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Adult Medical Countermeasures: Antidotes and Cytokines for Radiological and Nuclear Incidents and Terrorism

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Abstract

The war in Ukraine raises concerns for potential hazards of radiological incidents and their impact on humans, especially families. Preparedness and response to radiological and nuclear incidents necessitates familiarity with pharmaceutical countermeasures, including antidotes and cytokines. Searches found no published study comparing adult indications and dosing among standard references. This study addresses this gap by collecting, tabulating, and disseminating information to health care professionals. Expert consensus chose the following references to compare adult indications and dosing of medical countermeasures for radiation exposure and internal contamination with radioactive materials: *Advanced Hazmat Life Support (AHLS) for Radiological Incidents & Terrorism*, *DailyMed*, *Internal Contamination Clinical Reference*, *Medical Aspects of Radiation Incidents*, *Medical Management of Radiological Casualties*, *Micromedex*, *National Stockpiles for Radiological and Nuclear Emergencies: Policy Advice*, *POISINDEX*, and *Radiation Emergency Medical Management (REMM)*. This is the first study comparing adult indications and dosing for medical countermeasures among common references for radiological and nuclear incidents.

Introduction

Disasters occur in many forms. Natural hazards include climatological events, such as floods, tornadoes, and hurricanes, as well as geological incidents, such as earthquakes, volcanic eruptions, and landslides.[1] There are also technological hazards, such as power outages, cybersecurity breaches, and hazardous materials incidents that include nuclear and radiological disasters.[1] Recent events in Ukraine and the Middle East highlight the fact that warfare and terrorism remain ongoing challenges for disaster planning and response. Nowhere are these challenges more daunting than for chemical, biological, radiological, and nuclear (CBRN) incidents, or when CBRN agents are used in terrorism attacks or warfare. Preparing for and managing radiological and nuclear casualties is particularly problematic because of the following: (1) There are a large number of radionuclides with which individuals might be externally or internally contaminated. (2) There are few antidotes for internal contamination with radionuclides, and relatively few countermeasures for those exposed to radioactive sources. (3) CBRN incidents are low-probability, high-consequence events. (4) Planners and responders lack familiarity and experience with CBRN threats. We hypothesized that the multiple standard references relied upon for these events have inconsistencies between them, with a lack of clarity that supports rapid and accurate utilization.

The unique management problems posed by pediatric casualties during a disaster motivated our previous study.[2] However, the United Nations, its Children's Fund (UNICEF), and the World Health Organization (WHO), along with other national and international bodies and experts, recognize that children are best cared for in a holistic manner, integrating care with their parents, families, and caregivers. This holistic approach keeps families united as much as possible during a disaster, enhancing family adaptation to and recovery from disasters.[3–5] Therefore, WRAP-EM

(https://wrap-em.org/) conducted this study to assess existing, standard references detailing adult medical countermeasures and antidotes for radiological and nuclear incidents, including acts of war and terrorism, to complement the previously published pediatric study on this topic.[2]

WRAP-EM is an alliance of pediatric preparedness and response experts from 6 states (Arizona, California, Nevada, Oregon, Utah, and Washington). WRAP-EM initially received federal grant support from the Administration for Preparedness and Response (ASPR) in 2019 to focus on regional pediatric capacity and capabilities for all hazards. During gap analysis of selected references, the WRAP-EM program identified the need for medical countermeasures with pediatric considerations for dosing and administration during a CBRN incident. This gap included the need for a quick reference with pediatric dosing and administration guidance. Therefore, WRAP-EM assembled an interdisciplinary group of health care practitioners and national CBRN subject matter experts (SMEs) called the CBRN Focus Group, a working group with administrative support. As well as collaboration with participants from the HRSA-funded pediatric Pandemic network. This team includes individuals with experience and/or training in CBRN response, disaster preparedness, emergency medicine, epidemiology, trauma surgery, hospital medicine, clinical pharmacy, pharmacology, poison control center response, public health, medical toxicology, and related disciplines.

WRAP-EM's CBRN Focus Group formed a Countermeasures Sub-Group to study medications for radiological and nuclear incidents with the following objectives: (1) to perform a search of standard references available for adult dosing and administration considerations, (2) to compare these standard references, detailing adult indications and dosing, and assessing the differences among them, (3) to collect, tabulate and then disseminate adult dosing and administration recommendations from these references to health care professionals caring for families, specifically for adults in this study, and (4) to document whether each countermeasure or antidote is U.S. Food and Drug Administration (FDA) approved for use in adults.

Materials and Methods

This paper is a comparative analysis of standard references that address adult indications and dosing for medical countermeasures and antidotes for radiological and nuclear incidents. The databases and medical references were selected by expert consensus to represent those that would be likely to be accessed during a radiological or nuclear emergency. These selected standard references include U.S. civilian and military governmental, open-access resources; proprietary medical and pharmaceutical databases; and continuing education courses that responders commonly attend to prepare for radiological and nuclear incidents. The selected standard references are listed alphabetically below:

Advanced Hazmat Life Support (AHLS) for Radiological Incidents and Terrorism (https://www.ahls.org/site/take-a-course/radiological-incidents-and-terrorism-course/) is an interdisciplinary, international, 4-hour, continuing education course whose textbook is in its fifth edition (2020), that is copresented by the American Academy of Clinical Toxicology (AACT) (https://www.clintox.org/) and AHLS (https://www.ahls.org/site/) within the Arizona Emergency Medicine Research Center (https://emergencymed.arizona.edu/aemrc) at the University of Arizona College of Medicine.[6] The AACT is an international multi-disciplinary organization uniting scientists and clinicians to promote research, education, prevention, and treatment of diseases caused by chemicals, drugs, and toxins.

DailyMed (https://dailymed.nlm.nih.gov/dailymed/) is a U.S. National Library of Medicine (NLM), National Institutes of Health (NIH) searchable database.[7] It contains 148,970 of the most recent labels for medications and medical products submitted to the FDA. *DailyMed* presents the labeling and prescribing information in an easy-to-read format.

Internal Contamination Clinical Reference (ICCR) (https://www.cdc.gov/nceh/radiation/emergencies/iccr.htm) is an app from the U.S. Centers for Disease Control and Prevention (CDC).[8]

The Medical Aspects of Radiation Incidents (https://orise.orau.gov/resources/reacts/documents/medical-aspects-of-radiation-incidents.pdf) is a handbook in its fourth edition (2017), produced by the Radiation Emergency Assistance Center/Training Site (REAC/TS) (https://orise.orau.gov/reacts/index.html).[9] REAC/TS is a radiation emergency medical response asset of the U.S. Department of Energy/National Nuclear Security Administration (DOE/NNSA). REAC/TS provides emergency response and subject matter expertise for medical management of patients from radiation incidents. REAC/TS is operated for the DOE by the Oak Ridge Associated Universities (ORAU) (https://www.orau.org/). REAC/TS also teaches a number of continuing medical education courses (https://orise.orau.gov/reacts/continuing-medical-education/index.html), including *Radiation Emergency Medicine* (https://orise.orau.gov/reacts/continuing-medical-education/radiation-emergency-medicine.html).

Medical Management of Radiological Casualties (https://afrri.usuhs.edu/sites/default/files/media/documents/affri_-_medical_management_of_rad_casualties_5th_edition_0.pdf) is a handbook in its fifth edition (2022), produced by the Armed Forces Radiobiology Research Institute (AFRRI) (https://afrri.usuhs.edu/home).[10] AFRRI is responsible for preserving and protecting the health and performance of U.S. military personnel operating in potentially radiologically contaminated environments. AFRRI provides rapidly deployable radiation medicine expertise to radiological or nuclear events, domestically or abroad, through its Medical Radiobiology Advisory Team (MRAT) (https://afrri.usuhs.edu/education-mrat). AFFRI also teaches the *Medical Effects of Ionizing Radiation (MEIR) Course* (https://afrri.usuhs.edu/meir-course). From January to June 2024, the MEIR course has a pre-course asynchronous lecture set (4.5 hours) completed prior to the live, 2-day MEIR course that is taught at major U.S. military bases throughout the United States and abroad. Starting in July 2024, the MEIR course will be virtual learning, conducted through the Canvas Learning Management System with 40 continuing education hours of synchronous and asynchronous learning over 5 days. This will be offered quarterly and will replace most live MEIR courses globally.

Micromedex® (https://www.merative.com/clinical-decision-support) is a database that provides access to full-text, tertiary literature, including referenced information about pharmaceuticals and toxicology.[11]

National Stockpiles for Radiological and Nuclear Emergencies: Policy Advice (https://iris.who.int/bitstream/handle/10665/365681/9789240067875-eng.pdf?sequence=1) is a publication of the World Health Organization (WHO) (https://www.who.int/publications/i/item/9789240067875).[12] It is available in 3 languages: English, Japanese, and Ukrainian. This monograph describes protocols and practices regarding national stockpiles of medical countermeasures for radiation emergencies, especially medications to treat people affected by radiological and nuclear emergencies. This monograph

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details guidelines for establishing and managing a formulary for a national stockpile of medications to care for affected people. It includes examples from Argentina, Brazil, France, Germany, Japan, the Republic of Korea, the Russian Federation, and the United States of America.

Poisindex® (https://www.aapcc.org/npds-FAQs) is a database (supported by Merative Micromedex® software) sponsored by the America's Poison Centers (APC) and used by poison center staff to code and respond to calls for assistance. *Poisindex*® has information on more than 445,000 chemical and household products to assist in the management of calls.[13]

Radiation Medical Emergency Management (REMM) (https://remm.hhs.gov/) is a website produced by the US Department of Health and Human Services (HHS), Administration for Strategic Preparedness and Response (ASPR).[14] It provides guidance for health care providers, primarily physicians, about the clinical diagnosis and treatment of radiation injury during radiological and nuclear emergencies. Its guidance is evidence-based, usable information that is understandable to those without formal radiation medicine expertise. It also provides guidance for the wider health care community to plan for and respond to radiation mass casualty incidents. *REMM* is also available as an app, *Mobile REMM* (https://remm.hhs.gov/downloadmremm.htm).

We considered including *Management of Persons Contaminated with Radionuclides: Recommendations of the National Council on Radiation Protection and Measurements (NCRP Report No. 161)*; however, we decided not to because it consists of 2 volumes, totaling 1032 pages, and is incorporated by reference into many of the standard references above.[15]

If a medical countermeasure or antidote for radiological and nuclear incidents was listed in any of the selected standard references, we included it in this study. This was done to identify which references did or did not include each of the countermeasures and antidotes.

We conducted a literature search with a medical librarian to see if any previous similar human study had been published in the English medical literature. Embase was searched from 1947 through January 2024 and PubMed was searched from 1996 through January 2024 with the search details in Table 1. We further delineated whether each standard reference was (1) a U.S. governmental, open-access resource, (2) available as an app, or (3) associated with continuing education courses (Table 2).

We identified pharmaceutical countermeasures or antidotes for radiological and nuclear incidents and terrorism in each standard reference listed above. Then we systematically abstracted and tabularized the following information for each medication: generic name, indication(s), FDA approval status for use in adults, mechanism of action, dosage, and route of administration (Table 3). We also standardized the format for each medication's dosage and route in Table 3, while maintaining the specific dosage and route as originally listed in each standard reference. While all medications in Table 3 are countermeasures for radiological and nuclear incidents and terrorism, we divided them into 3 major sections for clarity: (1) antidotes for internal contamination with radionuclides, (2) cytokines to treat the hematopoietic subsyndrome of the acute radiation syndrome (ARS), and (3) a topical dressing for ionizing radiation burns (Table 3). Once the data was collated and standardized, we performed a comparison analysis for each of the medications listed. This study is Institutional Review Board (IRB) exempt.

Table 1. Literature search

Databases	Dates Searched	Search Terms
Embase	1947 through January 2024	Radiation, Ionizing Radiation, Radioactive Hazard Release, Radiation and Radiation Related Phenomena, Radiometry, Radioactive Contamination, Radiation Injury, Radiation Injuries, Acute Radiation Syndrome, Radiologic Health, Atomic Warfare, Fallout, Radioactive Fallout, Nuclear Accident, Nuclear Reactors, Nuclear Weapon(s), Nuclear Warfare, Terrorism, Radioactive Terrorism, Countermeasure, Medical Countermeasure(s), Health Countermeasures, Antidote(s)
PubMed	1966 through January 2024	

Table 2. Reference characteristics

References	U.S. Governmental, Open-Access	Available as an App	Continuing Education Courses Available from these Sponsoring Organizations
Advanced Hazmat Life Support (AHLS) for Radiological Incidents & Terrorism	No	No	Yes from Advanced Hazmat Life Support (AHLS)
DailyMed	Yes	No	No
Internal Contamination Clinical Reference (ICCR)	Yes	Yes	Yes from the U.S. Centers for Disease Control and Prevention (CDC)
Medical Aspects of Radiation Incidents	Yes	No	Yes from the Radiation Emergency Assistance Center/Training Site (REAC/TS)
Medical Management of Radiological Casualties	Yes	No	Yes from the Armed Forces Radiobiology Research Institute (AFRRI)
Micromedex®	No	Yes, with paid subscription	No
National Stockpiles for Radiological and Nuclear Emergencies: Policy Advice	No	No	No
Poisindex®	No	No	No
Radiation Emergency Medical Management (REMM)	Yes	Yes	No

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Table 3. Adult medical countermeasures: antidotes and cytokines for radiological and nuclear incidents and terrorism

Medication	Indication	FDA Status	Mechanism of Action	Sources with Indication(s) or Dosing for Specific Radionuclides	Consensus Dosing	Alternative Dosing
Antidotes	Radioisotopes					
Acetylcysteine (NAC)	Cobalt (Co)	Not FDA approved for cobalt chelation	Chelator	MARI (Co) MMRC (Co)	IV: 300 mg/kg in D5W over 24 h	None
Aluminum hydroxide	Fluorine (F) Phosphorus (P) Radium (Ra) Strontium (Sr)	Not FDA approved for F, P, Ra, or Sr	Alters absorption	MARI (F, Ra, Sr) MMRC (F, Ra, Sr) PD (F, Sr) REMM (Ra, Sr, P)	**F, Ra, Sr:** PO: 60–100 mL once	REMM: **P:** 600 mg tab PO TID or 320 mg/5 mL TID
Calcium gluconate	Phosphorus (P) Radium (Ra) Strontium (Sr)	Not FDA approved for P, Ra, or Sr	Alters absorption	MARI (Ra, Sr) MMRC (Ra, Sr) PD (Ra, Sr) REMM (Ra, Sr)	**Ra & Sr:** PO: 10 g powder in a 30 mL vial; add water and drink **P**: No indication or dosing listed	PD, REMM: **Ra & Sr:** IV: 5 ampoules (500 mg Ca/amp) in 500 mL D5W over 4–6 h Duration: 6 d, begin therapy <12 h of radionuclide intake if possible
Calcium chloride 10% solution	Radium (Ra) Strontium (Sr)	Not FDA approved for Ra or Sr	Alters absorption	MARI (Ra, Sr) MMRC (Ra, Sr)	**Ra & Sr:** IV: 200 mg to 1 g q1–3 days Slow infusion not to exceed 1 mL/min	None
Deferoxamine (DFOA)	Iron (Fe) Manganese (Mn) Mercury (Hg) Neptunium (Np) Plutonium (Pu)	FDA approved for Fe, but not Mn, Hg, Np, or Pu	Chelator	DM (Fe) MARI (Fe, Mn, Np, Pu) MMRC (Fe, Mn, Np, Pu) MM (Fe) PD (Fe, Mn, Np, Pu) REMM (Pu)	**Fe**: IM (not for patients with cardiovascular shock): 1 g initially, then 500 mg q4 h × 2 doses, subsequent doses of 500 mg may be administered q4 - 12 h IV (preferred for patients with cardiovascular shock): Initial dose of 1000 mg not to exceed 15 mg/kg/h then 500 mg q4 h × 2 doses, subsequent doses of 500 mg may be administered q4 – 12 h; as soon as clinical condition permits, transition to IM administration IM and IV: Max daily dose 6000 mg in 24 h	MARI, MMRC, REMM: **Fe, Mn, Np, Pu**: IM (preferred route): 2 ampules (500 mg DFOA/amp) IV (slow infusion): 2 ampules (500 mg DFOA/amp) at 15 mg/kg/h Repeat as indicated as 500 mg IM or IV q4 h × 2 doses; then 500 mg IM or IV q12 h for 3 days
Diethylenetriamine pentaacetate (DTPA) **Calcium or Zinc**	Americium (Am) Curium (Cm) Plutonium (Pu)	FDA approved for Am, Cm, and Pu	Chelator	AHLS (Am, Cm, Pu) DM (Am, Cm, Pu) ICCR (Am, Cm, Pu) MARI (Am, Cm, Pu) MMRC (Am, Cm, Pu) MM (Am, Cm, Pu) NSRNE (Am, Cm, Pu) PD (Am, Cm, Pu) REMM (Am, Cm, Pu)	**Am, Cm, Pu:** IV: 1 g in 5 mL of D5W or NS slow push over 3 – 4 minutes or in 100–250 mL D5W or NS over 30 minutes Administer initial dose of Ca-DTPA during 1st 24 h after internal contamination then switch to Zn-DTPA Nebulized solution: 1 g, diluted 1:1 with sterile water or NS over 20 minutes Ca-DTPA is recommended as the first dose. If additional treatment is needed, treatment should be switched to Zn-DTPA. This treatment sequence is recommended because Ca-DTPA is more effective than Zn-DTPA during the first 24 h after internal contamination.	

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Table 3. (*Continued*)

Medication	Indication	FDA Status	Mechanism of Action	Sources with Indication(s) or Dosing for Specific Radionuclides	Consensus Dosing	Alternative Dosing
					Zn-DTPA is the preferred treatment for pregnant women with internal contamination because Ca-DTPA causes zinc depletion with results from animal studies suggesting teratogenic risk in humans.	
Dimercaprol (BAL)	Antimony (Sb) Arsenic (As) Bismuth (Bi) Gold (Au) Mercury (Hg) Nickel (Ni) Polonium (Po)	FDA approved for As, Au, Hg, but not the others in the previous column	Chelator	DM (As, Au, Hg) MARI (Sb, As, Bi, Au, Hg, Ni, Po) MMRC (Sb, As, Bi, Au, Hg, Ni, Po) MM (As, Au, Hg) PD (Sb, As, Bi, Au, Hg, Ni, Po) REMM (As, Au, Hg, Po)	**As, Au, Hg:** IM: Mild poisoning: 2.5 mg/kg QID for 2 days, then BID on day 3, then once daily thereafter for 10 days Severe poisoning: 3 mg/kg q4 h for 2 days, then QID day 3, then BID thereafter for 10 days	MARI, MMRC, PD: **Sb, As, Bi, Au, Hg, Ni, Po:** IM: 2.5 mg/kg (or less) q4 h × 2 days, then BID for 1 day, then daily for days 5–10 REMM: **As, Au, Hg, Po:** IM: 2.5 mg/kg QID (days 1 and 2), then BID (day 3), then daily (days 4–10)
Edetate calcium disodium (EDTA)	Cadmium (Cd) Chromium (Cr) Cobalt (Co) Copper (Cu) Iridium (Ir) Lead (Pb) Manganese (Mn) Mercury (Hg) Nickel (Ni) Plutonium (Pu) Ruthenium (Ru) Yttrium (Y) Zinc (Zn) Zirconium (Zr)	FDA approved for Pb, but not the others in the previous column	Chelator	DM (Pb) MARI (Cd, Cr, Co, Cu, Ir, Pb, Mn, Hg, Ni, Pu, Ru, Y, Zn, Zr) MMRC (Cd, Cr, Co, Cu, Ir, Pb, Mn, Hg, Ni, Pu, Ru, Y, Zn, Zr) MM (Pb) PD (Cd, Cr, Co, Cu, Ir, Pb, Mn, Hg, Ni, Pu, Ru, Y, Zn, Zr) REMM (Co, Ir, Pb, Pu, Y)	**Cd, Cr, Co, Cu, Ir, Pb, Mn, Hg, Ni, Pu, Ru, Y, Zn, Zr:** IV: 1000 mg/m^2/day added to 500 mL D5W or NS infused over 8 – 12 h	DM, MM: **Pb:** Asymptomatic with blood concentration >20 mcg/dL and <70 mcg/dL IM: 1000 mg/m^2/day divided into equal doses q8 – 12 h Lidocaine or procaine should be added to minimize pain at the injection site. Final lidocaine or procaine concentration of 5 mg/mL (0.5%) can be obtained as follows: 0.25 mL of 10% lidocaine solution per 5 mL concentrated EDTA; 1 mL of 1% lidocaine or procaine solution per mL of concentrated EDTA. IV: 1000 mg/m^2/day in 250–500 mL D5W or NS over 8–12 h When blood lead concentration >70 mcg/dL or clinical symptoms consistent with lead poisoning present, recommended EDTA be used with BAL.
Penicillamine	Antimony (Sb) Bismuth (Bi) Copper (Cu) Gallium (Ga) Gold (Au) Palladium (Pd) Polonium (Po)	FDA approved for Cu in Wilson's disease, but not the others in the previous column	Chelator	MARI (Sb, Bi, Cu, Ga, Au, Pd, Po) MMRC (Sb, Bi, Cu, Ga, Au, Pd, Po) PD (Sb, Bi, Cu, Ga, Au, Pd, Po) REMM (Cu, Po)	**Sb, Bi, Cu, Ga, Au, Pd, Po:** PO: 250 mg daily between meals and at bedtime May increase to 4 or 5 g daily in divided doses	REMM: **Cu and Po:** PO: 0.75–1.5 g (250 mg/capsule) daily May increase to 4 or 5 g daily
Potassium iodide (KI)	Iodine (I)	FDA approved for iOSAT, Thyrosafe, and	Distributes differently and Enhances elimination by	AHLS (I) DM (I) ICCR (I)	PO: 130 mg daily (tablets or liquid) **>40 years:** for projected thyroid dose ≥500 cGy	None

(*Continued*)

Table 3. (*Continued*)

Medication	Indication	FDA Status	Mechanism of Action	Sources with Indication(s) or Dosing for Specific Radionuclides	Consensus Dosing	Alternative Dosing
		Potassium Iodide Oral Solution USP, 65 mg/mL from Mission Pharmacal Company	blocking thyroid uptake of radioiodine	MARI (I) MMRC (I) MM (I) NSRNE (I) PD (I) REMM (I)	**18–40 years:** for projected thyroid dose ≥10 cGy **Pregnant or lactating women:** for projected thyroid dose ≥5 cGy Duration: Except for pregnant and lactating women, above doses can be continued as daily doses if the predicted thyroid gland exposure continues at 5 cGy (5 rad) or more.	
Potassium phosphate, dibasic	Phosphorus (P–32)	Not FDA approved	Alters absorption	MARI (P–32) MMRC (P–32) PD (P–32) REMM (P–32)	PO: 1–2 tablets (250 mg/tab) QID with full glass of water each time at meals and at bedtime.	None
Propylthiouracil (PTU)	Iodine (I)	Not FDA approved	Distributes differently and enhances elimination by diminishing thyroid radioiodine retention	MARI (I) MMRC (I) PD (I) REMM (I)	PO: 2 tablets (50 mg/tab) TID for 8 days	None
Prussian blue insoluble	Cesium (Cs) Rubidium (Rb) Thallium (Tl) (radioactive & nonradioactive Tl)	FDA approved for radioactive Cs and radioactive and non-radioactive Tl, but not Rb	Alters absorption and reabsorption, enhances elimination	AHLS (Cs, Tl) DM (Cs, Tl) ICCR (Cs, Tl) MARI (Cs, Rb, Tl) MMRC (Cs, Rb, Tl) MM (Cs, Tl) NSRNE (Cs, Tl) PD (Cs, Rb, Tl) REMM (Cs, Tl)	PO: 3 g TID for at least 30 days	ICCR, REMM: PO: 1–3 g TID, up to 10–12 g/day based on Goiânia incident data ICCR: Capsules may be opened up and mixed with food MM: **Cs**: Base duration on weekly measurement of urine and fecal radioactivity **Tl**: Continue until a normal 24 h urine thallium test (less than 5 mcg/L) is obtained and radiation level (if applicable) is acceptable REMM: Minimum 30-day course per FDA. Obtain bioassay and whole body counting to assess treatment of efficacy. Duration of therapy depends on total body burden and response to treatment.
Sodium alginate	Barium (Ba) Strontium (Sr)	Not FDA approved	Alters absorption	NSRNE (Sr) PD (Sr) REMM (Sr)	**Sr:** PO: 10 g daily for several days Initiated before or within 2 h of intake for the optimal effect The absorbed dose increases if given later **Ba:** No indication or dosing listed	REMM: **Sr:** PO: 5 g BID × 1 day, then 1 g QID Take with a full glass of water

(*Continued*)

Table 3. (*Continued*)

Medication	Indication	FDA Status	Mechanism of Action	Sources with Indication(s) or Dosing for Specific Radionuclides	Consensus Dosing	Alternative Dosing
Sodium bicarbonate (for uranium only)	Uranium (U)	Not FDA approved	Renal protective, does not alter the pharmacokinetics	MARI (U) MMRC (U) NSRNE (U) PD (U) REMM (U)	PO or IV to alkalize urine, no dosing listed	NSRNE: IV: Max 1.5 mmol/kg body weight per hour given in 1 L NS or in D5W Volume can be lowered to 250 mL, although infusion rate of 1.5 mmol/kg body weight should not be exceeded PO: 2 tablets (1–1.3 g) q4 h Urinary pH is monitored hourly during treatment to maintain a range of 8–9. Daily dose adjusted to therapeutic pH goal and therapy continued for 3 days REMM: IV: 2 ampules (44.3 mEq bicarbonate ampule) in 1000 mL D5W or NS, or 1-2 mEq/kg in 250 mL NS slow infusion. Administer therapy until urine pH is 8-9, continue for 3 days
Succimer (DMSA) capsule	Arsenic (As) Bismuth (Bi) Cadmium (Cd) Cobalt (Co) Lead (Pb) Polonium (Po)	FDA approved for children with Pb poisoning, but not the other elements in the previous column	Chelator	MARI (As, Bi, Cd, Co, Po) MMRC (As, Bi, Cd, Co, Po) REMM (Co, Po)	**As, Bi, Cd, Co, Po:** PO: 10 mg/kg or 350 mg/m^2 q8 h × 5 days, then reduce frequency to q12 h for an additional 2 weeks of therapy. Course of therapy: 19 days	None
Water diuresis	Sodium (Na) Tritium (H)	Not FDA approved	Enhances elimination	MARI (H) MMRC (H) PD (H) REMM (H)	**H–3:** PO: >3–4 L/day for 3 weeks **Na:** No indication or dosing listed	None
Cytokines						
Filgrastim	Acute exposure to myelosuppressive doses of radiation ≥2 gray (hematopoietic subsyndrome of the acute radiation syndrome)	FDA approved	Granulocyte colony-stimulating factor	AHLS DM MARI MMRC MM NSRNE PD REMM	subQ: 10 mcg/kg/day Administer ASAP following confirmed/suspected exposure ≥200 rad or 2 gray or 200 cGy Continue until ANC >1000/mm^3 for 3 consecutive CBCs or exceeds 10,000/mm^3 after radiation-induced nadir	PD: subQ 2.5–5 mcg/kg/day Administer within 24–72 hours postexposure A proposed set of protocols recommends colony-stimulating factors be given to patients who are exposed to 3 Gy (300 rad) but are otherwise healthy and to patients exposed to 2 Gy (200 rad) who have trauma or burn injuries. Continued until the absolute neutrophil count is 1000/mm^3
Pegfilgrastim	Acute exposure to myelosuppressive doses of radiation ≥2 gray (hematopoietic subsyndrome of the acute radiation syndrome)	FDA approved	Granulocyte colony-stimulating factor	AHLS DM MARI MMRC MM NSRNE PD REMM	subQ: 6 mg 1 week apart × 2 doses Administer 1st dose ASAP after suspected or confirmed exposure to ionizing radiation ≥200 rad or 2 gray or 200 cGy	PD: subQ: 6 mg once Within 24–72 h of exposure when granulocyte levels are falling, with daily therapy continued until ANC >1000/mm3

(*Continued*)

Table 3. (*Continued*)

Medication	Indication	FDA Status	Mechanism of Action	Sources with Indication(s) or Dosing for Specific Radionuclides	Consensus Dosing	Alternative Dosing
Sargramostim	Acute exposure to myelosuppressive doses of radiation ≥2 gray (hematopoietic subsyndrome of the acute radiation syndrome)	FDA approved	Granulocyte macrophage colony-stimulating factor	AHLS DM MARI MMRC MM NSRNE PD REMM	Adult >40 kg subQ: 7 mcg/kg daily Administer ASAP after suspected/confirmed exposure to ionizing radiation doses ≥200 rad or 2 gray or 200 cGy Continue administration until the ANC remains >1000/mm^3 for 3 consecutive CBCs or >10,000/mm^3 after a radiation-induced nadir.	MARI: subQ: 5–10 mcg/kg/day or 200–400 mcg/m^2/day For patients expected to experience severe neutropenia MMRC: subQ: 7–12 mcg/kg/day For patients expected to experience severe neutropenia PD: subQ: 5–10 mcg/kg daily Administer within 24–72 hours postexposure. A proposed set of protocols recommends that colony-stimulating factors be given to patients who are exposed to 3 Gy (300 rad) but are otherwise healthy and patients exposed to 2 Gy (200 rad) who have trauma or burn injuries. Continued until the absolute neutrophil count is 1000/mm^3
Other growth factors						
Romiplostim	Acute exposure to myelosuppressive doses of radiation ≥2 gray (hematopoietic subsyndrome of the acute radiation syndrome)	FDA approved	Thrombopoietin receptor agonist mimetic	AHLS DM MMRC MM NSRNE REMM	subQ: 10 mcg/kg once Administer ASAP after suspected or confirmed exposure to radiation levels ≥2 gray (Gy)	None
Topical dressing for ionizing dermatitis and cutaneous radiation injury with dry desquamation						
SilverIon	Radiation dermatitis and cutaneous radiation injury with dry desquamation	FDA approved	Reduces time to eschar removal, allowing treatment to progress to the next stage of wound closure	None	None	None

AHLS, Advanced Hazmat Life Support; *DM*, DailyMed; *ICCR*, Internal Contamination Clinical Reference; *MARI*, Medical Aspects of Radiation Incidents; *MM*, Micromedex; *MMRC*, Medical Management of Radiological Casualties; *NSRNE*, National Stockpiles for Radiological and Nuclear Emergencies; *PD*, Poisindex; *REMM*, Radiation Emergency Medical Management.

Results

Our literature search (Table 1) found no similar published study other than WRAP-EM's recently published pediatric study on this topic.[2] Of the 9 selected standard references for adult medical countermeasures for radiological and nuclear incidents and terrorism, 5 (55.6%) are governmental, open-access resources (Table 2). Of the 9 references, 3 (33.3%) offer an app (*ICCR* and *REMM* without purchase and *Micromedex*® with subscription), and 4 (44.4%) of the sponsoring organizations offer continuing education courses for health care professionals to teach details of using these antidotes and cytokines (Table 2).

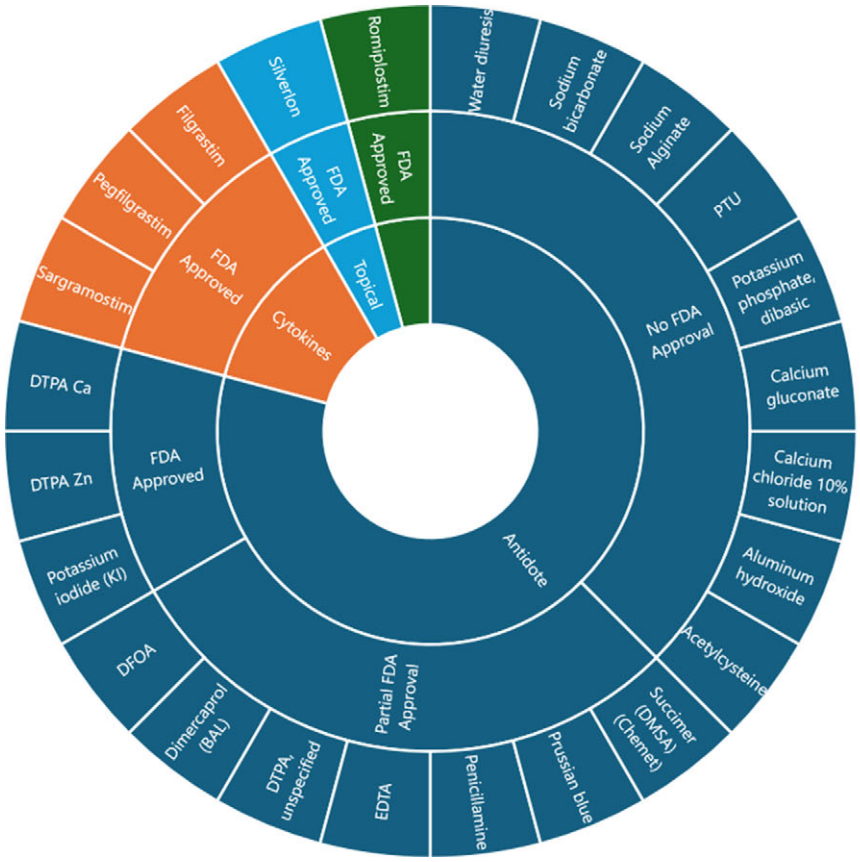
We found 24 medical countermeasures for radiological and nuclear incidents and terrorism (Table 3). Types of countermeasures and antidotal mechanisms of action (pharmacokinetic versus pharmacodynamic) are depicted in Figure 1. Of the 24 countermeasures, 15 (62.5%) have FDA approval for specific radiological threats. Nine selected standard references had no listed adult indication or dosing for Silverlon (Table 3). Nine countermeasures with adult dosing or administration recommendations did not have FDA approval for the cited indications.

Discussion

WRAP-EM recently published a summary of medical countermeasures and antidotes used to treat children affected by radiological and nuclear incidents.[2] Given increasing recognition that children are best cared for holistically with their families, we recognized the need for a companion study addressing adults affected by radiological and nuclear incidents. To our knowledge, this is the first study comparing indication and dosing recommendations from recognized sources for adult countermeasures and antidotes for radiological and nuclear incidents. The 9 standard references selected for this study varied in which countermeasures or antidotes they included, indications and dosing, media (app, database, pdf, printed book and/or eBook, or website), accessibility (proprietary or governmental), and whether the sponsoring organization provided continuing education. Adult indications and dosing in the selected standard references stem from FDA-approved labeling (62.5%) or *NCRP Report No. 161* (37.5%).[15]

Nuclear and radiation exposure incidents constitute low probability but potentially high-consequence events. Radiological and nuclear threat scenarios fall into 3 broad categories: (1) nuclear detonations, (2) nuclear power plant incidents, and (3) radiation exposure accidents, as well as "dirty bombs" and other radiological dispersal devices. To date, nuclear and radiation exposure incidents have been uncommon. Most clinicians, public health officials, and preparedness and response personnel thus have little, if any, experience in dealing with these events. Specifically, they are likely to be unfamiliar with the medical countermeasures available to mitigate against health hazards caused by exposure to the isotopes involved in such events.

Fortunately, of the >8000 isotopes known to exist, about a dozen constitute the greatest threats, versus the rarity of a nuclear detonation resulting in exposure to numerous aerosolized and gaseous radioisotopes.[9–10] The types of isotope exposure risk by source are highlighted in Table 4.



Abbreviations	
FDA	Food and Drug Administration
DPTA	Diethylenetriaminepentaacetate
Ca	Calcium
Zn	Zinc
DFOA	Deferoxamine
EDTA	Edetate calcium disodium
DMSA	Dimercaptosuccinic acid
PTU	Propylthiouracil

Figure 1. Adult Medical Countermeasures, Including Antidotes (dark blue), Cytokines (orange), a Thrombopoietin Receptor Agonist Mimetic (green), and an Antimicrobial Dressing (light blue) for Radiological and Nuclear Incidents and Terrorism and FDA Approval Status.

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Table 4. Isotope Exposure Risk Based on Source.[9–10]

Source	Isotope Exposure Risk
Medical/Academic	^{14}C, ^{252}Cf, ^{60}Co, ^{3}H, ^{125}I, ^{131}I, ^{32}P
Industrial	^{60}Co, ^{137}Cs, ^{192}Ir
Military	^{241}Am, ^{3}H, ^{239}Pu, ^{235}U, and ^{238}U
Fission Reactors	^{137}Cs, ^{131}I, ^{133}Xe, other noble gas radioisotopes

As the number of problematic isotopes involved in any of the 3 broad threat scenarios is quite limited, the provision of specific medical countermeasures against illness caused by exposure to these isotopes is a distinct possibility. Our review found that 24 such countermeasures have been deemed potentially useful by the authors of the 9 standard references considered in our study. Fifteen of these have indications approved for such use by the FDA (Figure 1).

Our study compares recommendations provided in 9 standard references. These references vary in the number of countermeasures they include as well as their indications, dosing, and accessibility. Recommendations vary somewhat among these 9 references and, in some cases, derive from "expert opinion" (Table 3).

Our study aims to provide clinicians and responders with information to make well-reasoned decisions regarding the use of radiation countermeasures and antidotes in adults affected by a radiation threat. Moreover, we sought to harmonize this information with what WRAP-EM recently published regarding children affected by radiological and nuclear incidents and terrorism. It is hoped that, by doing so, we can foster holistic care for families affected by nuclear or radiation threats.

Limitations

This study analyzed selected standard references for countermeasures for radiological incidents and terrorism but did not assess the primary literature for the basis of the listed indications and dosing (safety and efficacy). The standard references are continually updated, and this study captured recommendations at the time of the study. New information may have been incorporated into the references since data was abstracted for this study. The consensus panel chose 9 standard references; however, other sources are possible. This study only included English language references for human studies, not animal studies.

Conclusions

Gaps remain in countermeasures for radiological incidents and terrorism. This study analyzed 9 standard references to identify these gaps as areas for future research and development.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/dmp.2025.10190.

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Author contribution. The CBRN Focus Group, Pediatric Countermeasures Sub-Group of WRAP-EM, conceived this study. All authors helped design the study. All authors helped acquire, analyze, and interpret the data. All authors helped draft and revise the work and approved this submitted manuscript for publication and are accountable for this work.

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