RITN Acute Radiation Syndrome Treatment Guidelines

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Principles of ARS management at RITN centers

1) After a nuclear detonation, RITN and other cancer/blood and marrow transplant (BMT) centers may receive large numbers of irradiated casualties, especially those with little or no trauma or burns.

2) The goal of pre-incident planning and post-incident management is to maintain a "*functional equivalent*" of routine care for both casualties and existing patients at RITN centers.

3) Biodosimetry can predict prognosis and guide treatment.

4) Prioritization for myeloid cytokines (*e.g.,* G-CSF) and other key resources may be necessary due to limited supply of drug, staff, and space.

5) Patient tracking, psychosocial care and family re-unification will be key objectives.

6) Many evacuated patients will not require hospitalization, and thus outpatient facilities for housing and care will be required.

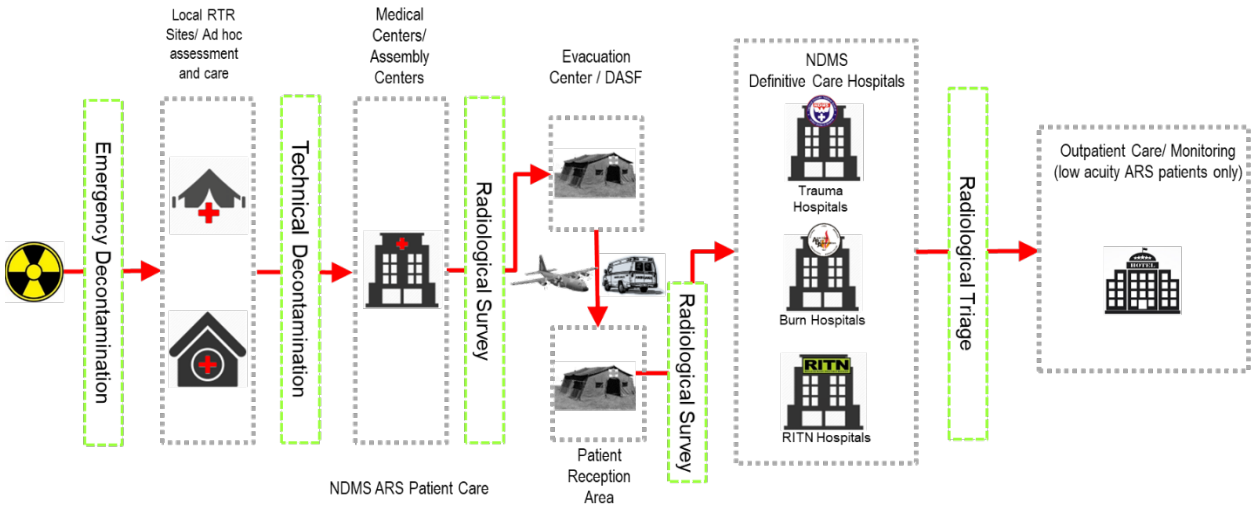
7) Current planning includes patient decontamination prior to transfer to RITN centers via the National Disaster Medical System or other entity. Most initial decontamination will have been self-decon due to large numbers of potential casualties so confirmation may be necessary. However, RITN centers should have plans to confirm adequate decontamination upon arrival.

If **adequate** resources are available, management of casualties with ARS should utilize the similar approaches and decision points as for patients with cancer receiving myelosuppressive therapy, including, if necessary:

1) Hospitalization
2) Prophylactic antibiotics and myeloid cytokines
3) Placement of venous access
4) Management of emesis, gastrointestinal toxicity and nutrition
5) Reverse isolation and dietary restrictions
6) Irradiated/leukocyte-depleted transfusions

Guidance on additional radiation-related issues, including internal decontamination, biodosimetry, adult and pediatric medical order sets and incident response are available at the National Library of Medicine website (www.remm.nlm.gov) and the Centers for Disease Control and Prevention radiation emergency site (https://www.cdc.gov/nceh/radiation/emergencies/index.htm).

Figure 1. Conceptual Flow of Casualties to a RITN Center



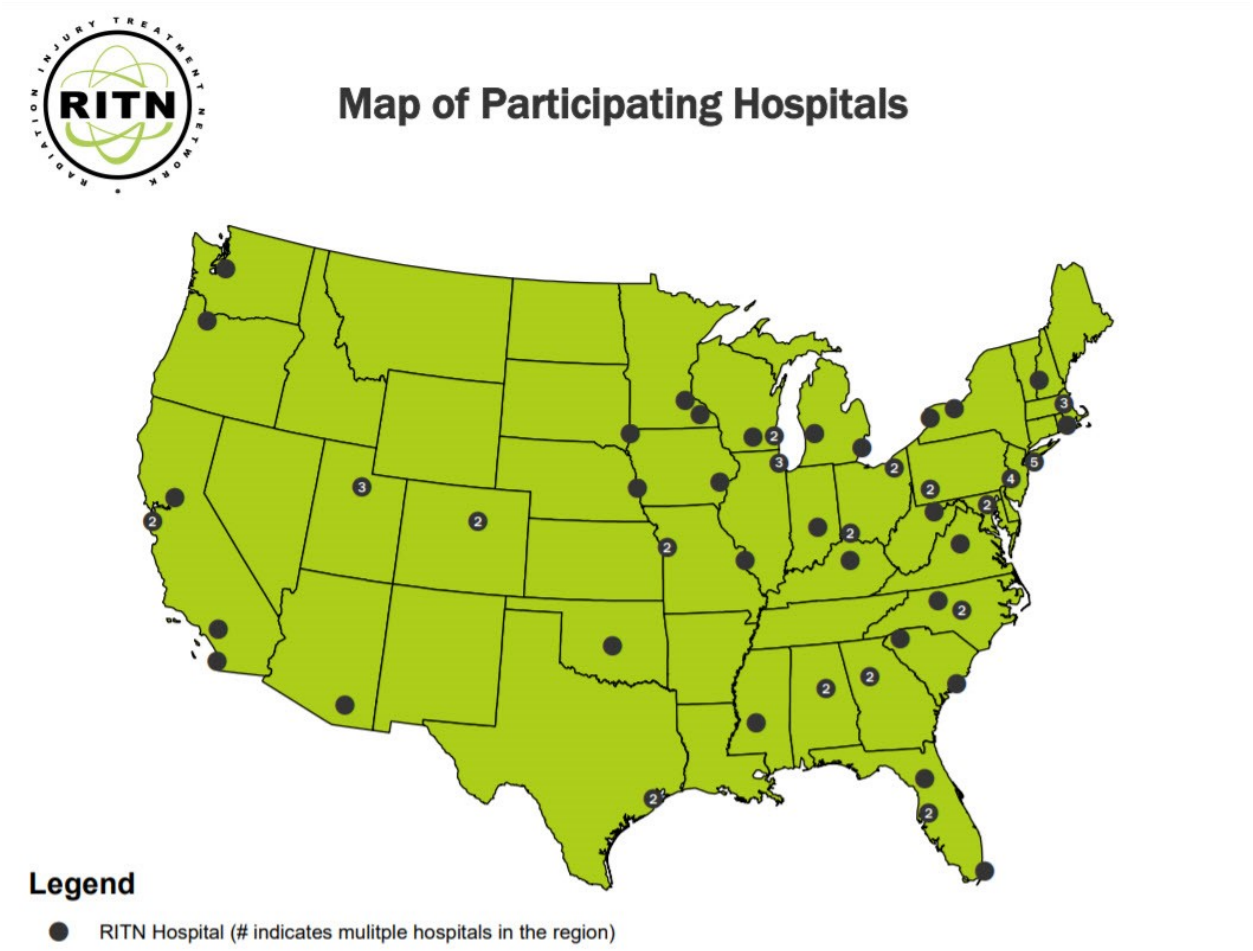
Expected response to a nuclear detonation. This stylized diagram illustrates the expected flow of casualties from the affected area to specialty centers around the country, including RITN. The injury pattern and required resources will vary depending on the location relative to the blast. Casualties are expected to undergo decontamination prior to triage for evacuation.

This is going to take time…likely a week or more for casualties with radiation only exposure to arrive at RITN hospitals. However, with self-evacuation particularly from locales with fallout and limited to no physical damage some casualities may arrive to nearby RITN or other medical centers who will need RITN consultation within days making RITN early alerts (first 12 hr) and ongoing situational awareness sharing essential. From RITN Overview Presentation, https://ritn.net/about/.

Figure 1 Definitions

- RTR – Radiation Triage, Treat, and Transport System
- DASF – Disaster Aeromedical Staging Facility
- NDMS – National Disaster Medical System

Figure 2. Map of RITN locations



*List of current RITN centers: www.ritn.net/about

Crisis standards after a nuclear detonation

Figure 3. Crisis standards after a nuclear detonation

Response Resource Availability and Crisis Standards of Care

Resource continuum:		Normal	Good	Fair/Poor
Operating conditions:		Normal/usual operating conditions, with normal "space, staff, and supplies"	Care functionally equivalent to normal but with constrained resources	Austere operating conditions: care with insufficient "space, staff, and/or supplies"
Response resource adequacy	Space	Usual patient care space fully utilized	—Patient care areas re-purposed (PACU) —Monitored units for ICU-level care	Facility damaged/unsafe, or, Non-patient care areas (e.g. classrooms, etc.) used for patient care
	Staff	Usual staff called in and utilized	Staff extension: —Brief deferrals of non-emergent service —Supervision of broader group of patients —Change in responsibilities, documentation, etc.	Trained staff unavailable or unable to adequately care for volume of patients even with extension techniques
	Supplies	Cached and usual supplies used	Conservation, adaptation, and substitution of supplies with occasional re-use of select supplies	Critical supplies lacking, possible re-allocation of life-sustaining resources
Standard of care continuum:		Medical Standards of Care		
		Conventional care[1]: usual care	Contingency Care[2]	Crisis standards of care[3]: austere operating conditions
			Indicator: potential need to implement "crisis standards of care"	**Trigger:** "crisis standards of care"

Incident demand / resource imbalance increases →

Risk of morbidity / mortality to patient increases →

1 "**Conventional capacity:** The spaces, staff, and supplies used are consistent with daily practices within the institution. These spaces and practices are used during a major mass casualty incident that triggers activation of the facility emergency operations plan."
2 "**Contingency capacity:** The spaces, staff, and supplies used are not consistent with daily practices but provide care that is functionally equivalent to usual patient care practices. These spaces or practices may be used temporarily during a major mass casualty incident or on a more sustained basis during a disaster (when the demands of the incident exceed community resources)."
3 "**Crisis capacity:** Adaptive spaces, staff, and supplies are not consistent with usual standards of care, but provide sufficient of care in the setting of a catastrophic disaster (i.e., provide the best possible care to patients given the circumstances and resources available). Crisis capacity activation constitutes a significant adjustment to standards of care."

* **Adapted from:**
Guidance for Establishing Crisis Standards of Care for Use in Disaster Situations, a Letter Report (Institute of Medicine of the National Academies, 2009, see especially pages 52-54).

*From https://www.remm.nlm.gov/stdsofcare.htm and adapted from Guidance for Establishing Crisis Standards of Care for Use in Disaster Situations, a Letter Report (Institute of Medicine of the National Academies, 2009, see especially pages 52-54).

Guidance for Establishing Crisis Standards of Care for Use in Disaster Situations, a Letter Report (https://www.remm.nlm.gov/stdsofcare.htm). The table describes the transition across different Standards of Care at individual medical venues, based on the imbalance between available resources and need. Transition from conventional (normal operations) to contingency indicates a functional equivalent of routine care through alterations in approach (*e.g.,* repurposing units, extending staff, substituting supplies). In contrast, transition to crisis standards occurs when a functional equivalent of normal care cannot be maintained (*e.g.,* severely injured casualties must be triaged to expectant care) because of inadequate resources. Initially resources will be used from the hospital, however those may deplete quickly. Mutual aid from regional partners may need to be requested once local resources have been exhausted. Some resources may be available through the Strategic National Stockpile (SNS) as regional resources run out. Facilities would need to contact their state SNS coordinator for inventory and request those available resources.

Figure 4. Conventional, contingency, and crisis care definitions and resource availability

BOX 1-2
Conventional, Contingency, and Crisis Care

Conventional capacity: The spaces, staff, and supplies used are consistent with daily practices within the institution. These spaces and practices are used during a major mass casualty incident that triggers activation of the facility emergency operations plan.

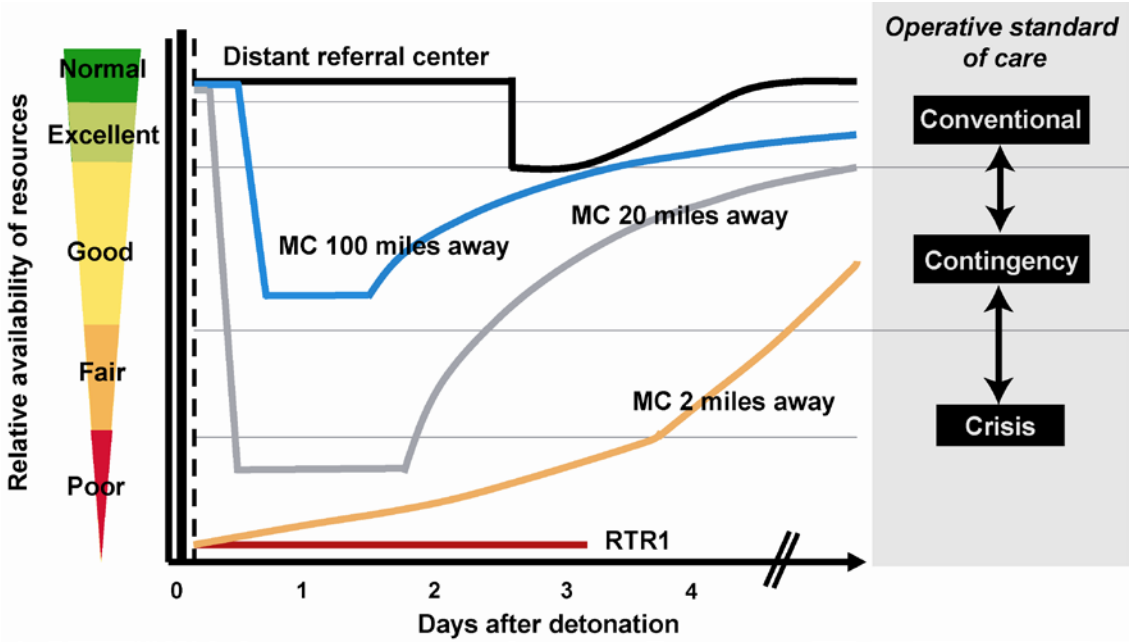
Contingency capacity: The spaces, staff, and supplies used are not consistent with daily practices, but provide care that is *functionally equivalent* to usual patient care. These spaces or practices may be used temporarily during a major mass casualty incident or on a more sustained basis during a disaster (when the demands of the incident exceed community resources).

Crisis capacity: Adaptive spaces, staff, and supplies are not consistent with usual standards of care, but provide sufficiency of care in the context of a catastrophic disaster (i.e., provide the best possible care to patients given the circumstances and resources available). Crisis capacity activation constitutes a significant adjustment to standards of care.

SOURCE: Hick et al., 2009.

Definitions of conventional, contingency and crisis care. For further details, see Hick et al. The National Acadamies of Science, Engineering, and Medicine (Institute of Medicine. 2013. *Crisis Standards of Care: A Toolkit for Indicators and Triggers.* Washington, DC: The National Academies Press. https://doi.org/10.17226/18338.)

Figure 5. Resources, operative standard and time after the event

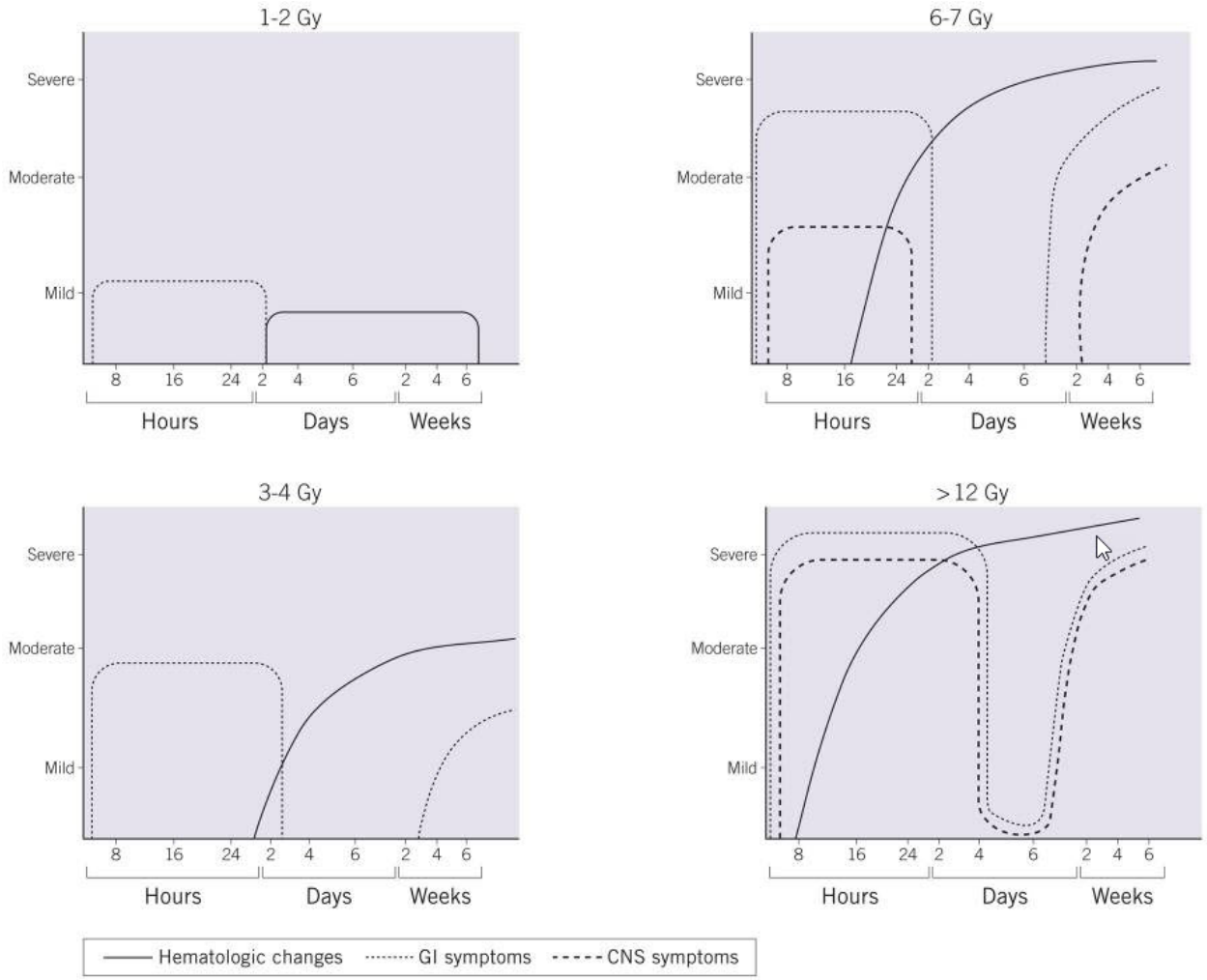


*From Medical Planning and Response Manual for a Nuclear Detonation Incident: A Practical Guide

Resources, operative standard and time after the event. Hypothetical representation of resource availability (left y-axis) after a nuclear detonation based on location, type of site, and relation to the operative standard of care (right y-axis). Centers close to the site would be immediately impacted and require crisis standards of care. RTR1 (see Figure 1) are impromptu triage sites established close to the epicenter and may be disbanded after a few days, as salvageable casualties are evacuated. Distance from the detonation will be the primary determinant of timing and severity of resource shortages at regional medical centers (MC). Referral centers in other regions (like RITN centers) may experience abrupt resource shortages due to patient transfers or depletion of nationwide supplies that require changes in operative standards. With appropriate pre-event planning and post-event management, these shortages and transfers should not require transition at referral centers to crisis standards.

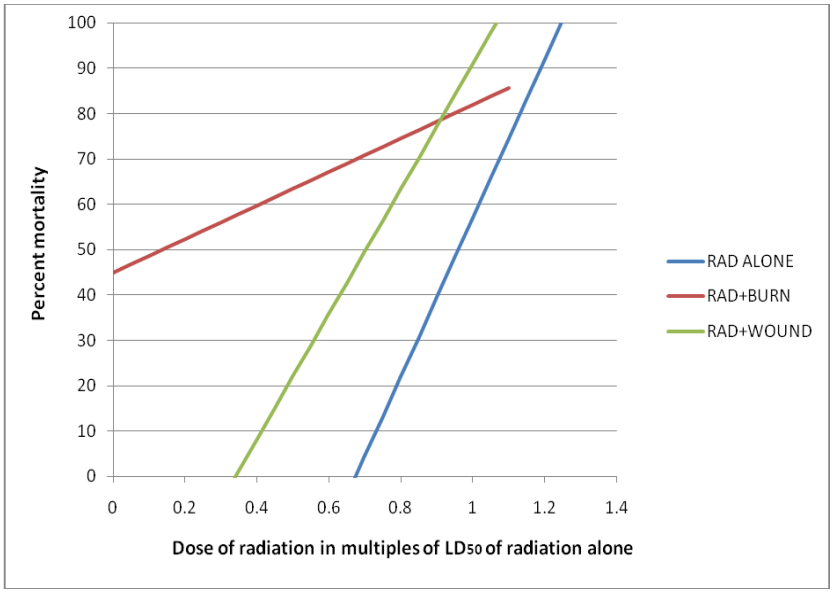
Acute Radiation Syndrome (ARS)

Figure 6. ARS signs and symptoms severity



Acute Radiation Syndrome (ARS). Timing and severity of hematological, gastrointestinal (GI) and central nervous system (CNS) symptoms relative to whole body (or near whole body) radiation dose. From DiCarlo, A. L. et. al. Disaster Med Public Health Prep. 2011 Mar; 5(0 1): S32–S44. doi: 10.1001/dmp.2011.17

Figure 7. Combined injury vs. radiation alone mortality



Combined injury increases mortality above radiation alone. Relationship between dose of radiation (rad) and probability of death for radiation alone and combined injuries (*i.e.,* with burn or wound) based on a meta-analysis of animal data. Adapted from Casagrande R and McVae J, unpublished data.

Casagrande R and McVae J. "RE: Question about a graph in RITN ARS Treatment Guidelines." Unpublished data. Message to Jen Aldrich. 1 October 2020. Email.

Casualty triage after a nuclear detonation

Figure 8. Radiation Only Casualty Estimates for a 10 kT IND

Radiation Dose (Gy)	Care Requirement	Casualty Estimate
Mild (0.75-1.5)	Self Recover and Monitoring	91,000
Moderate (1.5-5.3)	Outpatient Monitoring And Specialized Supportive Care	51,000
Severe (5.3-8.3)	Intensive Supportive Care	12,000
Expectant (>8.3)	Comfort Care	47,000
Combined Injury and Radiation (>1.5)	Stabilization and monitoring, pending resource availability	44,000

Estimate of 63,000 casualties for RITN

*****Radiation doses are estimates based on clinical presentation and laboratory values.*****

This table shows the range of possible casualties with radiation injury only, this information is based on computer modeling.

RITN plans to receive casualties with moderate to severe radiation exposure only and no other significant trauma. This means that the potential surge of patients could range from 10,000 to 63,000 casualties who would need to be treated at an RITN center or a hospital with similar care capability. RITN consultation for medical professionals will likely be needed for casualties and concerned citizens early in the incident and for weeks.

The vast majority of these casualties would only require blood count monitoring and other monitoring for Acute Radiation Syndrome (ARS).

Table adapted from: Knebel AR, Coleman CN, Cliffer KD; et al. Allocation of scarce resources after a nuclear detonation: setting the context. Disaster Med Public Health Prep. 2011;5 (Suppl 1):S20-S31.

Figure 9. Trauma and combined injury

Triage card 2: Triage category for TRAUMA and COMBINED INJURY affected by injury severity, radiation dose, and resource availability

Triage category for TRAUMA and COMBINED INJURY affected by injury severity, radiation dose and resource availability

Injury severity	Trauma* + radiation** = Combined injury			
≥Moderate trauma* + radiation >2 Gy**	Immediate	Delayed Immediate	Expectant Delayed	Expectant
	Trauma only	BURN >20% BSA worsens triage category (lowers priority) 1-2 levels		
Severe trauma*	Immediate	Immediate	Delayed	Expectant
Moderate trauma*	Delayed	Delayed	Immediate	Immediate
Minimal trauma*	Minimal	Minimal	Minimal	Minimal
Resource availability:	Normal	Good	Fair	Poor
Standard of care**:	Conventional	Contingency	Crisis	Crisis

Legend: Trauma and combined injury

*Adding >20% total body surface area burn to trauma worsen triage priority by 1 category (puts them *lower on the priority list*).

Radiation dose received by the whole body or a significant portion of the whole body. **At higher radiation doses (>6 Gy), triage category may worsen–as on Combined Injury card

***Institute of Medicine. *Guidance for establishing crisis standards of care for use in disaster situations: A letter report*. Washington, DC: Institute of Medicine, National Academies of Science; 2009.

Trauma category	Description
Combined injury	• Radiation dose of >2 Gy to whole body or significant portion of whole body *plus moderate or severe* trauma and/or burn injury.
Severe trauma	• Stabilization requires complex treatment; • >20% chance of death even with treatment.
Moderate trauma	• Without stabilization, potential for death within hours • <20% chance of death with stabilization and treatment.
Minimal trauma	• Injuries pose no significant risk to life and limb in next 3-4 days • Limited or no treatment prior to referral in the next 3-4 days.

NOTES: Triage for casualties with trauma or burn alone, in combination or with radiation injury. Most casualties transported to RITN centers are expected to have minimal or no traumatic or burn injuries, and thus be triaged according to "Radiation Injury Only" (Figure 8). Triage separates casualties into those who should receive Immediate care, those Delayed after the Immediate cohort, those who require Minimal intervention and those who should receive Expectant (*i.e.,* palliative only) management.

Under crisis standards, those with severe injuries are deprioritized to Delayed or Expectant because of their worse prognosis and their greater need for resources. Radiation dose >2Gy indicates whole body or to a significant portion of the whole body. Trauma and Combined Injury Triage card 2 is from Coleman, C., Weinstock, D., Casagrande, R., Hick, J., Bader, J., Chang, F., . . . Knebel, A. (2011). Triage and Treatment Tools for Use in a Scarce Resources-Crisis Standards of Care Setting After a Nuclear Detonation. Disaster Medicine and Public Health Preparedness, 5(S1), S111-S121. doi:10.1001/dmp.2011.22.

Combined injury:

There is a dramatic decrease in prognosis for casualties with both radiation exposure and trauma, when compared to casualties with radiation injury only.

During scarce resources conditions, emergency responders and first receivers will likely have to modify **conventional** clinical standards of care and adopt **contingency** and then **crisis** standards of care to maximize the number of lives saved. This change is best initiated using **predetermined criteria**, Scarce Resources Allocation and Triage Teams, and protocols as in Figure 3.

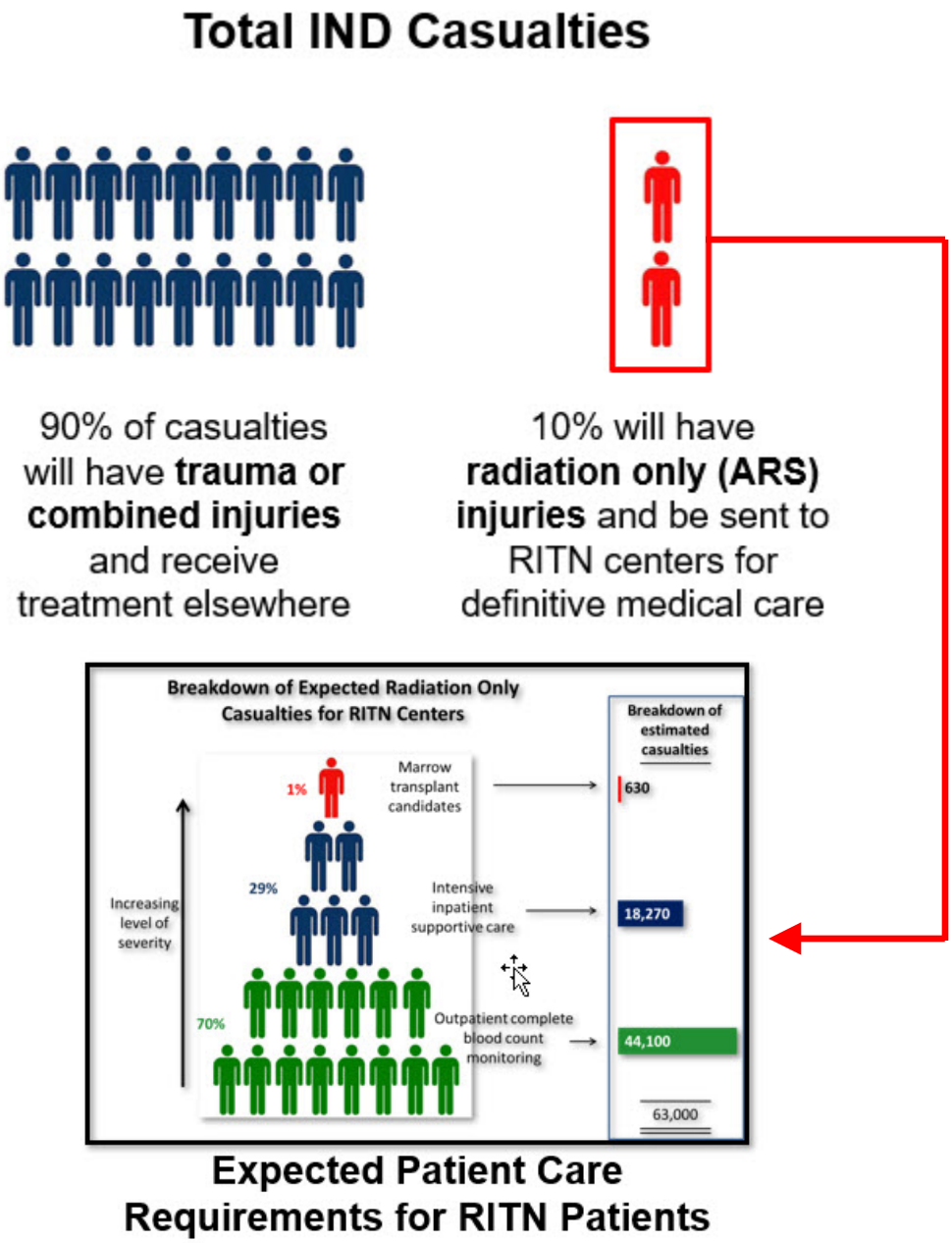
Figure 9 above presents an example of how triage categories could vary by resource scarcity; illustrating possible changes in prioritizing casualties with trauma alone versus combined injury for care after a nuclear detonation (Trauma has 3 categories: Minimal, Moderate and Severe [y-axis, left]; Combined injury: moderate trauma plus radiation dose > 2Gy [top row in Figure 9]; Resource availability [x-axis]: worsens from normal to poor [second row from bottom in Figure 9]; Standard of care changes from Conventional to Crisis [bottom row in Figure 9])

Based on Institute of Medicine Guidance for establishing crisis standards of care for use in disaster situations: A letter report. Washington, DC: Institute of Medicine, National Academies of Science; 2009. radiation casualties with >20% total body surface area burn and/or trauma worsen triage priority by 1 category… from likely to survive to expectant for those with 6 Gy or greater exposure.

Critical to medical management is re-triage as resource balance improves such that delayed or expectant might be rapidly changed to immediate.

From Coleman CN, Weinstock DM, Casagrande R; et al. Triage and treatment tools for use in a scarce resources-crisis standards of care setting after a nuclear detonation. Disaster Med Public Health Prep. 2011;5(Suppl 1):S111-S121.

Figure 10. ARS Casualty Profile



Only about 10% of the total casualties will have radiation only injuries and therefore be appropriate for RITN centers.

With radiation exposure only, casualties with 2-6 Gy doses are likely to have an improved outcome with specialized supportive care. Those with less than 2 Gy dose should not require significant medical resources for their care, they will self-recover or survive with outpatient care. Those with serious co-morbities in the 0.75- 2 Gy range may require hospitalization for general medical management.

Figure 10* illustrates the small percentage of casualties with "radiation only" marrow-toxic injuries that likely would be moved through NDMS to RITN centers calculated from Knebel AR, Coleman CN, Cliffer KD; et al. Allocation of scarce resources after a nuclear detonation: setting the context. Disaster Med Public Health Prep. 2011;5 (Suppl 1):S20-S31

The composition of casualties is very difficult to estimate. This figure conveys the point that the majority of casualties will require supportive care, frequently as an outpatient. The percentages shown here are an estimate determined by RITN based on interpretation of current publications and medical experience. These are for planning purposes only

*An RITN center may also receive trauma and radiation victims with some centers receiving all three if the facility has a burn unit. Also note that while growth factors should be given 24-48 hours post-incident, patients may arrive at RITN centers until a week to 10-days after the incident.

Biodosimetry based on signs and lymphocyte studies. Dose can be roughly estimated based on the presence and time to onset of vomiting, absolute lymphocyte count or the presence of dicentric chromosomes within peripheral blood lymphocytes (see Hick, J. et. al.). Vomiting can result from other factors (*e.g.,* anxiety, pain). Timing relative to exposure will be very difficult to assess, especially for casualties in the fallout zone who may be exposed over multiple hours. Dicentric chromosome analysis has very limited availability. Estimates of dose will also be available from ground measurements of radiation (*i.e.,* geographic dosimetry), which will be especially valuable for identifying large areas around the detonation with no radiation. The Weapons of Mass Destruction Civil Support Teams (WMD-CSTs) are the state's asset that will test for hot zones. The Federal Radiological Monitoring and Assessment Center, or FRMAC, will have federal level overview while the Department of Defense/U.S. Army Corps of Engineers (USACE) have charge of the survey functions. Further information and online algorithms for dosimetry are available at http://www.remm.nlm.gov/ars_wbd.htm.

Rough dose estimate: Hick, J., Bader, J., Coleman, C., Ansari, A., Chang, A., Salame-Alfie, A., . . . Koerner, J. (2018). Proposed "Exposure And Symptom Triage" (EAST) Tool to Assess Radiation Exposure After a Nuclear Detonation. *Disaster Medicine and Public Health Preparedness, 12*(3), 386-395. doi:10.1017/dmp.2017.86

Table 1 Biodosimetry Based on Acute Photon-Equivalent Exposures

Dose Estimate	Victims with Vomiting	Time to Onset of Vomiting	Absolute Lymphocyte Count†						Rate Constant for Lymphocyte Depletion‡	Dicentrics in Human Peripheral Blood Lymphocytes§	
			Day 0.5	Day 1	Day 2	Day 4	Day 6	Day 8		Per 50 Cells	Per 1000 Cells
Gy	*%*	*h*	←			$\times 10^9$ *cells/L*		→	*k*‡	*n*	
0	–	–	**2.45**	**2.45**	**2.45**	**2.45**	**2.45**	**2.45**	–	0.05–0.1	1–2
1	19		**2.30**	**2.16**	**1.90**	**1.48**	1.15	0.89	0.126	4	88
2	35	4.63	**2.16**	**1.90**	**1.48**	0.89	0.54	0.33	0.252	12	234
3	54	2.62	**2.03**	**1.68**	1.15	0.54	0.25	0.12	0.378	22	439
4	72	1.74	**1.90**	**1.48**	0.89	0.33	0.12	0.044	0.504	35	703
5	86	1.27	**1.79**	1.31	0.69	0.20	0.06	0.020	0.63	51	1024
6	94	0.99	**1.68**	1.15	0.54	0.12	0.03	0.006	0.756		
7	98	0.79	**1.58**	1.01	0.42	0.072	0.012	0.002	0.881		
8	99	0.66	**1.48**	0.89	0.33	0.044	0.006	<0.001	1.01		
9	100	0.56	1.39	0.79	0.25	0.030	0.003	<0.001	1.13		
10	100	0.48	1.31	0.70	0.20	0.020	0.001	<0.001	1.26		

* Depicted above are the 3 most useful elements of biodosimetry. Dose range is based on acute photon-equivalent exposures. The second column indicates the percentage of people who vomit, based on dose received and time to onset. The middle section depicts the time frame for development of lymphopenia. Blood lymphocyte counts are determined twice to predict a rate constant that is used to estimate exposure dose. The final column represents the current gold standard, which requires several days before results are known. Colony-stimulating factor therapy should be initiated when onset of vomiting or lymphocyte depletion kinetics suggests an exposure dose for which treatment is recommended (see Table 7). Therapy may be discontinued if results from chromosome dicentrics analysis indicate a lower estimate of whole-body dose.

† Normal range, $1.4–3.5 \times 10^9$ cells/L. Numbers in boldface fall within this range.

‡ The lymphocyte depletion rate is based on the model $Lt = 2.45 \times 10^9$ cells/L $\times e - k(D)t$, where Lt equals the lymphocyte count ($\times 10^9$ cells/L), 2.45×10^9 cells/L equals a constant representing the consensus mean lymphocyte count in the general population, k equals the lymphocyte depletion rate constant for a specific acute photon dose, and t equals the time after exposure (days).

§ Number of dicentric chromosomes in human peripheral blood lymphocytes.

From Waselenko, J. K. et. al. Ann Intern Med 2004;140:1037, Table 5.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15197022

Triage for casualties with radiation injury only affected by resource availability. Most casualties transported to RITN centers are expected to have minimal (e.g., broken arm or leg) or no traumatic or burn injuries, and thus fit into the "Radiation Injury Only" group. Triage separates casualties into those who should receive Immediate care, those Delayed after the Immediate cohort, those who require Minimal intervention and those who should receive Expectant (*i.e.,* palliative only) management. Under crisis standards, those who received >6 Gy irradiation are triaged to Delayed or Expectant. Radiation doses are whole body or to a significant portion of the whole body. Legend for standard of care and myeloid cytokine treatment is included in the next table. From the DHHS Scarce Resources Project.

Figure 11. Triage of Casualties with Radiation Only Injuries based on resource availability

Triage card 1: RADIATION ONLY—triage category affected by radiation dose and resource availability

Triage category affected by radiation dose and resource availability
RADIATION ONLY

Radiation Dose* (Gy)	Normal	Good	Fair	Poor
>10* Likely fatal (in higher range)	Expectant[3] / Immediate[2]	Expectant[3]	Expectant[3]	Expectant[3]
6-10* Severe	Immediate[2]	Immediate[2]	Delayed[2]	Expectant[3]
>2-6* Moderate	Immediate[1]	Immediate[1]	Immediate[1]	Immediate[1]
>0.5-<2* Minimal	Minimal B[3]	Minimal B[3]	Minimal B[3]	Minimal B[3]
<0.5* Minimal	Minimal A[3]	Minimal A[3]	Minimal A[3]	Minimal A[3]
Resource availability:	Normal	Good	Fair	Poor
Standard of care**:	Conventional	Contingency	Crisis	Crisis

Legend: Radiation Only

*Radiation dose received by the whole body or a significant portion of the whole body.

**Institute of Medicine. *Guidance for establishing crisis standards of care for use in disaster situations: A letter report*. Washington, DC: Institute of Medicine, National Academies of Science; 2009.

Minimal B: Consider repeating both biodosimetry and clinical reassessments, especially at high end of this dose range
Minimal A: <0.5 Those with physical dose estimates based on location below 0.5 Gy need not report for medical evaluation. Joining a registry may be suggested after the incident.

The purple/black split triage category for >10 Gy indicates that some victims may receive aggressive treatment at discretion of physician, especially if 10 Gy is received over prolonged time period.

Resource availability below NORMAL:
GOOD conditions allow for maintenance of "functionally-equivalent" care through contingency operations
FAIR conditions require delaying care for severe injuries after moderate injuries
POOR conditions require classifying severe injuries as expectant

Myeloid cytokine category	G-CSF recommendation
1	G-CSF indicated.
2	G-CSF indicated, lower priority than Category 1.
3	G-CSF not indicated.

ARS=acute radiation syndrome; G-CSF=granulocyte colony-stimulating factor.

NOTES: Triage for casualties with radiation injury only affected by resource availability. Most casualties transported to RITN centers are expected to have minimal or no traumatic or burn injuries, and thus fit into the "Radiation Injury Only" group. Triage separates casualties into those who should receive Immediate care, those Delayed after the Immediate cohort, those who require Minimal intervention and those who should receive Expectant (*i.e.*, palliative only) management. Under crisis standards, those who received >6 Gy irradiation are triaged to Delayed or Expectant. Radiation doses are whole body or to a significant portion of the whole body. Radiation Only Triage card 1 is from Coleman, C., Weinstock, D., Casagrande, R., Hick, J., Bader, J., Chang, F., . . . Knebel, A. (2011). Triage and Treatment Tools for Use in a Scarce Resources-Crisis Standards of Care Setting After a Nuclear Detonation. Disaster Medicine and Public Health Preparedness, 5(S1), S111-S121. doi:10.1001/dmp.2011.22.

Minimal B: Consider repeating both biodosimetry and clinical reassessments, especially at high end of this dose range

Minimal A: <0.5 Those with physical dose estimates based on location below 0.5 rem need not report for medical evaluation. Joining a registry may be suggested after the incident.

The red/black split triage category for >10 Gy indicates that some casualties may receive aggressive treatment at discretion of physician, especially if 10 Gy is received over prolonged time period.

Resource availability/conditions:

NORMAL: able to maintain regular conditions and care

GOOD: conditions allow for maintenance of "functionally-equivalent" care through contingency operations

FAIR: conditions require delaying care for casualties who received higher doses due to limited resources, as these casualties are less likely to survive and require more intense intervention

POOR: conditions require classifying high dose radiation injuries as expectant due to lack of resources

From the DHHS Scarce Resources Project. There may be special populations (*e.g.,* very young or very old, those with comorbid conditions) who received between 1-2 Gy radiation and would benefit from myeloid cytokines. Neupogen (G-CSF), Neulasta (PEG-G-CSF), and Leukine/sargramostim (GM-CSF) are FDA approved for this indication. Other myeloid cytokines, including biosimilar preparations of G-CSF, may be acceptable substitutes and are likely to be approved under emergency use authorizations (EUA) in the aftermath of a mass casualty event. Additional triage for myeloid cytokines is included in Figure 11 and Table 1. Notably, newer medical countermeasures and diagnostics are in development which could alter management. Updates will be provided as these move into patient care.

Triage of Casualties with Trauma and Combined Injuries based on resource availability

Triage for casualties with trauma or burn alone, in combination or with radiation injury. Most casualties transported to RITN centers are expected to have minimal and no traumatic or burn injuries. Most casualties sent to an RITN center will be triaged according to "Radiation Injury Only" (page 11). Triage separates casualties into those who should receive Immediate care, those Delayed after the Immediate cohort, those who require Minimal intervention and those who should receive Expectant (*i.e.,* palliative only) management. Under crisis standards, those with severe injuries are deprioritized to Delayed or Expectant because of their worse prognosis and their greater need for resources. Radiation dose >2Gy indicates whole body or to a significant portion of the whole body. Legend and definitions of trauma categories are on the next page. Adding > 15% body surface area burn to trauma reduces triage priority by 1 category.

Figure 12. Standards of Care by trauma category

Trauma category	Description
Combined injury	• Radiation dose of > 2Gy to whole body or significant portion of whole body ***plus*** *moderate or severe* trauma and/or burn injury (a)
Severe trauma	• Stabilization requires complex treatment; • >20% chance of death even with treatment.
Moderate trauma	• Without stabilization, potential for death within hours • <20% chance of death with stabilization and treatment.
Minimal trauma	• Injuries pose no significant risk to life and limb • Limited or no treatment necessary

From Guidance for Establishing Crisis Standards of Care for Use in Disaster Situations (https://www.ncbi.nlm.nih.gov/books/NBK219954/#ddd00045)

Triage and myeloid cytokine prioritization with "Normal" or "Good" resource availability.

Under these conditions, standards will be either conventional or contingency and the "functional standards of care" will be maintained. Definitions of trauma severity are listed on page 20. Radiation doses are to the whole body or a significant portion of the whole body. There may be patients with trauma or special populations (*e.g.,* very young or very old, those with comorbid conditions) who received between 1-2 Gy radiation and would benefit from myeloid cytokines.

In 2015 the FDA approved both Neupogen (G-CSF), Neulasta (PEG-G-CSF), and Leukine/sargramostim (GM-CSF) for treatment of radiation casualties.

Figure 13. Myeloid cytokines with "Normal" or "Good" resource availability
(See Figure 11 Myeloid Cytokine Category for definitions of 1, 2, and 3)

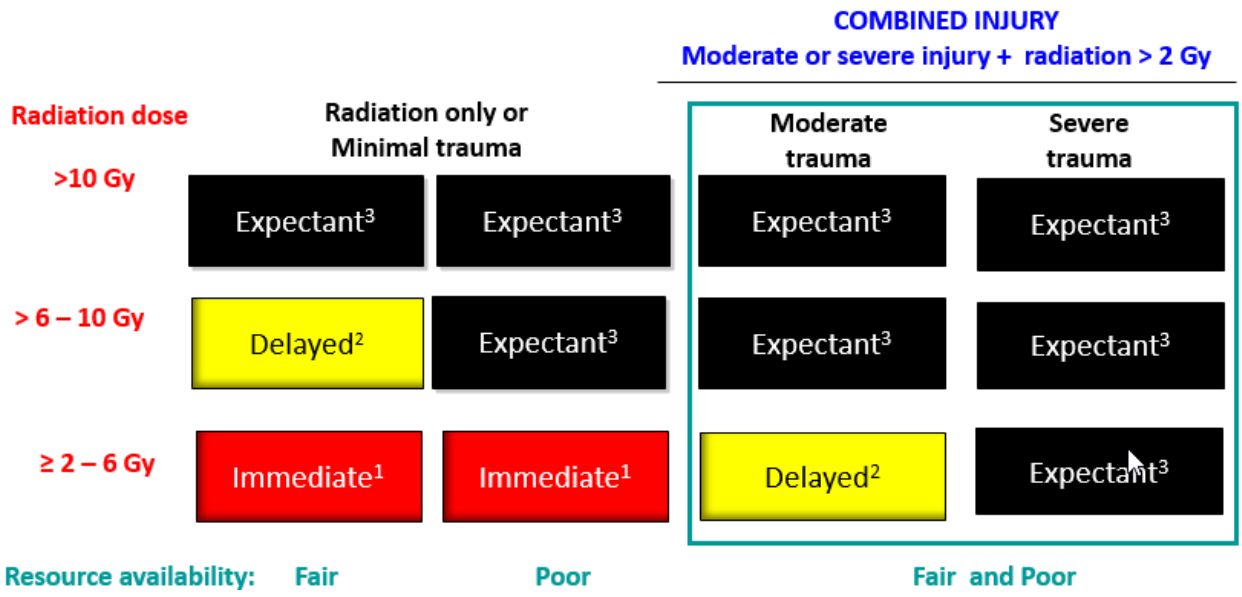
		COMBINED INJURY Moderate or severe injury + radiation > 2 Gy	
Radiation dose (Gy)	**Radiation only or Minimal trauma**	**Moderate trauma**	**Severe trauma**
>10 Gy	Expectant[3] Immediate[2]	Expectant[3]	Expectant[3]
> 6 – 10 Gy	Immediate[2]	Delayed[2]	Expectant[3]
≥ 2 – 6 Gy	Immediate[1]	Immediate[1]	Delayed[2]

Adapted from Coleman, C., Weinstock, D., Casagrande, R., Hick, J., Bader, J., Chang, F., . . . Knebel, A. (2011). Triage and Treatment Tools for Use in a Scarce Resources-Crisis Standards of Care Setting After a Nuclear Detonation. Disaster Medicine and Public Health Preparedness, 5(S1), S111-S121.

Triage and myeloid cytokine prioritization with "Fair" or "Poor" resource availability.

Under these conditions, crisis standards will be necessary. Definitions of trauma severity are in Figure 9. Radiation doses are to the whole body or a significant portion of the whole body. There may be patients with trauma or special populations (*e.g.* very young or very old, those with comorbid conditions) who received between 1-2 Gy radiation and would benefit from myeloid cytokines.

Figure 14. Myeloid cytokine prioritization with "Fair" or "Poor" resource availability
(See Figure 11 Myeloid Cytokine Category for definitions of 1, 2, and 3)



Adapted from Coleman, C., Weinstock, D., Casagrande, R., Hick, J., Bader, J., Chang, F., . . . Knebel, A. (2011). Triage and Treatment Tools for Use in a Scarce Resources-Crisis Standards of Care Setting After a Nuclear Detonation. Disaster Medicine and Public Health Preparedness, 5(S1), S111-S121.

ARS management

Myeloid cytokines

- In pivotal animal studies[1] of TBI, overall survival is improved if G-CSF or PEG-G-CSF is initiated within 24 hours after radiation exposure and continued until resolution of neutropenia
- In animal studies[2] with even 5% partial body shielding, G-CSF can be initiated 1, 3 or 5 days after irradiation with similar improvement in duration of neutropenia
- GM-CSF administered 48 hours post 6-7 Gy radiation in nonhuman primates (NHPs) significantly accelerated time to neutrophil, platelet, reticulocyte and lymphocyte recovery in reduced infections and 36% improved d60 survival[3]
- While G-CSF biosimilars have not been approved for this indication, existing data suggests similar effects to Neupogen and could be used with Emergency Use Authorization (EUA)
- Transfer to RITN centers is not expected for multiple days to weeks after exposure and many casualties will have received no or inconsistent cytokines prior to transfer
- At RITN centers, use of myeloid cytokines should be used with the goal of shortening neutropenia and preventing neutropenia-associated complications

[1] Schuening FG, et al., Effect of recombinant human granulocyte colony-stimulating factor on hematopoiesis of normal dogs and on hematopoietic recovery after otherwise lethal total body irradiation. Blood. 1989 Sep;74(4):1308-13.

[2] MacVittie TJ, et al., The Effect of Radiation Dose and Variation in Neupogen® Initiation Schedule on the Mitigation of Myelosuppression during the Concomitant GI-ARS and H-ARS in a Nonhuman Primate Model of High-dose Exposure with Marrow Sparing. Health Phys. 2015 Nov;109(5):427-39.

[3] Singh VK, Seed TM. An update on sargramostim for treatment of acute radiation syndrome. Drugs Today (Barc). 2018;54(11):679-693. doi:10.1358/dot.2018.54.11.2899370

Transfusions

- Unless the casualty is known to have received < 1Gy irradiation, all transfused blood products should be irradiated and/or leukoreduced whenever possible
- Assuming adequate resource availability, standard thresholds for transfusions should be utilized

Prophylactic antibiotics*

- Use standard approaches during neutropenia**:
  - Anti-HSV (*e.g.,* acyclovir)
  - Anti-bacterial (*e.g.,* levofloxacin)
  - Anti-fungal (*e.g.,* fluconazole)
  - Anti-VZV (*e.g.,* acyclovir)
  - Anti-PCP (*e.g.,* bactrim)
  - Monitoring for CMV reactivation
- After resolution of neutropenia in casualties who received higher doses (>4 Gy), consider:
  - Anti-VZV (*e.g.,* acyclovir)
  - Anti-PCP (*e.g.,* bactrim)
  - Monitoring for CMV reactivation

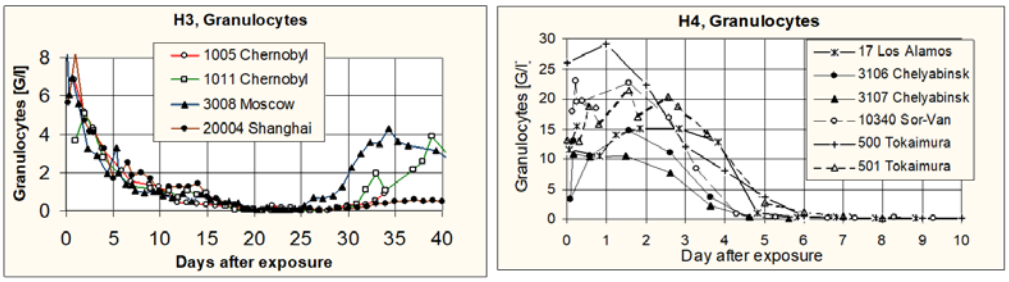
*The SNS may change formulary based on the priorities of federal planners and others.

**See American Society of Clinical Oncology (ASCO), Infectious Diseases Society of America (IDSA) and National Comprehensive Cancer Network (NCCN) treatment guidelines for fever and neutropenia.

Stem cell support

Although thousands of casualties may be transferred to RITN centers, there will be very few who would benefit from and will be eligible to receive stem cell support (see Figure 10).

Figure 15. Granulocyte kinetics with severe but reversible (H3) vs. irreversible (H4) toxicity

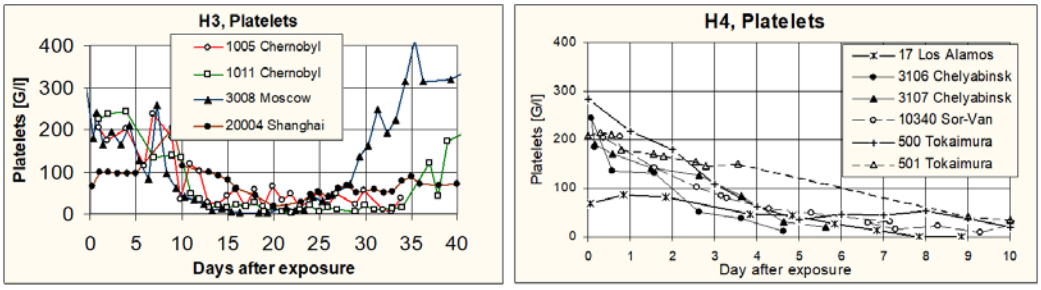


- **Decline between day 4 and 10**
- **Abortive recovery (shoulder)**
- **Nadir days 20 to 30**

- **Initial granulocytosis**
- **Nadir by day 6**

Peripheral blood cell kinetics can predict marrow recovery. Data from industrial radiation accidents suggests that casualties with reversible but severe hematologic toxicity (H3) have different peripheral blood platelet kinetics than casualties with irreversible (*i.e.,* myeloablative) toxicity (H4). Those with H4 have a progressive decline over 10 days while those with H3 have a "shoulder" on the curve characterized by a precipitous decline between 5-10 days after exposure. From Fliedner et al. Br J Radiol 2001;74:121.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11718381

Figure 16. Platelet kinetics with severe but reversible (H3) vs. irreversible (H4) toxicity



- **Shoulder on curve**
- **Nadir after day 10**

- **Progressive decline to day 10**

Decision to perform HLA typing and recruitment of a donor

Factors favoring HLA typing*

- Estimated whole body dose > 3 Gy
- Neutrophil count < 100/μl by day 6
- Rapid drop of platelets
- Expected to survive other injuries

Expedited HLA typing will be available using buccal swab, with high resolution DNA typing of HLA-A, -B, -C, -DRB1, and -DQB1

*Guidance for obtaining HLA-typing can be obtained by contacting the NMDP or the closest RITN center:

- NMDP HLA-typing guidance: 1 (800) MARROW2 or (612) 627-5800
- For an updated map and list of RITN centers: http://www.ritn.net/About/
- *RITN Participating Centers General Contact Directory*: http://www.ritn.net/Contact/

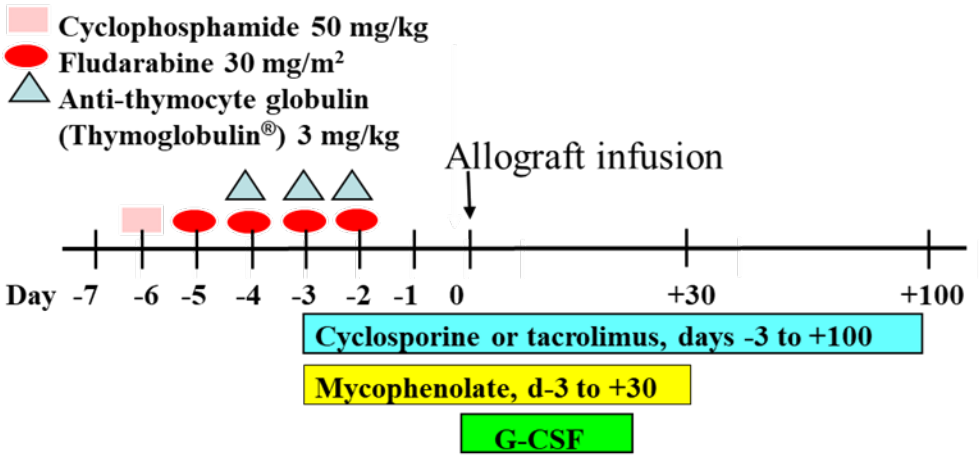
Decision to recruit a donor for evaluation

- If patient remains aplastic for >14 days
- Suitable donor is available:
  - 8/8 match (HLA-A, B-C, DRB1) using bone marrow or PBSCs
  - Alternatives, if a matched donor is unavailable:
    - At least 4/6 matched umbilical cord blood of adequate cell number (potentially 2 cord blood units for adults, 1 cord blood unit for children)
    - Haploidentical donor who has not had radiation exposure
    - Mismatched, related or unrelated donor with T-cell depletion

RITN approach for stem cell support of casualties with irreversible marrow toxicity

- Based on BMT Clinical Trials Network 0301 (https://web.emmes.com/study/bmt2/protocol/0301_protocol/0301_protocol.html)
- Donor matching and selection process:

Figure 17. Matched sib > 7-8/8 URD > 4/6 UCB with 2.5x10^7 MNCs/kg



The advent of post-transplant cyclophosphamide (PTCY) has dramatically improved outcomes for haploidentical transplants (REF). PTCY is therefore an alternative strategy in the absence of a matched related or unrelated donor. Cord blood transplantation is another alternative, but it remains largely restricted to those centers that have developed expertise and use cord blood often. Luznik, L., *et al.* HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. *Biol Blood Marrow Transplant* **14**, 641-650 (2008).

Additional Resources

Adult & Pediatric Medical Orders:

- Radiation Injury Treatment Network (RITN): https://ritn.net/treatment/
- Radiation Emergency Medical Management (REMM): https://www.remm.nlm.gov/adultorderform.htm

For crisis assistance including access to decorporation agents or guidance on their use call:

- REAC/TS: 865.576.1005 (24x7 - Ask for REAC/TS)
- Medical personnel caring for a few casualties with exposures in excess of 200 Rad (2 Gy) or with cytopenia should call REAC/TS.
- Radiation Emergency Assistance Center/Training Site (REAC/TS): www.orau.gov/reacts

Biodosimetry Tools:

- Three Dose Estimators REMM: https://www.remm.nlm.gov/ars_wbd.htm
- Software (BAT) - Armed Forces Radiobiology Research Institute (AFRRI): www.afrri.usuhs.mil
- Biodosimetry Assessment Tool (BAT)
    - For healthcare providers use immediately following an incident to identify casualties with high doses
- WinFrat – First Responders Radiological Assessment Triage tool (for Windows)
    - First 1st Responders to triage suspected causalities
- Learn more and request access: https://www.usuhs.edu/afrri/biodosimetrytools