Chapter XI. Effect of Irradiation on Other Forms of Injury

Section A: Infection

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Introduction:

Combined Injury Irradiation Plus Infection: General Principles

After TBI exposure, three events create the ideal conditions for infection: 1) reduced peripheral white blood cell counts, the major defense against infection; 2) damage to the small intestinal villi and barrier function allowing entry into the blood stream of intestinal microbes; and 3) the cytokine environment (1-17). The radiation response leads to tissue edema, compromised circulation, and exacerbates other conditions associated with the response to infectious agents (17). This chapter will review methods used over the past decades to study the interaction of infectious agents with irradiation, outline the available research tools, and propose some viable concepts for future study.

The effects of total body irradiation on humans have been described in irradiation dose dependent syndromes: hematopoietic syndrome (doses between 3 – 4.5 Gy total body irradiation), gastrointestinal syndrome (doses between 10 – 13 Gy), central nervous system syndrome (doses above 50 Gy), with significant overlap between these categories (17).

Much information regarding recovery and long-term survival after total body irradiation (TBI) has been gained from analysis of the Hiroshima and Nagasaki atomic bomb survivors, and survivors of nuclear radiation accidents over the past six decades (17). However, the greatest experience in understanding the effects of total body irradiation has come from clinical bone marrow transplantation (11-17). TBI is used to prepare the recipient for donor marrow injection. Other chapters in this textbook address the issues of irradiation beam quality (neutrons, photons, mixed beam), partial body irradiation, and dose rate. It is the purpose of this chapter to address the dose modifying aspects of irradiation exposure by adding the additional complication of infection.

The human microbiome represents the background on which an infectious agent may compromise recovery from radiation exposure.

The balance of bacterial taxa comprises the intestinal, aerodigestive tract, and the skin. Subtle, but continuous interactions between the immune system and these bacterial taxa maintain a homeostatic balance (18). Conditions under which a particular bacterial or viral agent upsets this balance are well known in clinical medicine. Conditions under which a pre-existing immune response (memory T-cells, antibody response of B-cells) exist will usually lead to control of potentially infectious agents (6-8). After TBI, peripheral blood lymphocyte counts rapidly drop as a result of inter-mitotic death. A transient increase in peripheral blood neutrophils has been associated with circulation of marginalized leukocytes on endothelial walls (20). These parameters have been used to diagnose the kinetics and magnitude of irradiation dose exposure, and are described in other chapters in this textbook.

Within 12 – 24 hours after TBI, peripheral blood counts are significantly lower and bone marrow cellularity begins to decrease leading to significant hypocellularity by 5 days after irradiation (3, 20). Depending on the irradiation dose sustained, and dose-rate, individuals would be most susceptible to invasion and/or proliferation of a pre-existing infectious agent, including

infectious bacteria and viruses (25-29). Depending on the geographic location of a radiation terrorist event, specific endemic infections (e.g. Histoplasma, Blastomyces, or Coccidiodes) may be risk factors. If patients live in an area where Strongyloides or Tuberculosis is prevalent, these are risk factors. There also may be an advantage for prophylaxis if an irradiated population is also known to be exposed to another terrorist agent such as an infectious agent like (Q fever).

Other chapters in this textbook deal with the triage of irradiated humans in a setting of a radiation terrorist event and address the importance of determining/estimating irradiation dose exposure. Those individuals receiving doses less than 3.0 Gy and show no evidence of other traumatic/combined injury would be advised to shelter at home and not enter environments in which infectious agents might be present such as a hospital (Table 1). Hospital acquired or nosocomial infections remain a problem in any event, as is the importance of handwashing and sanitation for caregivers and visitors. The hospital environment is no place for an individual recently subjected to TBI and experiencing a lowering white blood cell count. However, individuals, who have received a dose of 3 Gy or lower, but have a significant combined injury such as thermal burn, penetrating wound, concussion leading to unconsciousness, multiple bone fractures, or other conditions might be hospitalized. It is these individuals, who are at risk for significant infection, because of the dose modifying effect of infection plus irradiation.

Experimental animal model systems

Elegant experiments by Jacob Finkelstein, et al. (25), Jacqueline Williams, et al. (26-29), and others have used rodent models to quantitate effects of exposure to increasing doses of infectious agents. Influenza virus administration using intra-tracheal dose quantitation to mice has facilitated precise studies of the numbers of viral particles required to produce a clinical infection. Acute virus response is associated with inflammatory cells in areas of the lung, but is followed rapidly by a total lung oxidative stress response. Administration of antioxidants to virus infected mice has been demonstrated to decrease the lethality of given viral doses. Quantitative studies administering *Pseudomonas aeruginosa* bacteria to the lungs of mice confirm the dose response curve of number of bacteria administered to the lethality of infection. In these experiments, the baseline dose of infectious agent associated with lethality significant shifted by the combined injury effect of TBI. Administration of antibiotics or other anti-infectious agents can ameliorate the impact of this combined injury effect. Pseudomonas aeruginosa has recently been shown to use the ferroptosis pathway to exacerbate pulmonary damage (35), which can also be significant after TBI.

Recent studies have shown that some antibiotic agents have the beneficial effect of also serving as a radiation mitigator (1, 30).

In the intestinal microbiome, changes induced in total body irradiated mice (18, 32), some bacterial taxa (33-35) may be particularly harmful to the irradiated intestine or lung.

Significant information has been obtained from studies of total body irradiated non-human primates with respect to the importance of supportive care. MacVittie and colleagues demonstrated a clear shift of the lethality curve of TBI of Rhesus Macaque monkeys and also Cynomologous monkeys by supportive care initiatives including administration of broad

spectrum antibiotics and antifungal agents (20). Supportive care measures for these non-human primate experiments have followed clinical protocols used in clinical bone marrow transplant patients including when necessary administration of packed red blood cells, platelets, and white cell transfusions, given to patients with significant pancytopenia reduction in total peripheral blood components – red cells, platelets, and white cells. When combined with broad spectrum antibiotics and anti-fungal agents, this can lead to significant improvement in survival at all radiation doses. However, such intense supportive care measures, which replicate the treatment of patients in laminal flow rooms in bone marrow transplantation facilities are not practical in the setting of management of large numbers of radiation casualties. This issue has generated significant controversy in current research methods by which to treat TBI animals in experimental models (31).

The administration of broad spectrum antibiotics including combinations that include cephalosporins, vancomycin, tobramycin, and others have side effects including liver and kidney toxicity. Other considerations include the recent evidence that antibiotic administration to TBI, or chemotherapy treated recipients of bone marrow transplantation may in fact be deleterious, because the antibiotic regimen selectively removes anaerobic bacteria from the intestine including organisms, which may be beneficial when the balance of taxa in these organs is in the process of trying to achieve restoration (14-15, 21, 23, 36). Additional concerns with the use of excessive antibiotics include the risk of *Clostridium difficile* induced diarrhea or allergic reactions to antibiotics. Clinical consideration of these principles in a setting of the management of radiation casualties presents a challenge for physicians and caregivers.

Differentiation of individuals at risk for infection compared to those with existing infection.

A major controversy in clinical medicine is the issue of when to administer antimicrobial agents. Patients presenting with symptoms are often treated under conditions, which may not justify administration of new drugs (37).

Viral otitis media infection in children suddenly resolves without antibiotic treatment yet many pediatricians and families administer antibiotics in the absence of protocols or clinically established guidelines (38). When to treat patients with a clinical presentation of pneumonia is another example of this controversy since viral pneumonias will not benefit from treatment with antibiotics. This situation is very different in a setting of mass radiation casualties. Recent publications have described individuals with general management. Few have considered the possibility of combined mass exposure to irradiation and infectious agents. Such examples, could include: the management of large numbers of out-patients exposed to TBI doses less than 3.0 Gy, but in a setting of contaminated water supply or an existing seasonal or environmental infection risk.

Mechanisms of interaction of ionizing irradiation with infectious agents.

Experimental models for research in this area have uncovered new areas for research in the area of infection plus radiation exposure based on several known radiation induced cell death pathways (19, 35).

The mechanism by which the lung and intestinal intrinsic resistance to infectious agents is broken down after irradiation exposure. In the lung, filling of alveolar spaces with cytokines in the acute irradiation reaction leads to an environment for proliferation of those bacterial taxa already existing in the lung. Under these conditions, patients are best kept out of the hospital, where inhalation exposure to agents responsible for hospital acquired infection may be present (**Table 1**). Resistant microorganisms may be spread from patient-to-patient in the hospital setting, resulting in infections which may be harder to treat and thus additional antibiotic exposure and disruption of the normal microbiome. Because of the known risk for resistant infections in this environment, standard treatment protocols for specific types of infections are based on whether or not the patient has been at home or in a healthcare setting. There are specific isolation recommendations for patients with known contagious pathogens. (**Table 1**). However, compliance with isolation policies is not complete has been reported to be as low as 28% and would be expected to be even be lower in a mass casualty setting. (39).

The intestinal barrier function primarily in the ilium is comprised of mucin production by goblet cells, which are reduced in number after TBI (22). Furthermore, the microorganism changes in balance after TBI may compromise intestinal homeostasis.

Specific models of particular bacteria species interaction with the lung and intestinal epithelial cell barrier have provided insight into this mechanism of infection. Mice exposed to TBI activate multiple cell death pathways (These are described in another chapter in this textbook.). However, one death pathway involves depletion of glutathione peroxidase for synthesis of oxidized phospholipids mediated by acetyl-Co-A-synthase increase called ferroptosis (35). These data have demonstrated that a bacterial strain, found in low abundance, in the baseline microbiome, gains a proliferative advantage after irradiation, and because of its own production of 15-Lipoxygenase, can "hijack" the pro-ferroptosis pathways in intestinal epithelial cells leading to cell death and reduction of the barrier function (22). Recent data have demonstrated that there is a change in the intestinal microbiome taxa in experimental mouse models after exposure to TBI (18, 32).

Methods by which to study microbial interactions with radiation damaged tissues are now widely available.

Germ-free animal facilities are expensive, but very valuable in this regard. Raising mice in a bacterial free/germ-free environment is possible. Animals must be kept on a special, sometimes liquid diet. Methodology and references on how to set-up such a facility are widely available. Studies in germ-free animals are reconstituted by gavage of specific species of bacteria provide valuable information as to which strains of bacteria interact with the irradiated GI tract epithelium. Shaedler Flora (24) experiments are now available, and can be introductory into germ-free animals. There are 8 specific bacterial strains, which each can be tracked by 16 sRNA analysis using techniques of rt-PCR (discussed in another chapter in this textbook). Entry into the peripheral blood of a specific strain of bacteria under conditions of TBI with or without other factors: mouse genetics, mouse gender, specific diets in Shaedler mice can be used to provide insight into which bacteria enter the gut and under which conditions.

The use of intestinal organoids also provide the ability to study specific strains of bacteria interaction with epithelial cells.

Combining these techniques with the wide availability of transgenic and homologous recombinant deletion negative (knock-out) mice allows investigators to see which specific component to the immune system regulates the interaction of a particular bacterial strain with irradiation injured pulmonary or GI tract epithelium. These basic science studies are now at the cutting edge of research in understanding the role of the microbiome in irradiation injury.

Practical considerations in managing total body irradiation patients, who also have infection.

The best evidence for antimicrobial therapy in infected, irradiated patients comes from bone marrow transplantation programs (15-16, 21). The large transplant centers with the longest history of follow-up of successfully transplanted patients include those studies from the Hutchison Research Institute in Seattle, Minnesota Transplantation Program, Boston Dana-Farber Cancer Institute, MD Anderson Hospital, Johns Hopkins University in Baltimore, and others. All of these institutions have pioneered the use of broad spectrum antimicrobial agent prophylaxis in marrow transplant patients. There has been a biphasic historical use of total body radiation alternating with combination chemotherapy regimens including: Busulfan, as an example is a drug used to prepare patients for bone marrow transplant. One reason that TBI is often deleted from the preparation program is the issue of pulmonary toxicity. Radiation pneumonitis was a major complication in bone marrow transplant recipients, and attempts to minimize lung irradiation dose by using lung transmission blocks or treatment planning to reduce lung dose, led to defective preparation of the recipient due to survival of leukemia or lymphoma cells residing in rib and vertebral body bone marrow. However, substitution of Busulfan containing chemotherapy regimens for irradiation can lead to incomplete removal of cancer cells due to inability of the drug to reach protected sanctuary sites in the central nervous system or other organs.

Lessons learned from infections in immunocompromised patients.

Opportunistic infections, which put the irradiated individual at high risk for combined injury include infectious agents that were discovered largely from other clinical groups of immunocompromised patients. Human Immunodeficiency Virus (HIV) infected patients who are not on treatment will often develop opportunistic infections such as *Pneumocystis jiroveci* pneumonia (PJP), advanced Cytomegalovirus (CMV) infections and disseminated mycobacterial infections (Table 1).

Concerns about the rush to use antimicrobial agents in irradiated patients.

There is an expanding interest in rapid diagnosis of infectious agents before the standard 48 h bacterial culture protocols (40). While there is intense interest in diagnosing infectious agents rapidly, there is also an equal need to minimize the overuse of antibiotics and unwanted selection of resistant strains of bacteria. MRSA, antibiotic resistant gram negative bacteria including extended spectrum beta-lactamase producing organisms (ESBLs) and carbapenemase producing enterobacteriaceae (CRE) have become of great concern in hospital environments, particularly,

because of their difficulty to treat with non-toxic new antibiotics. However, there is also a challenge for emergency room physicians and intensive care units with respect to developing protocols for use of antimicrobial agents. In a setting of mass casualties from a radiation terrorist event, triage procedures will undoubtedly focus on physical combined injury scenarios first: thermal burn/radiation, penetrating wound/irradiation, fracture or concussion related injury, but dealing with infectious agents will be a critical consideration for all these patients (31).

Antibiotic Prophylaxis (Lessons Learned from Clinical Transplant Patients)

There are competing interests when initiating antibiotics in patients who are at increased risk for infection. While the goal is to prevent infections, there is also concern about the cost and toxicity of prolonged antibiotic therapy. For those with acute radiation sickness who are expected to have prolonged neutropenia, there may be a role for prophylactic antibiotics. The choice of regimens is generally based on the organisms that are most likely to cause infections in which there are readily available options. The duration of immunosuppression and type of immunosuppression are both factors in determining which regimens should be used. The presence of mucosal damage and prior exposure to infections that may relapse, such as cytomegalovirus (CMV) or herpes simplex virus (HSV) are also important considerations. Geography may also play an important role in determining exposure to endemic fungi such as *Histoplasma capsulatum* or *Coccidiodes imitis*. The risk of infections after stem cell transplant has been well described and could be used as a framework for the types of infections that would be expected in different times after exposure if there is not bone marrow recovery. In the first month, the greatest risk would be for infections related to traumatic injuries or damage to mucosal surfaces. This infection risk would include typical bacterial pathogens as well as an increased risk for mucocutaneous HSV, Candida infections, and pulmonary infections with *Aspergillus* and other molds. After one month, there would be another group of risk factors including disseminated infections with Candida, *Aspergillus*, CMV and Epstein-Barr Virus (EBV) as well as localized infections with PJP and *Toxoplasma*. If the duration of immunosuppression is longer than 6 months, the risk increases for other pathogens such as encapsulated bacteria and Nocardia.

In patients/radiation casualties, who are expected to be in a state of prolonged, severe neutropenia with an absolute neutrophil count (ANC) of <500 then a combination of a fluoroquinolones such as levofloxacin or ciprofloxacin along with fluconazole and acyclovir may be considered. The use of these agents must be weighed against the toxicities and the risk of resistance. In patients with prolonged immunosuppression, there may also be consideration for PJP prophylaxis. The most common antibiotic for this purpose is trimethoprim sulfamethoxazole with the recognition that this antibiotic can also cause myelosuppression.

In the setting of fevers with neutropenia, the general consensus is that blood cultures should be collected and antimicrobial therapy should be started. One of the questions is whether or not it is appropriate to manage such patients in the hospital or in the outpatient setting. In general, if the duration of neutropenia is expected to be prolonged (>7 days duration) and there is profound neutropenia (absolute neutrophil count [ANC] ≤100 cells/mm^3 and/or significant medical comorbidities, then patients should be admitted to the hospital for empirical therapy. Low risk

patients with an expected brief (≤7 days duration) duration of neutropenia and few co-morbidities can be considered for outpatient therapy (41).

The choice of antibiotics depends on any recent antibiotic exposure or prophylactic regimens as well as the likely pathogens. The initial workup should include blood cultures as well as cultures from any area where there are focal symptoms and initiation of antibiotics. The initial antibiotic regimen should include an anti-pseudomonal beta-lactam such as cefepime, meropenem or piperacillin tazobactam. The choice of antibiotic may be revised based on antibiotic allergies and the risk of resistance to one of these agents (42).

For those individuals, who require inpatient care, the need for intensive care management is largely dependent on the patient's clinical status. Using the analogy of recommendations for allogeneic hematopoietic stem cell transplant (HSCT) recipients, patients with bone marrow suppression which is severe and prolonged should be placed in rooms with >12 air exchanges/hour and high efficiency (>99%) particulate air (HEPA) filters capable of removing particles >0.3μm in diameter should be used. The use of laminar air flow rooms in this setting is controversial (43).

All allogeneic hematopoietic stem cell transplant (HSCT) recipients should be placed in rooms with >12 air exchanges per hour and point-of-use, high-efficiency (>99%) particulate air (HEPA) filters capable of removing particles >0.3 μm in diameter. This recommendation is particularly important for facilities undergoing construction and renovation. The need for environmental HEPA filtration for autologous HSCT recipients has not been established; however, the use of HEPA-filtered rooms should be considered for autologous HSCT recipients who have prolonged neutropenia, the major risk factor for nosocomial aspergillosis.

The use of laminar air flow rooms for bone marrow transplant recipients has been controversial. Such rooms contain filtered air that moves in parallel, unidirectional flow; the air enters the room from one wall and exits the room on the opposite wall. Although LAF protects patients from infection in aspergillosis outbreaks during hospital construction, its routine use may not be valuable for all HSCT recipients. Since 1983, rooms with laminar air flow have been preferred for allogeneic HSCT recipients with aplastic anemia and human leukocyte antigen-identical sibling donors because the reported death rate of patients in regular rooms was nearly four times higher. However, the survival of aplastic anemia HSCT recipients in the late 1990s exceeds that reported in the early 1980s, and no study has yet determined whether survival of HSCT recipients with aplastic anemia improves when they are treated in rooms with laminar air flow. Therefore, such rooms need not be constructed for every HSCT recipient, and use of available rooms is optional or may be limited in the case of mass irradiation casualties.

Hospital rooms should have directed airflow so that air enters at one side of the room and is exhausted at the opposite side. Each hospital room should be well sealed (e.g., around windows and electrical outlets). To provide consistent positive pressure in the HSCT recipient's room, consistent pressure differentials should be maintained between patients' rooms and the hallways or anterooms at >2.5 Pascals. In general, air pressure in hospital rooms of HSCT recipients should be higher than in adjoining hallways, toilets, and anterooms.

Conclusions from this chapter lead to a list of potential research topics.

1) Animal models showing the combined injury effect from the LD50/30 of (TBI) total body irradiation and specific pulmonary infection, wound infection, sepsis, H. influenza bacteria, viral infections influenza.

2) Study of different anatomic sites of infection in the setting of decreasing blood count and inflammatory cytokines after TBI.

3) Study of sources of Infection: At the radiation site (reactor accident, radiation terrorist event, the emergency room, in the the hospital).

4) Study of the outcomes of shelter in place for individuals with estimated radiation dose below 2 Gy in the absence of physical combined injury, and whether this policy reduces exposure to infectious agents – can animal models be used?

5) When to use antibiotics? What is the risk of inducing resistant organisms in the setting of low white blood cell counts after irradiation (What can be learned from the clinical bone marrow transplant experience?). Results of studies being carried out in bone marrow transplant patients not receiving antibiotic prophylaxis.

6) What antibiotics should be used after TBI in the patient with unplanned radiation exposure? Is there a logic to use of broad spectrum antibiotics before 48 h. bacterial cultures are obtained? Should there be blood cultures?

7) Given uncertainty in the biodosimetry or physical dosimetry of TBI or partial body irradiation dose sustained in a mass casualty event, who should be placed in the limited numbers of laminar flow rooms, and who should go to an ICU?

8) What is the mechanism of the toxicity of the combined infection/irradiation injury: a) at the molecular level, how do infectious agents compromise recovery of cells, tissues from radiation injury, and b) at the clinical level was infection present at initiation of TBI, or is it a hospital acquired infection by either inappropriate use of broad spectrum antibiotics, or unnecessary hospitalization in an infection prone environment?

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Table 1. Common Infectious Agents Acquired in the Hospital Setting

Common Infectious Agents Requiring Additional Precautions in Healthcare Facilities *, **

Pathogen	Precautions	Comments
Adenovirus pneumonia	Droplet + Contact	
Chicken pox (varicella)	Airborne	
Clostridium difficile	Contact	
Group A streptococcus Pharyngitis, pneumonia, Scarlet fever or serious invasive disease	Droplet	Also contact precautions if there is a major infection involving skin, a wound or a burn
Hepatitis A (children, incontinent)	Contact	Consider postexposure vaccination
Herpes zoster virus, disseminated (varicella)	Airborne	
Impetigo	Contact	
Influenza	Droplet	
Multi-drug resistant organisms	Contact	
Mumps	Droplet	
Mycobacterium tuberculosis	Airborne	Also contact precautions if extrapulmonary tuberculosis with a draining lesion
Mycoplasma	Droplet	
Neisseria meningitidis	Droplet	
Parainfluenza	Contact	
Parvovirus B 19	Droplet	
Pediculosis (lice)	Contact	
Pertussis (whopping cough)	Droplet	
Respiratory Syncytial Virus	Contact	
Rhinovirus	Droplet	
Staphylococcus aureus (resistant)	Contact	

* Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings (2007) Appendix A Updates September 2018.

** These are additional isolation indicators in addition to standard precautions. Not all healthcare facilities agree on the need for isolation for all of these.