpox Treatment

Currently there are no specific treatments for smallpox that would reduce the severity and duration of the disease or limit its transmissibility. Antiviral drugs have shown initial promise in

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205 Centers for Disease Control and Prevention, "Notice to Readers: Newly Licensed Smallpox Vaccine to Replace Old Smallpox Vaccine," *Morbidity and Mortality Weekly Report* 57, no. 8 (2008): 207.

206 Jahrling et al., "Smallpox and Related Orthopoxviruses," 229.

207 Grabenstein and Winkenwerder, "U.S. Military Smallpox Vaccination Program Experience," 3280.

208 Joanne Cono, Christine G. Casey, and David M. Bell, "Smallpox Vaccination and Adverse Reactions," *Morbidity and Mortality Weekly Report* 52, no. RR04 (2003): 1–2.

209 Grabenstein and Winkenwerder, "U.S. Military Smallpox Vaccination Program Experience," 3280.

210 At the time of this writing, the most current information on the U.S. Department of Defense Smallpox Vaccine Program can be found at www.smallpox.mil.

protecting against severe orthopox disease in primate models and research continues on developing safe and effective therapeutic interventions against the progression of smallpox.[211] However, management of smallpox patients today would focus primarily on containing the spread of the disease, balanced with providing necessary supportive care.[212] To that end, the AMA recommends that in limited smallpox outbreaks involving only a few patients, those patients should be hospitalized and confined to rooms with negative pressure and high efficiency particulate air filtration. For larger outbreaks, however, the AMA recommends home isolation and care whenever possible, with hospitalization of only very severely ill patients. The AMA further suggests that communities consider designation of specific hospitals for smallpox care, with the associated transfer of all other patients to other facilities.[213]

5. Smallpox Patient Management Parameters

The current *AMedP-8(C)* methodology now incorporates parameters for the efficacy of smallpox vaccination, administered both before and after exposure to the virus. Because there are no additional smallpox medical countermeasures or treatments that would alter the submodels characterizing the disease, the P8PEM methodology uses the same parameters as *AMedP-8(C)* for smallpox.

I. Tularemia Patients

1. The Effects of Tularemia

Tularemia is a zoonosis caused by the *Francisella tularensis* bacteria, endemic to North America and Eurasia. Humans can acquire tularemia through a variety of environmental exposures, including insect bites, handling infected animals, ingestion, and inhaling aerosolized contaminated dust. Tularemia has a diversity of clinical presentations, based on how it is acquired; these diverse presentations have been classified into seven specific categories. Symptoms overlap among the different categories of tularemia, and respiratory infection is very common. Pneumonia is the disease most frequently acquired due to inhalation, but it can also occur with other routes of exposure and is typically the cause of death from tularemia.[214]

The onset of tularemia acquired via inhalation is typically sudden, with high fever, headache, chills, generalized body aches, runny nose and sore throat. Even with antibiotic therapy, the illness can become moderately incapacitating in the first one or two days and remain

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211 Jahrling et al., "Smallpox and Related Orthopoxviruses," 231–32.

212 Henderson et al., "Smallpox as a Biological Weapon," 2132.

213 Ibid., 2133.

214 Matthew J. Hepburn, Arthur M. Friedlander, and Zygmunt F. Dembek, "Tularemia," in *Medical Aspects of Biological Warfare*, *Textbooks of Military Medicine,* ed. Zygmunt F. Dembek (Washington, DC: Government Printing Office, 2007), 172–73.

so for several days. In a set of controlled experiments on the behavioral effects of tularemia and sandfly fever in man, the ability of treated tularemia patients to perform a series of tasks dropped to about 70% of baseline by the end of the second day of illness, and had recovered to only 87% of baseline by the end of the fourth day.[215]

2. Tularemia Medical Management Principles

Medical management of tularemia focuses on shortening the course of illness and reducing its severity by administering antibiotics.

3. Tularemia Medical Countermeasures

Coincident with work on tularemia related to the offensive biological weapons program, researchers sought to develop a vaccine against the disease. The most successful of these efforts followed the isolation of the live vaccine strain (LVS) of tularemia in Russia in the 1950s and its transfer to the United States. The strain was tested as a live vaccine in MRVs in the 1950s and subsequently approved as an IND by the FDA in the 1960s.[216] The LVS vaccine has since been administered to hundreds of researchers at USAMRIID and is thought to have reduced the incidence of laboratory acquired tularemia.[217] Because it is a live vaccine, the LVS strain can cause disease when administered in quantities required to confer immunity; as a consequence of this and other issues, the FDA has removed it from its IND list and the vaccine is currently not licensed for use.[218] With renewed interest in tularemia as an agent of bioterrorism, including its designation by the CDC as a Category A agent, significant advances in the study of the organism's genetics and pathogenesis have recently been made.[219] These advances underlay ongoing efforts to develop a safe and effective vaccine.[220]

In cases where post-exposure prophylaxis could be implemented in time to prevent illness, the administration of antibiotics in a population at risk is recommended. The preferred choices are doxycycline, taken orally in 100 mg quantities twice daily, or ciprofloxacin, taken orally in 500 mg quantities twice daily. In either case, administration should continue for 14 days.[221]

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215 Earl A. Alluisi et al., "Behavioral Effects of Tularemia and Sandfly Fever in Man," *Journal of Infectious Diseases* 128, no. 6 (1973): 714.

216 Roger D. Pechous, Travis R. McCarthy, and Thomas C. Zahrt, "Working toward the Future: Insights into *Francisella Tularensis* Pathogenesis and Vaccine Development," *Microbiology and Molecular Biology Reviews* 73, no. 4 (2009): 702.

217 Hepburn, Friedlander, and Dembek, "Tularemia," 176–77.

218 Pechous, McCarthy, and Zahrt, "*Francisella Tularensis* Pathogenesis," 702.

219 Ibid., 706.

220 Hepburn, Friedlander, and Dembek, "Tularemia," 177.

221 David T. Dennis et al., "Tularemia as a Biological Weapon: Medical and Public Health Management," *Journal of the American Medical Association* 285, no. 21 (2001): 2770–71.

4. Tularemia Treatment

Antibiotic therapy is very effective in treating tularemia, with the overall case-fatality rate for reported cases of tularemia of all types reported in the United States currently less than 2%.[222]

The currently recommended antibiotic treatment for tularemia is streptomycin administered in 1g doses daily via the intramuscular route, with gentamicin as an acceptable alternative, administered daily in 5 mg/kg via the intramuscular or intravenous route. In either case, therapy should be continued for 10 days. In cases where the number of patients is large enough to prevent individual medical management, doxycycline or ciprofloxacin can be distributed to the patient population for oral administration in the same quantities and course as that recommended for post-exposure prophylaxis.[223]

5. Tularemia Patient Management Parameters

For tularemia, consideration of the medical countermeasures and treatment described above alter submodels for infectivity, lethality, injury profile, and duration of illness. The latent period submodel for tularemia is unaffected and remains the same as the one described in *AMedP-8(C)*.

a. Infectivity

A 1966 study of MRVs assessed the effectiveness of antibiotics in preventing the onset of disease following exposure to tularemia via inhalation.[224] In this study, 34 subjects were exposed to a respiratory challenge of 25,000 organisms and given tetracycline as a prophylaxis, in varying doses and for varying periods of time. Table 15[225] provides information on the antibiotic regimens tested in the study and their outcome.

Table 15. Tetracycline Prophylaxis of Human Airborne Tularemia

Daily Dose* (g)	Frequency	Duration (days)	No. of Subjects	No. Ill During Treatment	No. Ill After Treatment
1	Daily	15	10	0	2
1	Daily	28	8	0	0
2	Daily	14	8	0	0
1	Every 2nd Day	19	8	2	8

*Divided into morning and evening doses.

222 Ibid., 2767.

223 Ibid., 2770.

224 William D. Sawyer et al., "Antibiotic Prophylaxis and Therapy of Airborne Tularemia," *Bacteriological Reviews* 30, no. 3 (1966).

225 Ibid., 545. This table—including the title and the data contained within—is a replica of the one provided in the study.

All subjects who developed the disease during or after the period of prophylaxis were subsequently treated with streptomycin; all recovered quickly and without complications.

The study concluded that antibiotics could successfully be used to prevent onset of illness following respiratory challenge with tularemia, provided they were administered in sufficient amounts to suppress growth of intracellular organisms, and provided they were administered for a sufficient period of time.[226] Current recommendations for dose and duration of post-exposure antibiotic prophylaxis for tularemia are derived from this study.[227]

From these data, the P8PEM methodology assumes that if continued for the recommended 14-day duration, post-exposure prophylaxis will be completely protective against the onset of disease, with an efficacy of 100%.

b. Lethality

As noted, the lethality rate for treated cases of naturally occurring tularemia of all types is now less than 2%.[228] In the course of a number of controlled experiments in the 1950s and 1960s, hundreds of MRVs were exposed to tularemia via inhalation; all were treated with antibiotics and all survived. For example, clinical records for 118 human control subjects in three separate vaccine efficacy studies were used to develop the febrile performance model for tularemia used to generate earlier versions of *AMedP-8*; all of these subjects were successfully treated with antibiotics.[229]

Because no fatalities occurred among MRVs involved in tularemia experiments, and because the mortality rates are so low among naturally occurring cases, P8PEM considers treatment to be completely effective in preventing death from tularemia.

c. Injury Profile

Antibiotics both shorten the course of tularemia and reduce its severity. In one study of 16 human volunteers exposed to tularemia for the purposes of determining the associated degradation in work performance, antibiotic therapy was initiated in subjects at the onset of acute disease. Half of the subjects were given streptomycin by the intramuscular route, half were given oral doses of tetracycline.[230] In all cases, subjects developed signs and symptoms of tularemia consistent with those defined in *AMedP-8(C)* as comprising Stage 1 of the disease: high fever,

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226 Ibid., 547.

227 Dennis et al., "Tularemia as a Biological Weapon," 2771; Hepburn, Friedlander, and Dembek, "Tularemia," 176.

228 Dennis et al., "Tularemia as a Biological Weapon," 2767.

229 George H. Anno et al., "Consequence Analytic Tools for NBC Operations: Volume 1-Biological Agent Effects and Degraded Personnel Performance for Tularemia, Staphylococcal Enterotoxin B (Seb) and Q-Fever," (Alexandria, VA: Defense Special Weapons Agency, 1998), 25.

230 Alluisi et al., "Behavioral Effects of Tularemia," 711.

headache, chills, sore throat, myalgia, and chest pain. In no case, however, did the disease progress to pneumonia.[231] In addition, recovery from illness was rapid and did not appear to be associated with the extended period of profound weakness typical of untreated survivors.

For tularemia with treatment, the P8PEM methodology uses a single injury profile, shown in Table 16. This profile contains only two stages of illness, the first of which is the same as Stage 1 for untreated cases. However, with treatment, all patients avoid the pneumonic phase of the illness and progress directly to a recovery phase.

Table 16. Tularemia Injury Profile with Treatment

	Stage 1	Stage 2
Signs and Symptoms (S/S)	High fever, headache, chills, sore throat, myalgia, chest pain	Cessation of fever and resolution of symptoms.
S/S Severity	Severity Level 3 (Severe)	Severity Level 2 (Moderate)
Outlook	Individual will progress to Stage 2	RTD

d. Duration of Illness

The duration of illness submodel for tularemia with treatment is derived from the controlled human experiments described above. Unfortunately, the clinical records from these studies are not currently available, and published studies generally provide only summary statistics.

In the Alluisi study of performance degradation in tularemia and sandfly fever patients, all 16 tularemia patients developed clinical manifestations of illness between two and four days after exposure. Their temperatures peaked two days after onset of illness, and returned to normal two days later. One week after onset of illness, performance had recovered to 95% of baseline capability. [232]

In the Saslaw vaccine study, from which the infectivity model of tularemia is derived, some 20 control subjects developed tularemia following aerosol exposure. Overall, "therapy with 2 gm daily for 10 days of either streptomycin or tetracycline resulted in prompt amelioration of symptoms with no subsequent relapses."[233] The clinical records included in this study for illustrative purposes showed that patients were typically asymptomatic within two to three days after antibiotic therapy was initiated.

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231 Ibid., 713.

232 Ibid., 714.

233 Samuel Saslaw et al., "Tularemia Vaccine Study: Ii. Respiratory Challenge," *Archives of Internal Medicine* 107, no. 5 (1961): 145.

Finally, in the collection of 118 separate MRV records reviewed by Anno et al. in the development of earlier versions of *AMedP-8*, all patients were effectively treated with either streptomycin or tetracycline. In these cases, body temperature subsided to normal levels within one to two days after the antibiotic was administered and other signs and symptoms disappeared.[234]

The published data are not sufficiently complete or detailed enough to support developing a probabilistic distribution of duration of illness in treated cases. Thus, the P8PEM methodology assumes that the total duration of illness for tularemia is 10 days, or equal to the recommended course of antibiotic therapy. Patients spend four days in Stage 1, the maximum average duration of illness reported in the studies cited above, and the remaining six days in Stage 2.

J. Venezualan Equine Encephalitis (VEE) Patients

1. The Effects of VEE

VEE virus is a member of the *Alphavirus* genus of the family *Togaviridae*. Both epizootic and enzootic strains exist, and both cause disease with common manifestations in humans. In nature, equines and rodents serve as the natural hosts of the virus, and it is spread by mosquitoes. Human infections typically coincide with epizootic outbreaks in equines. Following its initial isolation in Venezuela in 1936, VEE virus was responsible for many large scale outbreaks among equines in Central America, and by association in humans, over the next several decades. These outbreaks had costly and dire consequences for local populations due to the economic impact of losing the equines on which they depended for agricultural production.[235]

The virus first reached the United States in 1971, when a major outbreak spread from Mexico to Texas. The number of both human and equine cases was so large that the U.S. Secretary of Agriculture declared a national emergency in July of that year. An aggressive immunization campaign and mosquito abatement efforts stopped the outbreak before it spread outside of Texas, and VEE has not been isolated in the United States since. Today, immunization against VEE is common for equines of all types throughout North and South America.[236]

Humans appear highly susceptible to infection with the VEE virus. While commonly spread by mosquitoes, experience with the virus in the laboratory has shown it to be highly infectious

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234 Anno et al., "Consequence Analytic Tools," 25.

235 Keith E. Steele et al., "Alphavirus Enchephalitides," in *Medical Aspects of Biological Warfare*, *Textbooks of Military Medicine*, ed. Zygmunt F. Dembek (Washington, DC: Government Printing Office, 2007), 242–44.

236 Ibid., 248.

via aerosol: VEE is responsible for more laboratory-acquired disease than any other arbovirus.[237] Essentially all human infections with VEE are symptomatic.[238]

The vast majority of VEE cases present as systemic viral infections. Onset of illness is sudden, and prostration is typical. Patients experience high fever, chills, throbbing headache, and malaise. Photophobia, sore throat, myalgia, and vomiting are common. After a period of two to three days, symptoms abate and patients begin to recover. Mild headache, fatigability, and weakness persist for about a week.[239]

A very small percentage of VEE patients develop encephalitis. In adults the rate of encephalitis is about 0.5% of infections, although in children the rate could be as high as 4%. Mortality rates among cases developing encephalitis also vary between adults and children, with adult mortality about 10% and child mortality as high as 35%. The overall mortality rate for adults infected with VEE is approximately 0.05%.[240]

2. VEE Medical Management Principles

Medical management of VEE patients focuses on providing supportive care to patients in the early, incapacitating phase of illness, and on monitoring patients over time for signs of encephalitis.

3. VEE Medical Countermeasures

Two VEE vaccines were developed by USAMRIID to protect at-risk laboratory and field personnel: a live attenuated vaccine, TC-83, and an inactivated vaccine, C-84.

Over 6,000 people received the TC-83 vaccine between 1965 and 1972. In approximately 20% of cases, vaccinated individuals failed to generate a minimum neutralizing antibody response and were, therefore, considered unprotected. In another 25% of cases, individuals experienced clinical reactions of sufficient severity to require bed rest. To overcome these disadvantages, the C-84 vaccine was developed. However, animal tests of this vaccine led to concerns that it did not protect against aerosol challenge, and it is currently administered only as a booster immunogen.[241]

At present these vaccines are available as INDs and are not generally available for widespread use. Efforts are ongoing to develop improved vaccines.

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237 Ibid., 242.

238 Ibid., 252.

239 Disease symptoms and duration are derived from a review of literature describing accidental VEE laboratory exposures described in Curling et al., *Technical Reference Manual*, 218–19.

240 Steele et al., "Alphavirus Enchephalitides,"252.

241 Ibid., 257–58.

4. VEE Treatment

There is no specific treatment for VEE. Treatment is limited to supportive care and management of symptoms. In rare cases of encephalitis, anticonvulsant medication and/or airway protection may be needed.

5. VEE Patient Management Parameters

Because there are no medical countermeasures or specific treatments for VEE that would change any of the component submodels of VEE human response, the P8PEM methodology uses the same parameters as *AMedP-8(C)* for VEE.

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4. Radiological Agents and Nuclear Weapons

Prompt nuclear effects include the initial radiation, static blast overpressure, and thermal fluence (radiant thermal energy) resulting from the detonation of a nuclear weapon.

A detonating fission or fusion weapon produces a variety of nuclear radiations These nuclear radiations include neutrons, gamma rays, alpha particles, and beta particles, which are biologically damaging and may significantly affect human health and performance. Exposure to ionizing radiation causes biological damage and may significantly affect human health and performance. [242] Initial radiation occurs at the time of the nuclear reaction, and consists of neutrons and gamma rays produced within the first minute after detonation. Residual radiation occurs long after the immediate blast and thermal effects have ended.

Fallout is radioactive material deposited after detonation. Fallout from nuclear detonations is significant because it is highly radioactive, geographically concentrated, and local. Fallout hazards include whole-body irradiation; cutaneous radiation injury from beta emitters deposited on the skin; and internal beta-particle irradiation from isotopes that are ingested, injected, or inhaled.[243]

A. Whole-Body Radiation Patients

Whole-body radiation injuries typically occur when an individual is exposed to a large amount of external radiation. This can be expected to occur as a result of proximity to a nuclear detonation, or by remaining in an area contaminated by fallout or a radiological dispersal device. Whole-body radiation injuries are characterized by an increasing complex of symptoms collectively known as Acute Radiation Syndrome (ARS).

1. The Effects of Whole-Body Radiation

Three characteristic sub-syndromes make up the typical clinical pattern of ARS and occur in the following order as the dose increases, hematopoietic, gastrointestinal, and neurovascular. These three sub-syndromes follow a similar clinical pattern that can be divided into three phases: a prodromal phase occurring during the first few hours after exposure; a latent phase, which becomes shorter with increasing dose; and a manifest phase of clinical illness. The time of onset, and the duration, severity, and degree of each phase are all, to a variable extent, dose dependent.

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[242] Richard J. Walker and T. Jan Cerveny, eds., *Medical Consequences of Nuclear Warfare*, *Textbooks of Military Medicine* (Washington, DC: Government Printing Office,1989).

[243] Ibid.

Symptoms of whole-body radiation injury as a function of dose are identified in *AMedP-8(C)*[244] and shown in Table 17.

Table 17. Whole-Body Radiation Dose Ranges

Dose Range (Gy)	Description
< 1.25	No observable effect in the majority of the population
1.25–< 3	A slight decrease in white blood cell and platelet count with possible beginning symptoms of bone marrow damage; survival is > 90% unless there are other injuries
3–< 5.3	Moderate to severe bone marrow damage occurs; lethality ranges from $LD_{5/60}$ to $LD_{10/60}$ to $LD_{50/60}$; these patients require greater than 30 days recovery, but other injuries would increase the injury severity and possible death
5.3–< 8.3	Severe bone marrow damage occurs; lethality ranges from $LD_{50/60}$ to $LD_{99/60}$; death occurs within 3.5 to 6 weeks with the radiation injury alone but is accelerated with other injuries; with other injuries death may occur within 2 weeks
≥ 8.3	Bone marrow pancytopenia and moderate intestinal damage occur including diarrhea; death is expected within 2 to 3 weeks; with other injuries death may occur within 2 weeks; at higher doses, combined gastrointestinal and bone marrow damage occur with hypotension and death is expected within 1 to 2.5 weeks or if other injuries are also present, within 6 days

2. Whole-Body Radiation Medical Management Principles

A precise history of exposure may be very difficult to obtain, since many individuals may not know if they have been exposed to radiation, or to what extent. Initial triage and management of victims with ARS will be based on clinical signs, symptoms, and physical examination, as well as on estimates of whole-body dose using clinical biodosimetry, dose reconstruction, and real-time environmental radiation measurements.[245] At the present time, dosimetry will not provide a picture sufficient to determine either the extent of radiation injury or the prognosis. However, in a mass casualty situation in an operational theater where time is critical, decisions based only on dosimetric data may be all that is practicable.[246]

244 NATO, *AMedP-8(C)*, Table A-22.

245 National Security Staff of the Interagency Policy Coordination Subcommittee for Preparedness and Response to Radiological and Nuclear Threats, "Planning Guidance for Response to a Nuclear Detonation: Second Edition," (2010), 80.

246 U.S. Department of the Army, "Treatment of Nuclear and Radiological Casualties," (Washington, DC: Government Printing Office, 2001), 3–16.

Approaches suitable for treatment of conventional injuries may be of little utility in irradiated subjects. Treatable radiation-associated injuries include only those with hematopoietic and gastrointestinal (GI) syndrome. Whole-body radiation is generally modeled as homogeneous and uniform, although in a nuclear weapon exposure scenario it may be more likely to be heterogeneous and non-uniform. Although the assumption of uniform homogeneity markedly affects the dose effect, severity of the sub-syndromes, and efficacy of supportive care, it is regarded as a more conservative assumption and is used in this study. Whole-body radiation confers hematopoietic and GI symptoms at doses below 10 Gy. There are multiple treatments that can be used to decrease the severity and time course of organ-specific injury. One is supportive care, which includes fluid and electrolyte replacement, platelet, erythrocyte, or whole-blood transfusions, antibiotics, anti-diarrheals, analgesics and nutrition. (It should be noted that much of this care does not directly address the radiation injury, but are intended to "support" the patient during recovery from the radiation injury.) Another is an antiemetic therapy, which can be used to treat nausea and vomiting from irradiation. The last are cytokine therapies, specifically hematopoietic growth factors, which can be used to speed hematopoietic recovery through neutrophil and/or thrombocyte recovery. In this analysis, treatments were characterized by a dose reduction factor (DRF), except for the use of antiemetics ondansetron and granisetron. These antiemetics had much more clinical data on symptom severity than the other treatments that were modeled. None of the cytokine treatments protect against doses above 10 Gy, the point at which the GI syndrome arises. RTD was not modeled at effective doses (after taking into account DRFs) above 3 Gy (about 4.5 Gy, untreated) because at six weeks, the patient is still modeled as being at a Severity Level of 3 or 4. Past this point, the patient would probably remain in medical care for weeks or months and have a long convalescence afterwards. Therefore, the patient probably would not RTD in any reasonable time. The basic principles of medical management of a radiation casualty are:[247]

- Treat any conventional injuries first
- Maintain ventilation and perfusion and stop hemorrhages
- Assess extent of radiation injury or dose of suspected patient[248, 249]
  - Perform measurement and bioassay, if appropriate, to determine radionuclide contamination
  - Record physical dosimetry measurements, if available
  - Observe/record prodromal signs (erythema), symptoms, and clinical bioassays

[247] Ibid.

[248] William F. Blakely, Charles A. Salter, and Pataje G. S. Prasanna, "Early-Response Biological Dosimetry-Recommended Countermeasure Enhancements for Mass-Casualty Radiological Incidents and Terrorism," *Health Physics* 89, no. 5 (2005).

[249] Jamie K. Waselenko et al., "Medical Management of the Acute Radiation Syndrome: Recommendations of the Strategic National Stockpile Radiation Working Group," *Annals of Internal Medicine* 140, no. 12 (2004).

  - Obtain a complete blood cell count (CBC) with white blood cell differential immediately, then every 6 hours for 2–3 days, and then twice a day for 4 days
  - Contact a qualified laboratory to evaluate performance of chromosome-aberration cytogenetic bioassay, using the "gold standard" dicentric assay for dose assessment
  - Consider other opportunistic dosimetry approaches as available
- Decontaminate external radionuclides and consider decorporation therapies for internal contamination, if present
- Manage microbial infections
- Administer antiemetics, parenteral fluids and electrolytes to reduce the symptoms of GI distress
- Administer cytokines, as available and indicated
- Provide cardiovascular support for patients with clinically significant hypotension and neurologic dysfunction (as resources and staff allow: These patients are not likely to survive injury to the vascular and GI systems combined with marrow aplasia).

Supportive care has been shown to increase the median lethal dose and decrease the severity of irradiation. MacVittie et al. used dogs to determine the median lethal dose for both untreated and treated animals.[250] The LD_{50} for untreated dogs was 2.60 Gy and, for treated dogs, it was 3.38 Gy. This provides a DRF of 1.3.[251] The supportive care given in this study was antibiotics, fluid and electrolyte replacement, and transfusions when needed. If the definition of supportive care was changed, such as adding antidiarrheals or GI decontamination, then the DRF may change. This gives a rough estimate, however, of what effect supportive care can have on survival. This DRF, as is the case for all DRFs, decreases the severity of symptoms by it, so that a 4.5 Gy dose to humans gives the severities associated with a 3.13 Gy dose to canines. It also changes the median lethal dose, so the new LD_{50} moves from 4.5 Gy (untreated) to 5.85 Gy (with supportive care) in the human response to whole-body irradiation and supportive care. [252]

Although none have been approved by the FDA to treat radiation casualties, there are some cytokines that may be beneficial in treating the hematopoietic syndrome. Five in particular have IND or Emergency Use Authorization (EUA) status at the FDA, so they would be more easily procured in the event of an emergency.[253] These drugs are granulocyte colony-stimulating factor,

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250 T.J. MacVittie et al., "The Relative Biological Effectiveness of Mixed Fission-Neutron-Gamma Radiation on the Hematopoietic Syndrome in the Canine: Effect of Therapy on Survival," *Radiation Research* 128, no. suppl 1 (1991).

251 Ibid.

252 George H. Anno et al., "Biological Effects of Protracted Exposure to Ionizing Radiation: Review, Analysis, and Model Development," (Los Angeles, CA: Pacific-Sierra Research Corp., 1991).

253 Mark H. Whitnall, *Radiation Countermeasures Symposium: Introduction* (Bethesda, MD: Armed Forces Radiobiology Research Institute, 2011).

(G-CSF), 5-Androstenediol, Genistein, CBLB502, and Ex-Rad. G-CSF in particular has an EUA that, after appropriate requests have been filed with the FDA, allows it to be used in an emergency situation.[254] Data are available on the use of G-CSF to treat ARS and the current study estimated a DRF for the use of this drug therapy to treat ARS. 5-Androstenediol, Genistein, CBLB502, and Ex-Rad have only been tested prophylactically, and are outside the focus of this study. The DRF for G-CSF increases the median lethal dose and decreases the severities for cardiovascular and immune symptoms. G-CSF does not affect the severity of upper or lower GI symptoms.

G-CSF is the most commonly recommended cytokine in radiation treatment articles. It is fairly well-received and the database is substantial and consistent across three species of animal models. The data for the DRF was derived from MacVittie et al.'s data on dogs given G-CSF and supportive care. These dogs, given a subcutaneous 5 mL bolus once a day starting the day after exposure as well as antibiotics, transfusions, and fluid and electrolyte therapy, had a median-lethal dose of 4.88 Gy.[255] The LD_{50} for supportive care in dogs was 3.38 Gy and the LD_{50} for unsupported dogs was 2.60 Gy.[256] Therefore, the DRF when compared with untreated dogs was 1.88 for dogs treated with both G-CSF and supportive care. The DRF when compared with dogs given just supportive care was 1.44. This value was used as a rough estimate of the DRF for G-CSF without supportive care. Some macaque data, however, seemed to indicate that the DRF may be smaller.[257][258] Since these macaques were only treated at one radiation dose and all macaques survived, however, no DRF could be determined from them.

To summarize, the DRFs determined for supportive care and G-CSF treatments are given in Table 18.

Table 18. Dose Reduction Factors

Treatment	Dose Reduction Factor
Supportive Care	1.3
G-CSF (Treatment)	1.44

254 Ibid.

255 Thomas J. MacVittie, Ann M. Farese, and William Jackson, "Defining the Full Therapeutic Potential of Recombinant Growth Factors in the Post Radiation-Accident Environment: The Effect of Supportive Care Plus Administration of G-Csf," *Health Physics* 89, no. 5 (2005).

256 Ibid.

257 Ann M. Farese et al., "Combined Administration of Recombinant Human Megakaryocyte Growth and Development Factor and Granulocyte Colony-Stimulating Factor Enhances Multilineage Hematopoietic Reconstitution in Nonhuman Primates after Radiation-Induced Marrow Aplasia," *Journal of Clinical Investigation* 97, no. 9 (1996).

258 Ann M. Farese et al., "Leridistim, a Chimeric Dual G-Csf and Il-3 Receptor Agonist, Enhances Multilineage Hematopoietic Recovery in a Nonhuman Primate Model of Radiation-Induced Myelosuppression: Effect of Schedule, Dose, and Route of Administration," *Stem Cells* 19, no. 6 (2001).

3. Whole-Body Radiation Medical Countermeasure: Radiation Antiemetic

During the 1990's, NATO pursued the approval of drugs that would suppress the upper GI symptoms of the ARS. After several years of testing and consideration, two candidate drugs were selected, with the eventual nomination of one as the recommended drug. The two drugs were granisetron and ondansetron. Both are 5-HT_3 receptor drugs that target serotonin and have been used in chemotherapy and post-operative patients. Several studies have sought to determine their effectiveness in alleviating upper GI symptoms in patients given radiation for cancer or other health problems. The studies have shown significant decreases in the severity of nausea and vomiting for radiation levels up to 10 Gy. No studies have looked at granisetron or ondansetron's effects at levels beyond this, so this treatment was not included in profiles for doses higher than 10 Gy.

Most studies showed that in the first 24 hours, the median severity level of patients was zero, regardless of dose level. After the first day, the median severity level was one, regardless of dose level. Table 19 shows the severity levels and doses in each study for the first 24 hours. Table 20 shows this same information, but for days after 24 hours (most studies did not break this down further). The doses are given in an equivalent prompt dose format. Most of the studies used fractionated doses, but these values were converted using Anno et al.'s Upper Gastrointestinal Distress Model (UGDM)[259] into equivalent prompt doses so they could more easily be compared with other studies using single doses of radiation. The percentages of patients at each severity level were similar across studies and across drugs. Therefore, both granisetron and ondansetron were modeled with the same efficacy. Spitzer et al.'s study[260] showed a much higher severity level than the other studies, but since the study only had 18 patients taking granisetron (labeled as G in the tables) and 15 patients taking ondansetron (labeled as O in the tables), the finding could just be the result of the small sample size. From this data, the IDA study team concluded that taking ondansetron or granisetron upon receiving radiation and at the recommended dose from then on brought the upper GI severity to zero (No Observable Effect) for the first 24 hours and one (Mild) for days after that. This was true of any dose level, up to 10 Gy.

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259 Anno et al., "Biological Effects of Protracted Exposure to Ionizing Radiation: Review, Analysis, and Model Development."

260 T.R. Spitzer et al., "Double-Blind, Randomized, Parallel-Group Study on the Efficacy and Safety of Oral Granisetron and Oral Ondansetron in the Prophylaxis of Nausea and Vomiting in Patients Receiving Hyperfractionated Total Body Irradiation," *Bone Marrow Transplantation* 26, no. 2 (2000).

Table 19. Treatment Data for First 24 Hours after Radiation

Study	Dose (EPD)	Severity 0	Severity 1	Severity 2	Severity 3
Henriksson[261]	2–3.5 Gy	-	-	-	-
Franzen[262]	2–3.5 Gy	-	-	-	-
Lanciano[263]	2–3.5 Gy	79%	12%	9%	0%
Spitzer[264]: G	5.5 Gy	44.4%	16.7%	38.9%	0%
Spitzer[265]: O	5.5 Gy	26.7%	20%	53.3%	0%
Dubois[266]	8–10 Gy	92% (combined)	92% (combined)	8%	0%

Table 20. Treatment Data for Post 24 Hours after Radiation

Study	Dose (EPD)	Severity 0	Severity 1	Severity 2	Severity 3
Henriksson[267]	2–3.5 Gy	45.5%	33.3%	18.2%	3%
Franzen[268]	2–3.5 Gy	17%	50%	33%	0%
Lanciano[269]	2–3.5 Gy	30%	31.2%	38.8%	0%
Spitzer[270]: G	5.5 Gy	11.1%	16.7%	72.2%	0%
Spitzer[271]: O	5.5 Gy	13.3%	13.4%	53.3%	20%
Dubois[272]	8–10 Gy	70% (combined)	70% (combined)	24%	6%

261 Roger Henriksson et al., "The Effect of Ondansetron on Radiation-Induced Emesis and Diarrhoea," *Acta Oncologica* 31, no. 7 (1992).

262 L. Franzen et al., "A Randomised Placebo Controlled Study with Ondansetron in Patients Undergoing Fractionated Radiotherapy," *Annals of Oncology* 7, no. 6 (1996).

263 Rachelle Lanciano et al., "The Efficacy and Safety of Once-Daily Kytril (Granisetron Hydrochloride) Tablets in the Prophylaxis of Nausea and Emesis Following Fractionated Upper Abdominal Radiotherapy," *Cancer Investigation* 19, no. 8 (2001).

264 Spitzer et al., "Double-Blind, Randomized, Parallel-Group Study."

265 Ibid.

266 Andre Dubois, Gregory L. King, and David R. Livengood, eds., *Radiation and the Gastrointestinal Tract* (Boca Raton, FL: CRC Press,1995).

267 Henriksson et al., "Effect of Ondansetron on Radiation-Induced Emesis and Diarrhoea."

268 Franzen et al., "Randomised Placebo Controlled Study with Ondansetron."

269 Lanciano et al., "Efficacy and Safety of Once-Daily Kytril (Granisetron Hydrochloride) Tablets."

270 Spitzer et al., "Double-Blind, Randomized, Parallel-Group Study."

271 Ibid.

272 Dubois, King, and Livengood, eds., *Radiation and the Gastrointestinal Tract*.

This will change the overall severity profile for all levels of radiation, up to 10 Gy. The whole-body radiation figures for upper GI symptoms, with and without treatment, are shown in Figure 2 through Figure 5. Antiemetics only change the upper GI symptoms, so no other symptom-specific profiles are shown.

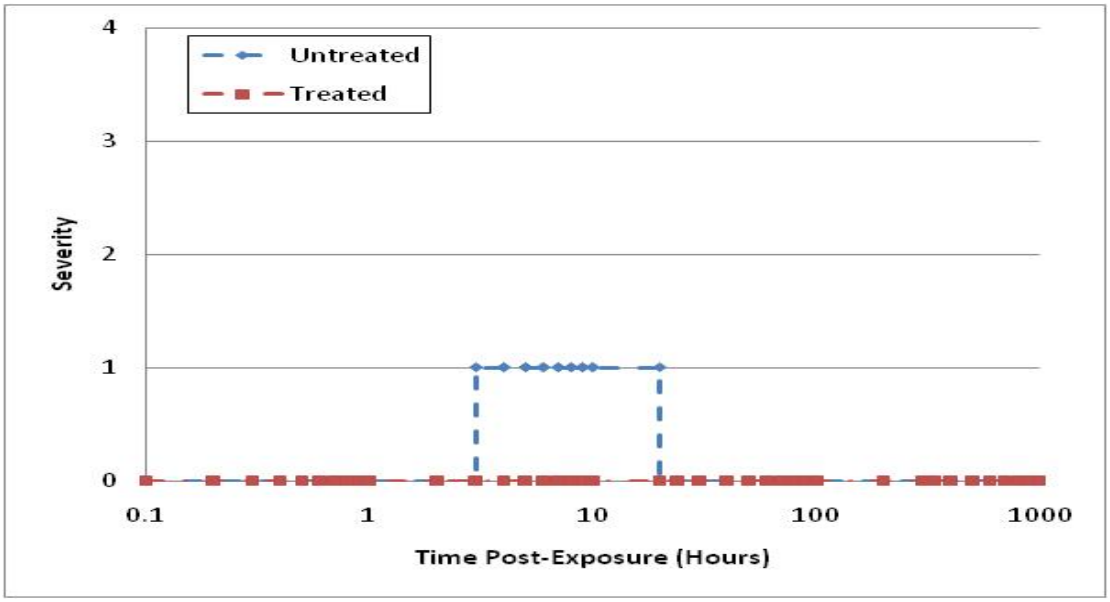

Figure 2. Whole-Body Radiation Upper Gastrointestinal Symptom Progressions for 1.25–<3 Gy

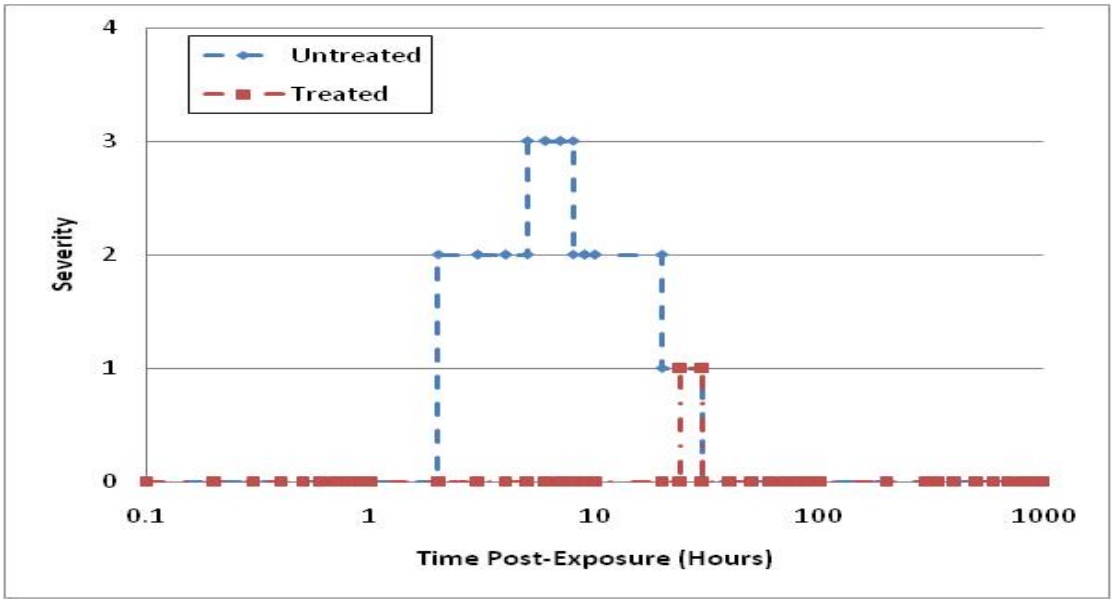

Figure 3. Whole-Body Radiation Upper Gastrointestinal Symptom Progressions for 3–<5.3 Gy

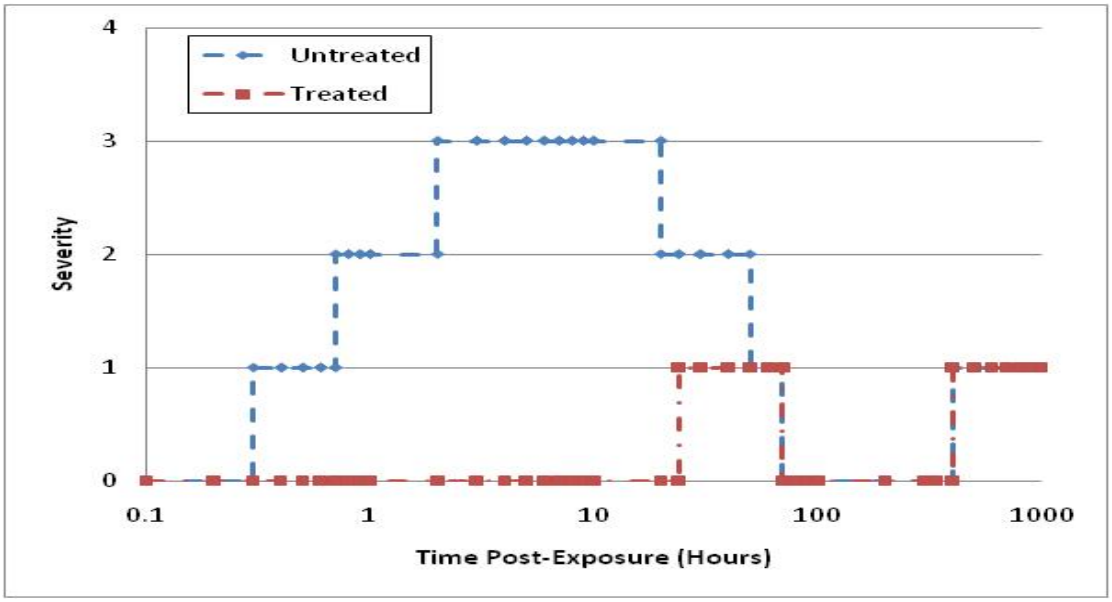

Figure 4. Whole-Body Radiation Upper Gastrointestinal Symptom Progressions for 5.3–<8.3 Gy

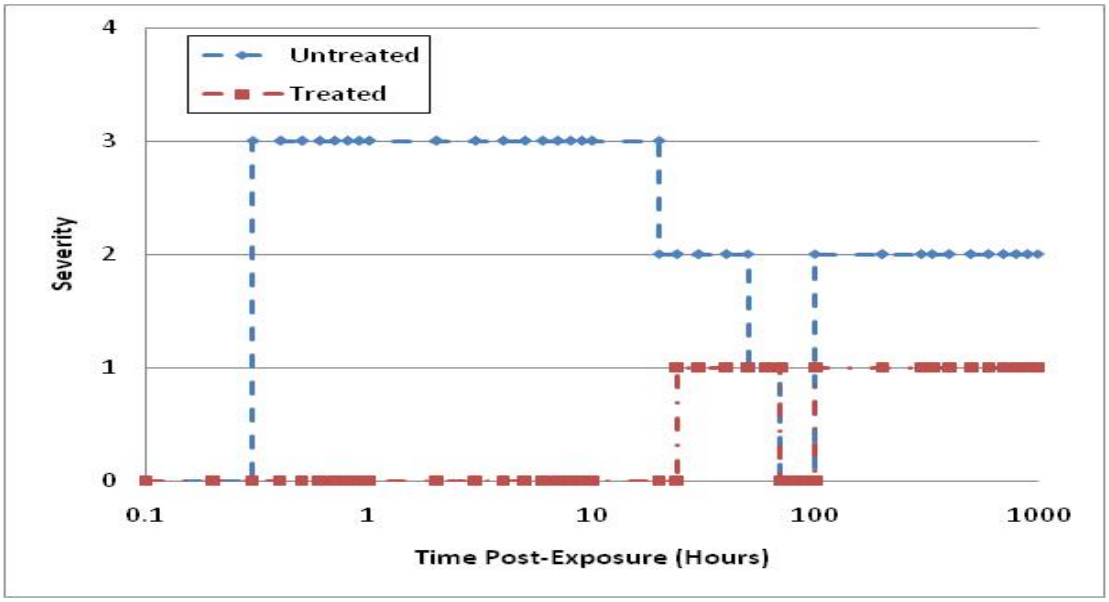

Figure 5. Whole-Body Radiation Upper Gastrointestinal Symptom Progressions for 8.3–10 Gy

These changes in the upper GI symptoms can also affect the overall symptom profiles for each of the different radiation doses. Since upper GI symptoms are generally the first symptoms to arise, taking the antiemetic prior to exposure can allow the solider to delay becoming WIA. This does not, however, affect the DOW or RTD times, since generally the most prominent symptoms at the end of the study period are cardiovascular and immune symptoms. The exception to this is at the 1.25–<3 Gy level. At this level, the only symptoms shown are mild upper GI symptoms in untreated patients in the first 24 hours. Therefore, at this dose level,

treated patients show no symptoms of radiation exposure. The new overall whole-body radiation injury profiles, as compared to the original untreated injury profiles for each dosage, are shown in Figure 6 through Figure 9.

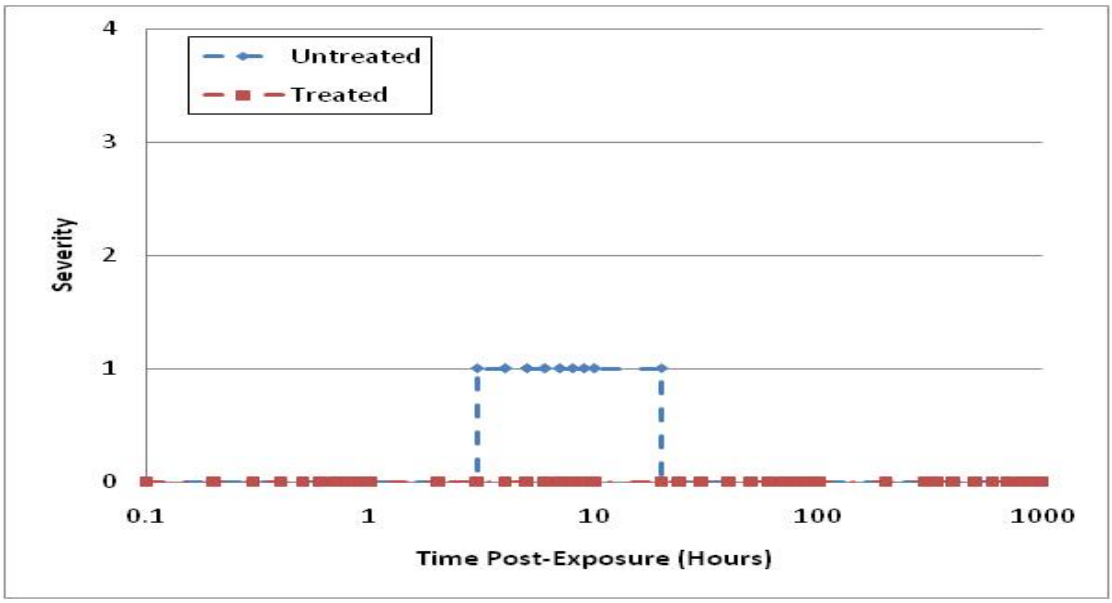

Figure 6. Whole-Body Radiation Injury Profile for 1.25–<3 Gy

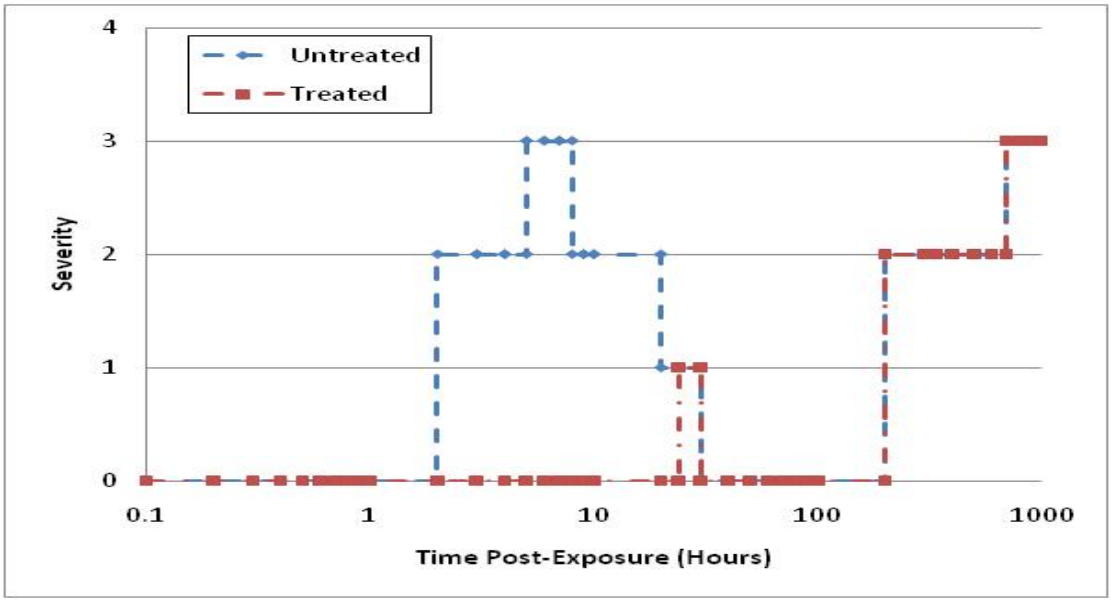

Figure 7. Whole-Body Radiation Injury Profile for 3–<5.3 Gy

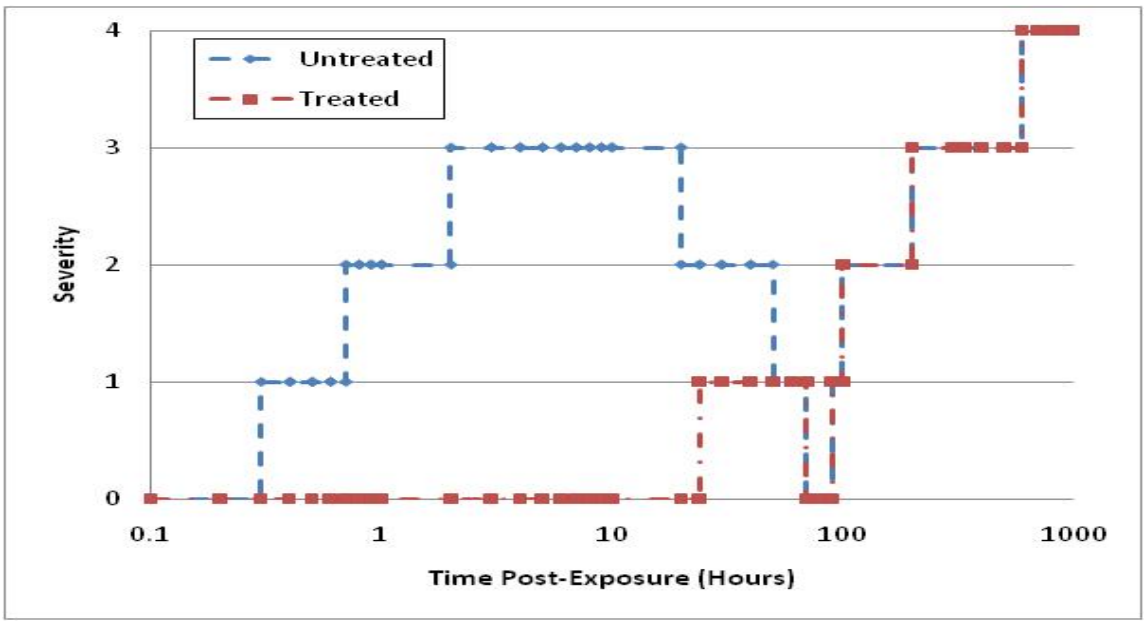

Figure 8. Whole-Body Radiation Injury Profile for 5.3–<8.3 Gy

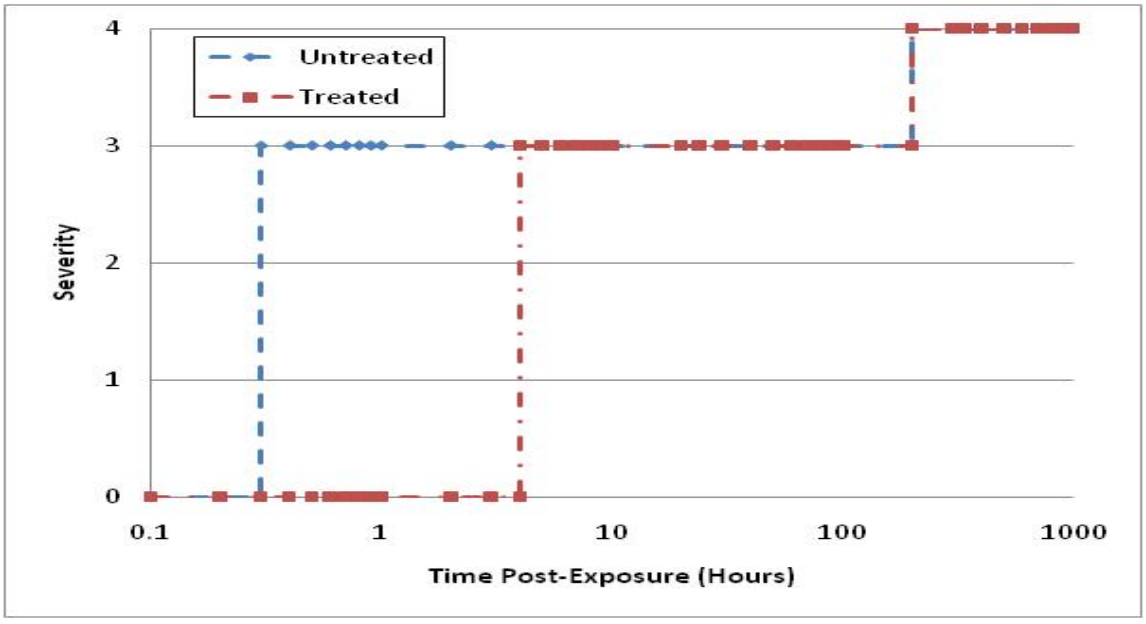

Figure 9. Whole-Body Radiation Injury Profile for 8.3–10 Gy

As the injury profiles indicate, issuing radiation antiemetics can significantly delay the onset of symptoms from radiation exposure. At the dose range of 1.25 to 3 Gy, it takes away any symptoms of radiation. At the dose range of 3 to 5.3 Gy, individuals do not become casualties (Severity Level 2) until after 200 hours if they are treated, as compared to two hours if they are not treated. At the dose range of 5.3 to 8.3 Gy, individuals do not reach Severity Level 1 until after 24 hours and do not reach Severity Level 2 until after 100 hours if they are treated. If they

are untreated, however, they reach Severity Level 1 after 0.3 hours and Severity Level 2 after 0.7 hours. At the dose range of 8.3 to 10 Gy, individuals become casualties (Severity Level 3) after 4 hours if treated, but after 0.3 hours if untreated. Therefore, antiemetic treatments delay the time to becoming a casualty. The amount depends on the definition of casualty and what dose the service member had. Since the upper GI symptoms occur before other, often more deadly, symptoms, the treatment does not appear to affect the number of DOWs or the RTD time.

There are some indications, however, that granisetron and ondansetron should not be used by military personnel before arriving at the hospital. The time to onset of nausea and vomiting often indicates how much radiation the individual has been exposed to. Knowing this dose can facilitate treatment for other symptoms, such as cardiovascular or immune symptoms, which can be more deadly than GI symptoms. Another difficulty with using antiemetics too early is that, since upper GI symptoms are often the first symptoms to manifest, individuals may then delay going to the hospital until much later. This can be a challenge because treatment for the radiation can start in advance of when actual symptoms appear, and this extra time could help save the soldier's life. Therefore, perhaps antiemetics should not be used by the soldier when initially exposed to radiation. These caveats should be taken into account when deciding whether or not service members should take the medication themselves and whether this would be modeled in any casualty estimates.

4. Whole-Body Radiation Patient Management Parameters

In the discussion above, DRFs were determined for supportive care and each of the cytokine treatments. The DRFs can be used to determine the severities that would be expected from a specific dose as given by its perceived dose. These DRFs can be combined. Therefore, if a patient is given supportive care and protective G-CSF, then the DRF would be 1.3 x 1.44, or 1.87. This multiplicative property does not occur when combining cytokine treatments, however. Further, the cytokine treatments, can only impact the severity of the cardiovascular and immune symptoms, while supportive care can impact the severity of all symptoms. None of the cytokine treatments impact doses above 10 Gy. Above that level, most cytokines cannot protect against the GI syndrome that arises.

Based on this analysis and the present operational resource capability, the IDA study team recommends using the DRF for supportive care (=1.3), since in a mass-casualty scenario it is unlikely that enough cytokines will be available to impact a significant number of patients. DOWs will still occur, but at a higher dose range than would normally be expected without treatment. With supportive medical treatment, it is expected that the LD_{50} would increase from 4.5 Gy to about 5.9 Gy. At doses above 6 Gy, death would be expected at the time modeled by the P8CEM "Radiation Time-to-Death" model.

RTD was not modeled at doses above 3 Gy since at six weeks the patient is still modeled as being at a Severity Level of 3 or 4. Past this point, the patient would probably remain in medical care for a period of time and have a long convalescence thereafter. As a result, the patient

probably would not RTD in any reasonable time, which would be taken into account in this study. The recommendations of this study regarding the modification of existing *AMedP-8(C)* casualty criteria, and the establishment of parameters for RTD and convalescence as a result of exposure to whole-body radiation are presented in Table 21.

Table 21. Treatment Modeling Parameters for Whole-Body Radiation

Dose Range (Gy)	Casualty Criteria			
	WIA	DOW	RTD	Convalescent
<1.25	0%	0%	0%	0%
1.25–<3	100%	0%	Day 3: 50% Week 6: 50%	0%
3–<5.3	100%	0%	0%	100%
5.3–<8.3	100%	50%	0%	50%
≥8.3	100%	100%	0%	0%

B. Cutaneous Radiation Patients

Acute local irradiation events may occur separately or coexist with the ARS. Radiation injury to the skin can result from both whole-body irradiation and localized-skin irradiation, such as skin contamination with beta-radiation emitting radionuclides.[273]

1. The Effects of Cutaneous Radiation

Symptoms of cutaneous radiation injury as a function of the dose to the skin are identified in *AMedP-8(C)*[274] and shown in Table 22.

[273] Military Medical Operations, Armed Forces Radiobiology Research Institute (AFRRI), *Medical Management of Radiological Casualties*, Online Third ed. (Bethesda, MD: AFRRI, 2010).

[274] NATO, *AMedP-8(C)*, Table A-21.

Table 22. Cutaneous Radiation Injury Dose Ranges

Dose Range (Gy)	Description
<2	No observable effect in the majority of the population
2–<15	12 hours to 5 weeks post-exposure: erythema, slight edema, possible increased pigmentation; 6 to 7 weeks post-exposure: dry desquamation
15–<40	Immediate itching; 1 to 3 weeks post-exposure: erythema, edema; 5 to 6 weeks post-exposure: subcutaneous tissue edema, blisters, moist desquamation; late effects (> 10 weeks)
40–<550	Immediate pain, tingling for 1 to 2 days; 1 to 2 weeks post-exposure: erythema, blisters, edema, pigmentation, erosions, ulceration, severe pain; severe late effects (> 10 weeks)
≥550	Immediate pain, tingling, swelling; 1 to 4 days post-exposure: blisters, early ischemia, substantial pain; tissue necrosis within 2 weeks, substantial pain

2. Cutaneous Radiation Medical Management Principles

The usual clinical experience with cutaneous radiation injury has been with relatively small areas of the skin irradiated by sealed radiation sources or from beams from sources such as x-ray machines, food irradiators, and equipment sterilizers.

The basic principles of medical management of a cutaneous radiation injury closely parallel the principles for medical management of thermal burns. Once tissue integrity has been dissolved, it is impossible to discriminate between a thermal burn, a chemical toxic reaction, or radiation injury.[275] The patient care team should remain cognizant of the evolution of cutaneous necrosis with radiation injury.[276]

- Infection control
  - Topical application of bacteriostatic agents and anti-inflammatory agents together with use of nonadherent dressings
  - As necessary, systemic antibacterial and virostatic medication
- Wound care, to include
  - Puncture of blisters and aspiration of blister fluids

[275] R.U. Peter, "Cutaneous Radiation Syndrome in Multi-Organ Failure," *The British Journal of Radiology* S27(2005).

[276] T.M. Fliedner, I. Friesecke, and K. Beyrer, eds., *Medical Management of Radiation Accidents: Manual on the Acute Radiation Syndrome* (London, UK: The British Institute of Radiology,2001); Military Medical Operations, *Medical Management of Radiological Casualties*; Carlos Rojas-Palma et al., eds., *Tmt Handbook: Triage, Monitoring and Treatment of People Exposed to Ionising Radiation Following a Malevolent Act* (Østerås, Norway: Norwegian Radiation Protection Authority,2009).

  - Administration of systemic anti-inflammatory and antiproliferative steroids to reduce edema
  - Management of radiation necrosis via anti-inflammatory treatment with topical corticosteroids, vascular therapy and surgery
  - Debridement of necrotic tissues
  - Excise of deep ulcerative lesions
  - Covering the wound bed with a good quality, full thickness skin graft
- Appropriate pain management.

3. Cutaneous Radiation Patient Management Parameters

Due to the prolonged symptomatology expected in a cutaneous radiation injury, and the symptomatic and supportive aspects of the recommended medical care, no changes to the injury profiles in *AMedP-8(C)* are recommended.

No DOWs will occur, and patients with exposures less than 40 Gy will RTD on or about the third day post-exposure. Patients with exposures at 40 Gy or more will require extensive wound care and are not expected to RTD, but will enter convalescent care. The recommendations of this study regarding the modification of existing *AMedP-8(C)* casualty criteria, and the establishment of parameters for RTD and convalescence as a result of the treatment of cutaneous radiation injuries are presented in Table 23.

Table 23. Treatment Modeling Parameters for Cutaneous Radiation Injury

Dose Range (Gy)	Casualty Criteria			
	WIA	DOW	RTD	Convalescent
<2	0%	0%	0%	0%
2–<15	100%	0%	Day 3: 100%	0%
15–<40	100%	0%	Day 3: 100%	0%
40–<550	100%	0%	0%	100%
≥550	100%	0%	0%	100%

C. Flash Burn Patients

Following the detonation of a tactical fission nuclear weapon, approximately 35% of the weapon's energy is dissipated as thermal energy. The general types of injuries resulting from this

energy are burns and eye injuries, including flash blindness and retinal burns.[277] Second-degree burns will be very common in nuclear combat and may be the most common injury to occur.

1. The Effects of Flash Burns

Flash burns result from the skin's exposure to a large quantity of thermal energy in a very brief time. This often leaves the affected area of the skin with a charred appearance. However, since the heat pulse occurs rapidly and the thermal conductivity of the skin is low, the burn is often superficial, killing only the outer dermal layers and leaving the germinal layer essentially undamaged. (In contrast, flame burn results from contact with a conventional fire, such as clothing or the remains of a building ignited by the fireball's thermal pulse.) [278] As the percentage of the surface burned increases, morbidity and the probability of mortality increases sharply. Burns that cover 30% or more of the body surface can be fatal without treatment.

Symptoms of flash burns, as a function of the percentage of the body surface area (%BSA) burned, are identified in *AMedP-8(C)*[279] as shown in Table 24.

Table 24. Flash Burn Symptoms

Insult Range (%BSA)	Description*
<1	No observable effect in the majority of the population†
1–<10	1st, 2nd and possible 3rd degree burns; electrolyte imbalance; pain
10–<20	Upper GI discomfort; 1st, 2nd and possible 3rd degree burns; electrolyte imbalance; increased pain
20–<30	Upper GI discomfort; 1st, 2nd and possible 3rd degree burns; fluid loss; decreased renal blood flow; compromise of the immune system; pain; lethality in 10%
≥30	Upper GI discomfort; 2nd and 3rd degree burns; hypovolemia; decreased renal blood flow; shock resulting from blood pressure decrease; cardiac distress; toxemia; multiple organ failure; lethality in ≥ 50%

* Estimation of burn lethality is approximate

† < 1 %BSA may include a larger area of first degree burns

2. Flash Burn Medical Management Principles

Burn injury is relatively common, and as such, many studies have been done on the efficacy of treatment and how long a patient remains in the hospital after a burn. Almost all treatment of

277 Walker and Cerveny, eds., *Medical Consequences of Nuclear Warfare*.

278 Ibid.

279 NATO, *AMedP-8(C)*, Table A-24.

burns can be defined as "supportive care." This includes fluid resuscitation, monitoring electrolytes, proper wound care, treating infections, and possible respiratory support. Skin grafts, whether autografts or allographs, may also be needed.[280]

Initial treatment of burn patients will be resuscitative. When such patients are first seen, a simple plan of treatment must include:[281]

- Airway maintenance with ventilatory support as needed
  - Tracheostomies, if large numbers of patients are seen requiring transportation over long distances early in the post-burn period
- Adequate fluid therapy, with careful recording of fluid input and output

Young, healthy service members who have uncomplicated burns may survive even extensive involvement with proper care. Patients with severe burns will suffer quite extensive fluid and electrolyte losses, resulting in severe hypovolemic shock requiring aggressive fluid replacement therapy as early as possible.

3. Flash Burn Patient Management Parameters

When considering the length of hospitalization, Wong and Ngim found that age, %BSA, full thickness %BSA, interval between injury and admission, type of thermal injury, status of respiratory injury and place of injury were significant predictors of length of hospital stay, although in the final model age, %BSA, full thickness %BSA, and status of respiratory injury are the only important variables: [282]

Length of Hospital Stay = 1.90+0.93(%BSA)+3.20(full thickness %BSA)+0.14(age)+6.97(status of respiratory injury)

Where status of respiratory injury is classified as 0 for none and 1 for confirmed inhalational injury.

Curreri et al. modeled the length of stay at the hospital as an inpatient, so it may be slightly shorter than the actual time to RTD. The time to RTD, or length of stay, was modeled as: [283]

Return to Duty = 102.5 * %BSA + 5.75 days.

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280 Bishara S. Atiyeh, S.William Gunn, and Shady N. Hayek, "State of the Art in Burn Treatment," *World Journal of Surgery* 29, no. 2 (2005).

281 U.S. Department of the Army, "Treatment of Nuclear and Radiological Casualties."

282 M.K. Wong and R.C.K. Ngim, "Burns Mortality and Hospitalization Time–a Prospective Statistical Study of 352 Patients in an Asian National Burn Centre," *Burns* 21, no. 1 (1995).

283 P. William Curreri et al., "Burn Injury. Analysis of Survival and Hospitalization Time for 937 Patients," *Annals of Surgery* 192, no. 4 (1980).

Both the model from Wong and Ngim and the model from Curreri agree within 10% for a 25 year old patient, with no respiratory burn, and 10–50 %BSA. The time to RTD was assumed to be the same as the length of hospital stay and the model was taken from Wong and Ngim's study.

There was not as much data on time to death. One study found an average time to death of nine days,[284] while another stated that 63.1% of non-survivors died in the first seven days after injury.[285]

These values, particularly the mortality model, are based on the best possible medical care. In a mass-casualty scenario, the best possible care would probably not be available. Therefore, the mortality would probably be higher than in this model and the length of hospital stay may also be changed.

Wong and Ngim analyzed 352 patients in an Asian National Burn Centre study to develop statistical predictive models for mortality and hospitalization time.[286] The model developed and described is a multivariate logistical regression. To predict mortality, Wong and Ngim found that the factors that were significantly different between the survivors and those who died included %BSA, full thickness %BSA, the interval between injury and admission, type of thermal injury and whether or not there were respiratory injuries, although only %BSA and the status of respiratory injuries had a significant discrete impact.

$$\text{Probability of death } = \left[1 + e^{8.32 - 0.15x - 2.96y}\right]^{-1}$$

Where x is the %BSA and y is the status of respiratory injury (0 for none and 1 for confirmed inhalational injury).

A more recent study by Song and Chua estimated mortality from data collected on burn patients in Singapore.[287] The mortality was modeled with an LA_{50} and a probit slope. The LA_{50} was found to be 55.6% of the total BSA. In a scenario where the burns are a result of nuclear thermal pulse, a casualty is very unlikely to receive a flash burn to more than 50 %BSA, so this LA_{50} was modified to 45 %BSA. The probit slope was 0.0539. With treatment, DOWs will still occur, but at a higher BSA than would normally be expected without treatment. The recommendation of this study regarding the modification of existing *AMedP-8(C)* casualty criteria, and the establishment of parameters for RTD and convalescence as a result of flash burns are presented in Table 25.

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284 Wong and Ngim, "Burns Mortality and Hospitalization Time."

285 Curreri et al., "Burn Injury."

286 Wong and Ngim, "Burns Mortality and Hospitalization Time."

287 Colin Song and Alvin Chua, "Epidemiology of Burn Injuries in Singapore from 1997 to 2003," *Burns* 31, no. suppl 1 (2005).

Table 25. Treatment Modeling Parameters for Burns

Thermal Insult Range (%BSA)	Casualty Criteria			
	WIA	DOW	RTD	Convalescent
<1	0%	0%	0%	0%
1–<15	100%	0%	Week 1–4: 100%	0%
15–<30	100%	<2%	Week 4–6: 50%	50%
30–<45	100%	2–50%	0%	>50%
≥45	100%	50–100%	0%	<50%

D. Primary Blast Injury Patients

An explosion may kill or maim a casualty in several ways. Whether it travels through air or water, the blast wave itself may cause internal damage to organs that contain air without leaving any external sign of injury. A blast may also propel fragments into a casualty, causing secondary blast injury, or can bodily displace an individual and cause tertiary blast injury upon impact.

Primary blast injury (PBI) is most likely to occur during a conflict between opponents with sophisticated weapons. Even so, the tragic worldwide increase in small-scale terrorist violence has given the medical community opportunities to supplement both wartime medical commentaries and findings from animal-model blast experimentation.

1. The Effects of Primary Blast Injury

When the blast wave acts directly upon the human body, rapid compression and decompression result in transmission of pressure waves through the tissues. These waves can be quite severe and will result in damage primarily at junctions between tissues of different densities (bone and muscle) or at the interface between tissue and air spaces. Lung tissue and the GI system, both of which contain air, are particularly susceptible to injury. The resulting tissue disruptions can lead to severe hemorrhage or to air embolism, either of which can be rapidly fatal. Perforation of the ear drums would be a common, but a minor, blast injury.

Injuries resulting from the blast waves will be caused by exposure to high pressures with very short rise times, and will consist primarily of internal injuries. For example, the threshold level for rupture of the eardrum is about 34.5 kPa (5 psi). Although this injury is very painful, it would not prevent an individual from accomplishing a critical military mission. The 250 kph (160 mph) winds that accompany the passage of a 34.5 kPa (5 psi) blast wave would be sufficiently strong to cause displacement and possible injuries. At the other end of the spectrum, a pressure level of 103 kPa (15 psi) will produce serious intrathoracic injuries, including alveolar and pulmonary vascular rupture, interstitial hemorrhage, edema, and air emboli. If the air emboli make their way into the arterial circulation, cerebral and myocardial infarctions may ensue. The initial outward signs of such pulmonary damage are frothy bleeding through the nostrils, dyspnea, and coughing. Victims may be in shock without any visible wounds. In addition,

serious abdominal injuries, including hepatic and splenic rupture, may result from a rapid and violent compression of the abdomen. [288]

Symptoms of PBI are a function of the static overpressure (kPa) as the nuclear blast wave passes over the casualty, and are identified in *AMedP-8(C)*[289] as shown in Table 26.

Table 26. Primary Blast Injury Symptoms

Insult Range (kPa)	Description
<50	No observable effect in the majority of the population
50–<140	Eardrum rupture in 50%; threshold lung damage; threshold gastrointestinal damage
140–<240	Burdening level lung damage in 50%; burdening level tympanic membrane rupture in 90%
240–<290	Burdening level lung damage in 90%; lethality in 10%
≥290	Lethality in ≥ 50%

2. Primary Blast Injury Medical Management Principles

Argyros describes the basic treatment for primary blast injury.[290] The first step in any treatment is to initiate life support measures if needed, including maintaining an adequate airway, ventilatory support if needed, and facilitating adequate circulation. Most primary blast victims suffer from ruptured tympanic membranes, but physicians should also look for hypopharyngeal petechiae or ecchymoses, fundoscopic evidence of retinal artery air emboli, or subcutaneous emphysema. Physical activity should be minimized even if the patient is ambulatory, since exertion after the blast can increase the severity of injury. Air evacuation may also be difficult for those with blast lung, due to the change in air pressure. The treatment of blast injuries, whether combined with other injuries or not, is best managed by applying accepted principles of combat surgery. Treatment is divided into four basic phases:[291]

- Resuscitative Care: Lifesaving resuscitative measures
- Surgery: Definitive surgery to improve the patient's condition
- Recovery: Minimal movement, transportation delayed until stabilized

[288] Walker and Cerveny, eds., *Medical Consequences of Nuclear Warfare*.

[289] NATO, *AMedP-8(C)*, Table A-23.

[290] Gregory J. Argyros, "Management of Primary Blast Injury," *Toxicology* 121, no. 1 (1997).

[291] Ronald F. Bellamy and Russ Zajtchuk, eds., *Conventional Warfare: Ballistic, Blast, and Burn Injuries*, *Textbooks of Military Medicine* (Washington, DC: Office of the Surgeon General,1991).

- Convalescence: Prolonged recovery period

3. Primary Blast Injury Patient Management Parameters

The time to RTD can vary from almost immediate, in the case of tympanic membrane rupture, to months, in the case of more severe blast lung or abdominal injuries. Richmond and Damon state that pulmonary hemorrhage improves in 24 hours and is resolved in a few weeks.[292] Damon et al. used sheep to determine the time to respiratory system recovery after a blast.[293] The greatest recovery in the sheep's lungs was evident in the first 24 hours, with further gradual improvement seen 2, 7, 14, and 21 days after exposure. After the twenty-first day, most animals had almost complete recovery of the pulmonary system at rest.[294] These animals had been given "sharp" rising reflected pressures ranging from 225 to 300 kPa (33 to 45 psig) with positive phase durations of 173 to 228 msec. The ambient pressure during the exposure was 83 kPa (12 psia).[295]

Pizov et al. looked at 15 patients with PBI resulting from explosions on two civilian buses in 1996.[296] Respiratory management included positive pressure ventilation in the majority of patients and other methods, such as high frequency jet ventilation, independent lung ventilation, nitric oxide, or extracorporeal membrane oxygenation in patients with severe PBI. Of the four with severe PBI, three died.[297] All six with moderate PBI survived, and four of five with mild BLI survived (one died of a head injury). Forty-seven were killed immediately at the site of the explosion, one died on arrival at the hospital and two had no lung injury.[298] Except for one who died from PBI two hours after admission, all patients showed improvement in oxygenation during the first 24 hours after injury. Of the three who died with severe PBI, one died from hypoxemia, severe intrapulmonary hemorrhage, and shock two hours after admission to the hospital, one died following a hemispheric stroke after complete clinical recovery from lung injury, and one died after 58 days from complications of respiratory failure and sepsis.[299] Four patients required prolonged mechanical ventilation and more than 21 days in the ICU.[300]

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292 Donald R. Richmond and Edward G. Damon, "Primary Blast Injuries in the Open and in Foxholes Resulting from Nuclear Type Detonations," (Los Alamos, NM: Technico Southwest Inc., 1991).

293 Edward G. Damon and Robert K. Jones, "Comparative Effects of Hyperoxia and Hyperbaric Pressure in Treatment of Primary Blast Injury," (Albuquerque, NM: Lovelace Foundation for Medical Education & Research, 1971).

294 Ibid.

295 Ibid.

296 Reuven Pizov et al., "Blast Lung Injury from an Explosion on a Civilian Bus," *Chest* 115, no. 1 (1999).

297 Ibid.

298 Ibid.

299 Ibid.

300 Ibid.

Avidan et al. looked at 29 patients who had PBI.[301] Seventy-six percent of these patients required mechanical ventilation, all within two hours of admission, for a median of four days. Therefore, late deterioration was rare.[302] Death from PBI in patients who survived the explosion is unusual.[303] Frykberg gave a rate of 11% injury specific mortality from PBI.[304] The median ICU and hospital stay for the entire study group was six and fourteen days, respectively, and two and six days for patients who did not require mechanical ventilation. Six months later, 76% were free of symptoms and had no respiratory handicap or therapy, while 24% had respiratory symptoms and/or some degree of respiratory dysfunction.[305]

DOWs are not expected to occur from PBI with treatment. At high burden levels (>290 kPa) most patients are expected to survive, but not RTD, remaining in a "convalescent" status for a prolonged period of time (beyond six weeks (1,000 hours)). The recommendation of this study regarding the modification of existing *AMedP-8(C)* casualty criteria, and the establishment of parameters for RTD and convalescence as a result of PBI are presented in Table 27.

Table 27. Treatment Modeling Parameters for Primary Blast Injuries

Exp. Range (kPa)	Casualty Criteria			
	WIA	DOW	RTD	Convalescent
<50	0%	0%	0%	0%
50–<140	100%	0%	Week 1: 100%	0%
140–<240	100%	0%	Week 3: 100%	0%
240–<290	100%	0%	Week 5: 100%	0%
≥290	100%	5–40%	0%	60–95%

E. Combined Injury Patients

1. The Effects of Combined Injuries

In the event of a radiation accident or nuclear detonation, many patients will likely suffer burns and traumatic injuries in addition to radiation. The initial triage of combined injury patients is based on these conventional injuries. The prognosis for all combined injuries is worse than for radiation injury alone. Animal studies indicate that when other injuries are accompanied

301 Vared Avidan et al., "Blast Lung Injury: Clinical Manifestations, Treatment, and Outcome," *American Journal of Surgery* 190, no. 6 (2005).

302 Ibid.

303 Ibid.

304 Eric R. Frykberg, "Medical Management of Disasters and Mass Casualties from Terrorist Bombings: How Can We Cope?," *Journal of Trauma* 53, no. 2 (2002).

305 Avidan et al., "Blast Lung Injury: Clinical Manifestations."

by sublethal doses of radiation, infections are much more difficult to control, and that wounds and fractures heal more slowly. Thus, potentially survivable burns and trauma will be fatal in a large percentage of persons who have also received significant injury from sublethal doses of radiation.

2. Combined Injury Medical Management Principles

Because of the delays in wound healing and the subsequent granulocytopenia and thrombocytopenia with injuries from nuclear weapons, most of the life-saving and reconstructive surgery must be performed within 36 hours after the exposure. Then, if possible, no surgery should be performed for the next 1.5–2 months post-exposure. All other medical management principles would follow from the wounds presented by the patient.

3. Combined Injury Medical Management Modeling Parameters

The recommendation of this study regarding the modification of existing *AMedP-8(C)* casualty criteria, and the establishment of parameters for RTD and convalescence as a result of combined injury cannot be summarized in a simple table. The significant impact of combined injuries is that lethality should be expected to result when any radiation dose above 2 Gy is combined with even moderate blast or burn trauma. At whole-body radiation doses greater than 1.25 Gy, at flash burns greater than 15% BSA, or primary blast levels greater than 140 kPa, DOW will occur.[306]

[306] U.S. Department of the Army, "Treatment of Nuclear and Radiological Casualties."

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5. Summary and Conclusion

A. Summary

Over the past several years, IDA has developed a symptom-based methodology, now promulgated as NATO STANAG 2553, *Allied Medical Publication 8: NATO Planning Guide for the Estimation of CBRN Casualties* (*AMedP-8(C)*), to estimate the number, type, and timing of casualties from a CBRN attack. During the development of *AMedP-8(C)*, the NATO CBRN Medical Working Group placed restrictions on the conditions IDA was able to be consider in the casualty estimation methodology: the impact of medical treatment would not be assessed, and the RTD casualty category would not be included.

This study extends the methodology to consider how medical intervention would influence the number of casualties in the DOW and RTD categories, and the times at which personnel would move into these categories. Moreover, medical management extends well beyond the immediate area of the battlefield, so extended therapy and long-term convalescent care are also considered. This document proposes the incorporation of an *AMedP-8(C)* patient estimation methodology, P8PEM, as an extension of the *AMedP-8(C)* casualty estimation methodology, P8CEM.

The P8PEM starts with the products of the P8CEM, specifically the estimate of the WIA casualties who will enter the medical system and become patients. Within the P8PEM, casualties are characterized within parameters that allow the user to consider the effect of medical treatment. To develop the P8PEM, IDA analyzed the recommended medical treatments for CBRN casualties, then identified the additional information required to estimate a patient's status for specific agents, such as the magnitude of the dose/dosage/insult or the specification of the disease stage.

The P8PEM identifies the WIA casualties as patients within the medical system and estimates the time at which these patients progress to other casualty categories including DOW, Convalescent, and RTD. The specific parameters for modeling the medical management of patients, which vary for the different CBRN agents and effects, are presented in the previous chapters of this document.

B. Conclusion

The effect of treatment on CBRN casualty status can be estimated using the available data. Some medical countermeasures can alter the dose response to CBRN agents and effects and, as a result, change the number of expected casualties. Medical treatment that is initiated after the onset of symptoms does not affect the time or rate of WIA. Medical treatment generally

decreases DOW. The number of patients who RTD or remain convalescent can also be estimated.

C. Recommendations

The results of this study should be considered for inclusion within the current medical planning and logistical tools and architecture to improve the medical planning process.

Appendix A
Illustrations

Figures

Tables

Appendix B
References

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Appendix C
Abbreviations

%BSA	Percent Body Surface Area
2-PAM Cl	Pralidoxime Chloride
ACh	Acetylcholine
AChE	Acetylcholinesterase
ACIP	Advisory Committee on Immunization Practices
AMA	American Medical Association
AMedP-8(C)	*Allied Medical Publication 8: NATO Planning Guide for the Estimation of CBRN Casualties*
ARS	Acute Radiation Syndrome
ATNAA	Antidote Treatment Nerve Agent Auto-Injector
AVA	Anthrax Vaccine Adsorbed
BSA	Burn Surface Area
CBC	Complete Blood Count
CBRN	Chemical, Biological, Radiological, and Nuclear
CDC	Centers for Disease Control and Prevention
CNS	Central Nervous System
CPR	Cardiopulmonary Resuscitation
CRN	Chemical, Radiological, and Nuclear
DNA	Deoxyribonucleic Acid
DOD	Department of Defense
DOW	Died of Wounds
DRF	Dose Reduction Factor
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GA	Tabun
GB	Sarin
G-CSF	Granulocyte Colony-Stimulating Factor
GD	Soman
GI	Gastrointestinal
Gy	Gray
HBAT	Heptavalent Botulinum Antitoxin
HD	Sulfur Mustard
hMabs	Human-Compatible Monoclonal Antibodies
ICU	Intensive Care Unit
IDA	Institute for Defense Analyses
IM	Intramuscular
IND	Investigational New Drug
IV	Intravenous

KIA	Killed in Action
kPa	Kilopascal
LA_{50}	Median Lethal Burn Area
$LD_{10/60}$	Dose Resulting in Lethality for 10% of the Exposed Population within 60 Days
$LD_{5/60}$	Dose Resulting in Lethality for 5% of the Exposed Population within 60 Days
LD_{50}	Median Lethal Dose
$LD_{50/60}$	Dose Resulting in Lethality for 50% of the Exposed Population within 60 Days
$LD_{99/60}$	Dose Resulting in Lethality for 99% of the Exposed Population within 60 Days
LVS	Live Vaccine Strain
MRV	Military Research Volunteer
NATO	North Atlantic Treaty Organization
OTSG	Office of the Surgeon General (U.S. Army)
P2S	Pralidoxime Mesylate
P8CEM	AMedP-8(C) Casualty Estimation Methodology
P8PEM	AMedP-8(C) Patient Estimation Methodology
PB	Pyridostigmine Bromide
PBI	Primary Blast Injury
PR	Protection Ratio
RBC-ChE	Red Blood Cell Cholinesterase
RTD	Return to Duty
SEB	Staphylococcal Enterotoxin B
STANAG	Standardization Agreements
UGDM	Upper Gastrointestinal Distress Model
US	United States
USAMRICD	United States Army Medical Research Institute for Chemical Defense
USAMRIID	United States Army Medical Research Institute of Infectious Diseases
VEE	Venezuelan Equine Encephalitis
VX	O-Ethyl-S-(2-diisopropylaminoethyl) methyl phosphonothiolate
WHO	World Health Organization
WIA	Wounded in Action

REPORT DOCUMENTATION PAGE		Form Approved OMB No. 0704-0188

1. REPORT DATE (DD-MM-YY)	2. REPORT TYPE	3. DATES COVERED (From – To)
March 2012	Final	

4. TITLE AND SUBTITLE	5a. CONTRACT NO.
The Impact of Medical Care on Casualty Estimates from Battlefield Exposure to Chemical, Biological and Radiological Agents and Nuclear Weapon Effects	DASW01-04-C-0003
	5b. GRANT NO.
	5c. PROGRAM ELEMENT NO(S).

6. AUTHOR(S)	5d. PROJECT NO.
Carl A. Curling, Julia K. Burr, Lucas A. LaViolet, Kristen A. Bishop, Preston J. Lee	
	5e. TASK NO. CA-6-3079
	5f. WORK UNIT NO.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)	8. PERFORMING ORGANIZATION REPORT NO.
Institute for Defense Analyses 4850 Mark Center Drive Alexandria, VA 22311-1882	IDA D-4465

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR'S / MONITOR'S ACRONYM(S)
Office of the Surgeon General of The Army Health Care Operations (DASG-HCO-G34) 7700 Arlington Blvd, Ste 5143 Falls Church, VA 22042-5143	OTSG
	11. SPONSOR'S / MONITOR'S REPORT NO(S).

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for public release; distribution is unclassified.

13. SUPPLEMENTARY NOTES

14. ABSTRACT

This study analyzed the impact of medical care on the chemical, biological, radiological, and nuclear (CBRN) casualty estimation methodology described in NATO Allied Medical Publication 8 (*AMedP-8(C)*): NATO Planning Guide for the Estimation of CBRN Casualties. This document proposes the *AMedP-8(C)* patient estimation methodology (P8PEM) as an extension of the *AMedP-8(C)* casualty estimation methodology (P8CEM). Starting with the products of the P8CEM, specifically the estimate of the Wounded in Action (WIA) casualties entering the medical system, the P8PEM characterizes these casualties using parameters that allow the user to consider the effect of medical treatment. The P8PEM both identifies the WIA casualties as patients within the medical system and estimates the time at which they progress to other casualty categories including Died of Wounds (DOW), Return to Duty (RTD), and Convalescent. By contrasting the outputs of the P8PEM with those of the P8CEM, users can easily quantify the benefit of medical care to patients and estimate the burden to the medical system. Including the results of this study within the current medical planning and logistical tools and architecture will improve the medical planning process.

15. SUBJECT TERMS

Medical care, treatment, casualty estimation, return to duty, convalescent care, died of wounds, P8CEM, P8PEM, CBRN, chemical casualty, biological casualty, radiological casualty, nuclear casualty

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NO. OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			MAJ Ricardo A. Reyes
U	U	U	UU	120	19b. TELEPHONE NUMBER (Include Area Code) 703-681-8188

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