Chemical, biological, radiological and nuclear incidents will require integrated emergency services' responses

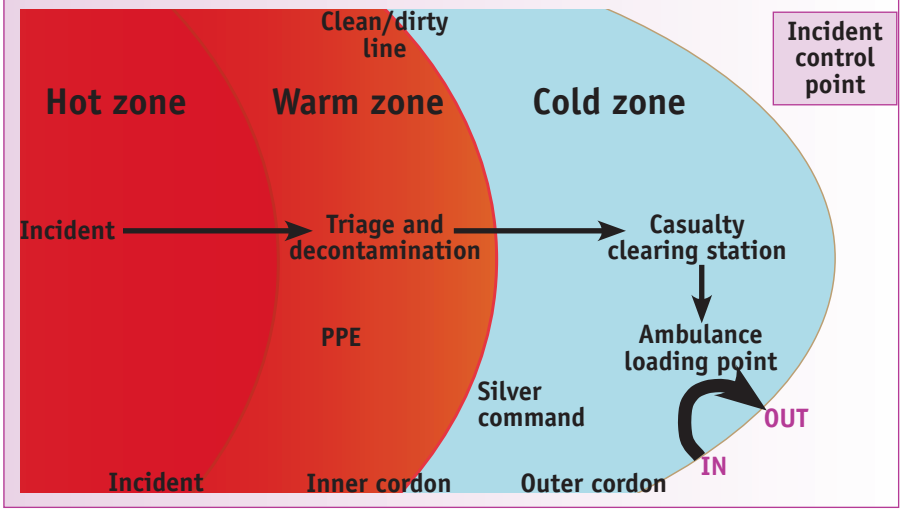
In the first article of a new series on emergency medicine Ed England describes the responses that will need to be made by health professionals to a chemical, biological, radiological or nuclear accident or attack.

Protect and survive

Chemical, biological, radiological and nuclear (CBRN) accidents and threats are a reality. In the event of an incident, what can pharmacists do? An understanding of the subject and being able to communicate the facts to the public will help considerably, but the practicalities of dealing with the aftermath presents more complex issues. The most obvious of these centre on the logistical challenges to ensure the availability of medicines at the time and place they are required. This article gives a background to the potential health consequences of a CBRN accident or attack and an overview of the medicines that may be needed. References and further reading are provided below to give you an opportunity to discover more about this area of emergency medicine.

The scene of a CBRN incident is divided into zones and the first priority is to move casualties to an uncontaminated atmosphere. The hot zone is the area in which the contamination occurs and where the fire and rescue service operates to extract casualties.[1] Triage and decontamination take place in the warm zone, where personal protective equipment (PPE) is used by the emergency services. Casualty clearing and ambulance loading take place in the cold zone (the post-decontamination area). Medical presence usually starts at the interface between the warm and cold zones, and treatment may start in the cold zone before ambulances transfer patients to hospitals (see Box 1).[2] Currently the Department of Health (DH) is implementing the Hazardous Area Response Team programme, which will enable ambulance services (in exceptional circumstances) to treat patients in the hot zone.[3]

Box 1. Zones at a chemical or biological incident[2]



Chemical incidents

The Health Protection Agency (HPA) has produced guidance on what to do if a patient has been exposed to a chemical incident.[4] The steps involved are:

- ☐ Decontaminate the patient.
- ☐ Stabilise airway, control haemorrhage and set up IV access if required.
- ☐ Assess cause, give antidotes if appropriate, reassess, alert Health Protection Teams and obtain expert advice (such as the National Poisons Information Service).

Management of chemical incidents requires knowledge of the specific agent involved, which is usually initially determined from the victims' symptoms. When the chemical is identified specific antidotes can be given.[4,5] Chemical agents can be divided into two broad categories; lethal and non-lethal, and a short summary of the chemicals discussed in the HPA guidance is presented in Box 2.[4,6,7]

Box 2. Potential chemical agents[4,6,7]

	Examples of immediate effects	Overview of treatment
Lethal:		
Blood agents Cyanide	After severe exposure convulsions may occur in 20–30 seconds followed by collapse and death from respiratory or cardiac arrest.	Decontaminate, give oxygen, correct acidosis. Specific antidotes are available (either dicobalt edetate or sodium nitrite with sodium thiosulphate).
Lung damaging agents Chlorine	Respiratory irritation, tearing, chest pain, dyspnoea, coughing, pulmonary damage.	Give oxygen, decontaminate, give inhaled salbutamol and steroids.
Nerve agents Sarin, Soman, Tabun	Diarrhoea, micturition, vomiting, pinpoint pupils, cardiac arrhythmias, bronchospasm, convulsions, salivation, tearing.	Give oxygen, decontaminate, give: atropine, pralidoxime, diazepam.
Vesicant Mustard gas	Severe damage to respiratory tract, skin and eyes.	Give oxygen, inhaled salbutamol +/- steroid. Decontaminate. Give generous analgesia, hydrocortisone ointment +/_ oral antihistamines. No antidote.
Non-lethal:		
Riot control gases Tear gas (CS — or chlorobenzyl-malononitrile gas)	Tearing and running nose, blurred vision, burning sensation in mucous membranes, chest tightness and shortness of breath.	Decontaminate. Treat skin irritation and itching/erythema.

A small drop of nerve agent on the skin or the inhalation of vapour can be fatal and most deaths are the result of respiratory arrest.[4] The professional emergency response team members are also vulnerable to Sarin, Soman and Tabun because these nerve agents tend to release gas as they evaporate (called off-gassing).[6]

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Nerve agents inhibit acetylcholinesterase (AChE) which prevents the breakdown of acetylcholine (ACh). With time the bond between AChE and the nerve agent becomes irreversible, referred to as aging (Figure 1), and how long this takes depends on the specific agent. For Soman the half-life of aging is 2–6 minutes, while for other agents it may be between 5–48 hours. Once the bond has aged, the production of new AChE can take from weeks to months.[8]

The HPA and DH offer specific advice for the management of people exposed to nerve agents, including doses of atropine, pralidoxime and diazepam.[4,9] Atropine is an antimuscarinic and competitively and reversibly blocks ACh binding to muscarinic receptors. The administration of atropine

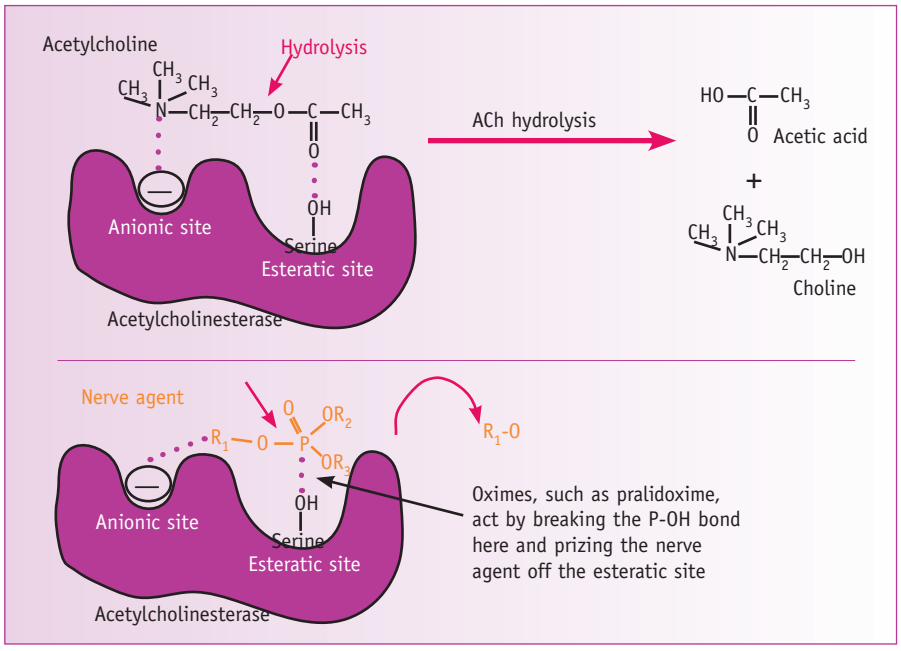

Figure 1 (opposite). Illustration of how acetylcholine (ACh) and nerve agents bind with acetylcholinesterase (AChE).
Top panel: ACh is electrostatically attracted (purple dotted lines) to the anionic and esteratic sites of AChE, and hydrolysis is catalysed at the esteratic site to form acetic acid and choline.
Bottom panel: A nerve agent (orange molecule) is also electrostatically attracted to the esteratic site, which it phosphorylates. It may, depending on the agent, also be electrostatically attracted to the anionic site. The phospho-OR_1 bond (red arrow) breaks and OR_1 leaves the anionic site, but the phospho-serine bond strengthens with time, referred to as 'aging'. This prevents ACh from interacting with AChE and being broken down. AChE is blocked but depending on the nerve agent and the time it has been bound with the enzyme, AChE can be (a) slowly hydrolyzed and regain its activity, (b) rapidly regenerated with an oxime, which splits the P-OH bond and prizes the nerve agent off serine at the esteratic site or (c) 'aged' whereby the phospho-serine bond is strengthened so that AChE cannot regenerate and new AChE must be synthesized.

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blocks the parasympathetic effects of excessive secretions and smooth muscle activation caused by the nerve agents, but it does not affect paralysis.[8] Pralidoxime is also recommended — it restores function of the nicotinic receptors at the neuromuscular junction and reverses paralysis of respiratory muscles and central apnoea,[5] but has little effect on muscarinic symptoms.[8] The oximes, such as pralidoxime, reactivate AChE which is reversibly bound to a nerve agent, by splitting the phosphorous-enzyme bond and thereby prising the nerve agent off the AChE (Figure 1). Therefore the oximes need to be given quickly before the bond has aged. The rapid aging of Soman, for example, means that the oximes do not have the opportunity to reactivate AChE. Diazepam is then recommended to manage the nerve agent dose-related induction of convulsions and agitation.[8]

Pyridostigmine is sometimes advised as a pre-treatment when there is a threat of nerve agent use. Pyridostigmine reversibly binds to part of AChE by carbamylation, preventing the nerve agent from binding. Pyridostigmine needs to be taken every eight hours because when it disassociates AChE activity is restored. Pyridostigmine does not penetrate the CNS and therefore does not affect performance — but neither does it protect against nerve agent-induced seizures.[10]

Biological incidents

A biological incident may be caused by the release of organisms into water, food or the air. They may occur naturally as well as being intentional.[11] Treatment of biological contamination of the general public requires a different approach to contamination of military personnel. The general population has a wider range of ages and health conditions than military personnel (who tend to be fit young adults) and are vulnerable to contamination of food and water supplies.[12] Biological threats have the potential for mass dissemination in the population and this is especially true for agents with prolonged incubation periods because the release of these agents might not be evident until after the incubation period has ended.[13] For example, smallpox usually has an incubation period of 10–16 days[11] before symptoms appear.

With biological incidents there is the potential for confusion with chemical

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poisoning.[11] The clinician needs to be aware that a differential diagnosis is necessary to identify the contamination or

Box 3. Biological diseases discussed in HPA guidance[6,11,12,14]

	Disease*	Biological agent	Transmission	Person to person	Prophylaxis and treatment
Bacteria	Anthrax[A]	*Bacillus anthracis*	Spores, aerosol, food	No	Vaccine, antibiotics
	Brucella[B]	*Brucella spp.*	Aerosol, contaminated milk products, direct contact	No	Antibiotics
	Glanders[B]	*Burkholderia mallei*	Aerosol, direct contact	Very low risk	Antibiotics
	Melioidosis[B]	*Burkholderia pseudomallei*	Aerosol, contaminated water, direct contact	Very low risk	Antibiotics
	Plague[A]	*Yersinia pestis*	Aerosol, droplets or flea vectors	Yes – Pneumonic plague	Vaccine in development, antibiotics
	Q fever[B]	*Coxiella burnetii*	Aerosol, contaminated milk products	No	Antibiotics
	Tularemia[A]	*Francisella tularensis*	Aerosol, tick or insect bites, contaminated food or water, direct contact	Very low risk	Vaccine, antibiotics
Toxin	Botulism[A]	*Clostridium botulinum* (botulinum toxins)	Aerosol, contaminated food or water	No	Toxoid vaccine, antitoxin Antibiotics (for wound botulism)
Viruses	SARS[C]	Human coronavirus	Aerosol, droplet, direct contact	Yes	Antibiotics
	Smallpox[A]	*Variola major*	Direct contact, body fluids	Yes	Vaccine
	Viral equine encephalitis[B]	*Alphaviruses*	Aerosol, mosquito bite	Very low risk	Supportive
	Viral haemorrhagic fever[A]	*Filoviruses and Arenaviruses, bunyaviruses, flaviviruses* (eg, *Ebola virus, Lassa virus*)	Varies. Includes aerosol, tick or insect bites, direct contact. Nosocomial	Yes – high risk for some	Supportive. Antiviral for lassa fever and Congo-Crimean haemorrhagic fever

**Note: Superscript denotes National Institute of Allergy and Infectious Diseases Category A, B, and C priority pathogens*

Box 4. Factors associated with biological agents presenting an increased risk to public health[12]

- ☐ High morbidity or mortality
- ☐ Potential for mass production and mass dissemination
- ☐ Respiratory transmission (easy to disseminate infection)
- ☐ Stable in the environment
- ☐ Person to person transmission (respiratory or contact spread)
- ☐ Public awareness (because this may result in mass fear or panic)
- ☐ Requirement for multiple health protection measures

outbreak of disease. The HPA guides offer some assistance in making a diagnosis[11] and a summary of the biological diseases discussed in the guidance is presented in Box 3. An accurate diagnosis and rapid treatment can counter biological incidents,[6] however, specialised testing and advice is usually necessary.

The threat that a range of biological agents pose to the civilian population has been evaluated by The Centres for Disease Control and Prevention[12] and is based on a risk assessment of some of the factors shown in Box 4. Category A agents are given the highest priority for preparedness, Category B agents require work to address awareness and capability deficiencies and Category C agents will be further assessed for their potential to threaten large populations.[12] To illustrate this the categories are indicated against the diseases listed in Box 3.[14]

An example of a potential biological threat is pneumonic plague, which has an incubation period of 2–4 days[11] and is invariably fatal if appropriate treatment is not started within 24 hours.[15] After exposure to *Yersinia pestis* or contact with a case of pneumonic disease, antibiotic prophylaxis should be started (first-line treatment is currently ciprofloxacin). Treatment with antibiotics should be started as early as possible and patients should be carefully monitored because shock can develop, caused by the release of endotoxins following bacteriolysis.[16]

Plague is considered a re-emerging disease and antibiotic-resistant strains are developing.[17] Alternative treatments are being investigated, including vaccines. Commercial vaccines are available in other countries; however, protection is delayed by at least one week after vaccination.[16]

Guidance on pre- and post- exposure prophylaxis to biological threats is available from the HPA, and the DH has prepared Patient Group Directions (PGD) for the supply of antibiotics after exposure (see further reading below). The PGDs provide for an initial supply of five days of ciprofloxacin and then completion of the course with ciprofloxacin or doxycycline, depending on the infectious agent. The HPA advice is also supported by detailed information on the Clinical Knowledge Summaries website.

The development of genetically and advanced biological warfare agents will present new threats. Genetically modified agents may be developed to include antibiotic resistance, increased aerosol stability or increased pathogenesis. However, the developments of advanced biological warfare agents present more of a threat. Agents may be engineered to target specific biological systems using knowledge derived from the study of organisms' genomes and proteins. The development of agents to prevent attacks on a genome present new challenges in medical countermeasures.[18]

Radiation and nuclear incidents

Everyone is exposed to radiation on a daily basis. The natural background exposure in the UK is around 2.2millisievert (a chest X-ray exposes a patient to around 20 microsievert).[19] However, exposure to ionising radiation (such as being in the presence of alpha or beta particles or gamma or X-rays) may result in injures, because the transfer of energy to cells may cause a permanent alteration in cell functioning or genetic material.[20]

The dose of ionizing radiation is dependent on duration of exposure, distance from the source and shielding; the dose measurements are explained in Box 5. A person who has been exposed to radiation is not a health hazard to anyone else. However, people who have become contaminated with radioactive material (on their clothes or by inhalation or ingestion) are hazardous to others until the radioactive source is removed.[19] After inhalation or ingestion, radionucleotides may have a preference for particular organs — for example, plutonium isotopes concentrate

Box 5. Radiation dose measurements[20]

Absorbed dose:	Energy absorbed per mass. Units are the gray, Gy (1 joule per kilogramme of tissue).
Equivalent dose:	The absorbed dose averaged over a tissue or organ multiplied by a specific radiation weighting factor. Units are the sievert, Sv (1 joule per kilogramme of tissue).
Effective dose:	The equivalent dose to each tissue and organ is multiplied by a tissue weighting factor. Units are the sievert.
Whole-body exposure:	All tissues are uniformly irradiated by external exposure. Units are the gray.
Specific radiation weighting factor:	Accounts for the effectiveness of damaging tissue for a given type of radiation.
Specific tissue weighting factor:	Accounts for sensitivity of different tissues to effects of radiation.

in the bone and liver and radioiodine concentrates in the thyroid.[20]

Acute radiation syndrome (ARS) follows a large, usually external exposure of all or most of the body to penetrating radiation of 1sievert (Sv) and above.[19] The mean lethal dose to kill 50% of humans at 60 days is between 3.25Gray (Gy) and 4Gy and this increases to between 6Gy and 7Gy for a person supported with antibiotics and transfusions.[21] There are three classic syndromes associated with exposure to radiation, resulting from actions on distinct physiological systems, each with unique sensitivities to radiation effects and these can be predicted from knowledge of the dose of radiation.[22] The physiological systems affected by radiation are:

- Bone marrow (haemopoietic): the destruction of the bone marrow resulting in infection and haemorrhage.
- Gastrointestinal: destructive and irreparable changes in the GI tract and bone marrow usually cause infection, dehydration, and electrolyte imbalance.
- Cardiovascular /central nervous system syndromes: collapse of the circulatory system and increased pressure in the confining cranial vault as the result of increased fluid content caused by oedema, vasculitis, and meningitis.

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Box 6. Four phases of acute radiation syndrome[21,22]

a. Prodromal phase: Nausea, vomiting, anorexia and sometimes diarrhoea; usually occurs in the first 48 hours, but may develop six days after exposure.
b. Latent phase: A short period in which symptoms improve and the person appears to recover. This is a transient phase lasting from days to months.
c. Manifest illness: Intense immunosuppression with symptoms dependent on specific syndrome. This may last for weeks, and if the person survives this stage recovery is likely.
d. Recovery or death. The recovery process lasts from several weeks up to two years.

The symptoms depend on the dose, and may appear within hours or weeks. High doses will result in compression of the phases into a period of hours before death.

Each syndrome can be divided into the four phases described in Box 6.

In a radiation incident triage and treatment of life-threatening injury usually take place before decontamination. The contamination is assessed and the patient's clothes are removed to reduce external contamination. The initial symptoms of ARS are non-specific and therefore treatment of other injuries and surgery takes priority. The patient is symptomatically treated for:[19]

- nausea and vomiting (cyclizine, ondansetron)
- diarrhoea
- pain (opiates)
- erythema
- fluid loss.

Prophylaxis of nausea and vomiting is not recommended because their onset and development are used as 'tools' to help calculate dose exposure. At high dose radiation this would be impractical anyway because onset time for vomiting is very short.[21] At low doses of radiation vomiting usually only lasts 48–72 hours and prolonged treatment is not necessary.

Medical countermeasures broadly fall into three categories. *Radioprotectants* prevent radiation-induced cellular and molecular damage, *radiation mitigators* accelerate recovery or repair after radiation injury and *radionucleotide eliminators* discorporate or block absorption of internalised radionucleotides.[23] Readers are referred to the supplied references and further reading suggestions at the end of the article for information about specific countermeasures.

Potassium iodine/iodate (stable iodine) is probably the best known radioprotectant and provides some protection to the thyroid gland by competitively inhibiting the uptake of radioiodine (I^{131}, I^{125}). Stable iodine should be administered as soon as possible, and if it is administered within four hours of exposure it can reduce radioiodine uptake by 50%.[21] Following an incident the priority is the protection of new born babies, children aged less than 10 years and pregnant and nursing women,[24] because the young efficiently concentrate iodine. A PGD is available on the DH website (see further reading below). Stable iodine is rarely indicated for those aged more than 40 years[24] — it offers no protection from ionizing radiation, bone marrow suppression or if radioiodine is not present — in fact it may be toxic (for example, it can induce anaphylaxis).[21]

Colony stimulating factors (CSFs) may be used to treat bone marrow suppression. The rationale for using CSFs is that they improve neutrophil recovery in patients with cancer, they have probably decreased the period of neutropenia in a small number of radiation accident victims and improved survival has been demonstrated in animal studies.[21] The CSFs are not licensed for this indication, but guidelines suggest these medicines may be given to any adult with a whole body or significant partial-body exposure greater than 3Gy, with a lower threshold of 2Gy for people aged less than 12 years, more than 60 years and those with significant trauma or burns.[21]

Patients who have been contaminated with radioactive material are susceptible to infection because of a breach of natural barriers, for example from wounds and translocation of commensal bacteria to the liver and spleen and from the immune suppression.[21,25] However, the potential delay in the fall in the leucocyte count provides time to treat existing infections.

The prophylaxis and management of infections in patients with extreme neutropenia is usually the same as for patients who have had stem cell transplants or haematological malignancies. Patients who are seropositive to, or with a medical history of herpes will require prophylaxis and/or treatment with antivirals because herpes reactivation is common in immunocompromised patients. Prophylaxis and/or treatment of oral candidiasis may be needed, and invasive aspergillosis and candidiasis may develop.[25] Infections should be treated according to culture findings and local microbiology advice should be sought.

The need for vaccination should be assessed in consultation with an appropriate specialist. Live vaccines can cause severe or fatal infections in immunosuppressed individuals because of extensive replication of the vaccine strain.[26]

Conclusion

In the event of a CBRN incident an early response is likely to be the most effective in reducing morbidity and mortality. Health professionals have access to a wide range of support and resources to assist in managing the potential consequences.

This article provides a brief background to this specialised area of emergency care. Hopefully, it also provides reassurance about the ongoing work to assure the safety of the public and provides signposting to useful resources in the event that the unexpected does happen. ✣

Declarations of interest

The author has no interests to declare.

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Further reading:

UK resources:

1. CBRN. *Incidents: A Guide to clinical management and health protection.* Available at http://www.hpa.org.uk/web/HPAweb&Page&HPAwebAutoListName/Page/1158934607980 Written primarily for front-line health care professionals in emergency departments.
2. Clinical Knowledge Summaries. (Website is http://cks.library.nhs.uk). Source of evidence-based and practical NHS information about managing deliberate release conditions in primary care (linked to the HPA guidance).
3. Department of Health Emergency Planning. Available at http://www.dh.gov.uk/en/Managingyourorganisation/Emergencyplanning/index.htm The website contains information on NHS contingency plans and advice on preparing for specific types of disasters and attacks (including patient group directions).
4. Health Protection Agency. (Website is http://www.hpa.org.uk). Authoritative scientific/medical information and specialist advice on response to major incidents and other emergencies.
5. Toxbase. (Website is http://www.toxbase.org — Registration is required). The primary clinical toxicology database of the National Poisons Information Service.
6. UK Resilience. (Website is http://www.ukresilience.gov.uk/). A resource for civil protection practitioners, supporting the work which goes on across the UK to improve emergency preparedness.

US resources:

1. Centers for Disease Control and prevention: Radiation Emergencies (Website is http://www.bt.cdc.gov/radiation/). Information to help people be prepared for a radiation emergency.
2. Oak Ridge Institute for Science and Education (Website is http://orise.orau.gov/reacts/pubs-resources.htm). Publications and resources for emergency medical response to radiation incidents from The Radiation Emergency Assistance Center/Training Site (REAC/TS).
3. Centers for Disease Control and Prevention Emergency Preparedness & Response (Website is http://www.bt.cdc.gov). US Department of Health and Human Services information and advice.
4. Armed Forces Radiobiology Research Institute. (Website is http://www.afrri.usuhs.mil). Useful US references for the medical management of radiological casualties.

World Health Organization:

http://www.who.int/csr/delibepidemics/biochemguide/en/
Public health response to biological and chemical weapons: WHO guidance (2004).

http://www.who.int/ionizing_radiation/a_e/en/
Useful information on the management of radiation emergencies.