Chapter 5

INFECTIOUS COMPLICATIONS OF RADIATION INJURY

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INTRODUCTION

Infection with normally harmless indigenous microorganisms is a major cause of morbidity and mortality when normal host defenses have been compromised. These opportunistic pathogens are responsible for hundreds of thousands of serious infections in injured and immunosuppressed patients in the United States annually, and the mortality rate for these infections can range from 50% to 70%.[1,2] Advances in surgical and resuscitation techniques are increasing the immediate survival of victims of severe trauma, but many die later from overwhelming infections. In trauma victims who survive the first few days after the event, sepsis is the second major cause of death (with head injury the first).

The nature of the postinjury events that are responsible for infection is illustrated in Figure 5-1. Both radiation and trauma can cause damage to or destruction of tissues. The insult triggers an inflammatory response which, via mediators, activates significant physiological and immunological processes, including disturbances of permeability in the intestine. Leakage of endotoxin from the intestinal lumen can occur, and facultative anaerobic flora increase in numbers in the gut. As this happens, macrophages and other cells contribute to a suppression of the immune system. This early immunosuppression may be beneficial and not pose a serious hazard because mucosal bacterial populations are not excessive at this time.

If the physiological and immunological deficiencies associated with trauma or radiation exposure are not resolved, then suppression of immunity persists. Subsequently, mucosal microorganisms, such as those in the intestine, multiply dramatically and may translocate to other tissues. Many enteric flora find their way to wound surfaces, where they begin to predominate. The best management of opportunistic infections is to use interventions that interrupt or compensate for these processes, thereby preventing overwhelming infection and shock.

INFECTIONS ASSOCIATED WITH CONVENTIONAL INJURIES

Incidence and Type of Pathogens

The nature of the microbial agents responsible for most opportunistic infections has changed since antibiotics were first used, but the incidence of infection has changed relatively little. For example, data from early World War II show a 6% incidence of infections in soft-tissue wounds in 926 patients, a 14% incidence of serious infections with compound fractures in 674 patients, and a 22% incidence of burn infections in 591 patients.[3] The incidence of infection was not much different for soldiers injured in the 1973 Yom Kippur War in Israel (Table 5-1). The overall incidence of infection was 22% in 420 patients.[4] Of those, 49 burn patients had a 35% incidence of infection; 99 patients with fractures, 18%

incidence; 178 patients with soft-tissue injuries, 6%; and 53 patients with penetrating abdominal wounds and perforated colon, 30%.

With the increased use of antibiotics, organisms such as *Clostridium perfringens* (which causes gas gangrene) have become less important. Others have become more troublesome, especially gram-negative organisms such as the *Pseudomonas* or *Klebsiella* species or *Escherichia coli*. Other important opportunistic pathogens are *Streptococcus fecalis* and *Staphylococcus aureus* as well as the *Enterobacter* and *Bacteroides* species. However, many other microorganisms have also been implicated in opportunistic infections.

Because gram-negative bacteria can live in soil, they have evolved ways to adapt to the antibiotics produced naturally by other soil microorganisms, and they maintain this ability to adaptively resist the antibiotic drugs that are used to fight infection. Thus, gram-negative organisms are serious threats in a hospital environment. Hospitals are contaminated with antibiotics, so only resistant organisms can colonize that environment. In studies of infections among tornado casualties in Lubbock, Texas, in 1970, seventy-eight isolates of gram-negative bacteria were obtained from twenty-four hospitalized patients, versus eleven isolates in twenty-three victims treated as outpatients. These results suggest that many of the organisms were acquired in the hospital.[5]

A low incidence of infection was seen among British soldiers injured in the Falkland Islands War in 1982.[6,7] One reason may have been that the patients were treated either on a makeshift hospital ship, the HMS *Uganda,* or in an abandoned icehouse at Ajax Bay. Neither facility had been used previously as a hospital and thus did not contain antibiotic-resistant bacteria.

Causes of Opportunistic Infections

Immunosuppression is a consequence of injury and is an underlying cause of many infectious complications. Four other factors also contribute to post-trauma infections. In decreasing order of importance, they are *(a)* the presence of foreign bodies in wounds; *(b)* the time lag between injury and surgery; *(c)* the number, location, and extent of wounds; and *(d)* the virulence of the organism.

The influence of a foreign body on infection is seen in studies of the minimum dose of *C. perfringens* spores required to cause lethal infections in guinea pigs.[8] The dose required when spores were injected alone was 1×10^6. If the spores were inoculated into crushed muscle, then only 1×10^3 spores were needed. When sterile dirt was added to the spores injected into crushed muscle, then one spore instead of one million was required for lethality. Similarly, $1\text{-}5 \times 10^6$ injected staphylococci caused a lesion in humans, but if the organisms were introduced on a buried silk suture, as few as 1×10^2 bacteria produced spreading cellulitis.[9]

This effect of foreign material or damaged tissue on the development of infections demonstrates the need for early surgical management and debridement of wounds. Even the placement of originally sterile materials into the body of a patient can provide a focus for infection. Inert biomaterials, such as catheters and other invasive devices, can become covered with biofilms in which indigenous bacteria move onto the surface and become surrounded by exopolysaccharides and the host's accreted macromolecules.[10] These biofilms also form on detritus and dead tissue. Bacteria in these colonies cannot be cultured by usual means, and they are more resistant to antibodies, phagocytes, and antibiotics. For example, *P. aeruginosa* in a biofilm can withstand forty times the concentration of tobramycin that kills floating cells. Therefore, the best intervention is the early removal of material that can support the development of biofilm. Because only living tissue resists the formation of a biofilm, debridement is an important treatment. Artificial devices, such as catheters, should be used carefully.

Resistant biofilms have a greater chance to develop on dead tissue and detritus if the time interval between injury and surgical resolution is prolonged. In a study of gas gangrene, 511 patients (162 of whom became infected) had a 15% increased incidence of infection for each day between injury and debridement.[11] These data from World War I are relevant today because a similar situation could develop with mass casualties in a modern conventional or nuclear war.

The incidence of infection is also influenced by the nature of the wounds. Data from the 1973 Yom Kippur War in Israel (Table 5-1) show that burns of less than 25% of the body surface were rarely complicated by infection, but all burns of more than 25% of the body surface were associated with infectious complications.[4] Perforation of the colon was more often associated with infection than was abdominal penetration without perforation of the colon. Fractures involving the femur were also frequently associated with infection.

In general, it is the failure of normal host barriers and defense mechanisms that permits infection by opportunistic pathogens. Once these deficiencies develop, a variety of otherwise harmless microorganisms can take over. Their uncontrolled multiplication in tissues of compromised hosts leads to the accumulation of both toxic microbial products and the products of host responses, which causes shock and death.

Little is known about the lethal mechanisms of most bacteria. Gram-positive organisms, such as *S. aureus,* produce a variety of extracellular protein toxins. Gram-negative organisms can produce extracellular toxins, but they also have a lipopolysaccharide (LPS) cell wall component known as endotoxin which, if present in sufficient quantities, can induce a variety of toxic host responses that mimic many of the responses associated with overwhelming bacterial infections. However, microbial pathogenesis is probably not due to a single factor. For example, although C3H/HeJ mice are low responders to endotoxin effects, they are easily infected with doses of gram-negative bacteria that cannot be established

in other mouse strains.[12] The C3H/HeJ mice die with numbers of organisms in their tissues similar to numbers seen at death in other strains of mice challenged with higher doses of bacteria. Other data illustrating the importance of multiple virulence factors can be taken from a survey of twenty-four *Aeromonas* isolates that were grouped according to high virulence and low virulence for mice challenged intraperitoneally.[13] The high-virulence group of bacteria was more often positive for a variety of factors (Table 5-2) not found among the low-virulence strains. The shock syndrome resulting from the accumulation of lethal numbers of gram-positive bacteria in host tissues is similar to the syndrome involving gram-negative bacteria.[14]

INFECTIONS ASSOCIATED WITH RADIATION INJURY

Importance of Infection

Opportunistic pathogens are not only a major complication of conventional injuries, but also a major cause of morbidity or mortality in radiation-associated injury. Histological specimens of spleen, liver, lymph node, intestinal wall, and other tissues were taken from patients dying from the effects of the atomic blasts over Hiroshima and Nagasaki in 1945. Many specimens revealed microscopic bacterial colonies of both gram-positive and gram-negative bacteria growing freely in the tissues. There is a relationship in animals between infections and deaths after whole-body radiation doses in the midlethal range.[15] A curve based on mouse data depicting increased incidence of infection can be drawn parallel to but preceding the mortality curve. All mice that developed bacteremia after irradiation died, whereas those with no bacteremia survived. Studies such as these show that infection is an important cause of death during the hematopoietic sub-syndrome.

Infection and Combined Injury

More recently, data from severely injured victims of the 1986 Chernobyl disaster also illustrate the serious threat of infections for radiation victims. Of twenty-nine deaths (not counting the two persons killed by the explosion), most were caused by infections associated with burns and hematological injury due to radiation exposure. This type of combined injury is predicted to be the most common trauma problem that will be seen in nuclear warfare. Insults that are sublethal or minimally lethal when occurring alone will act synergistically when occurring together. For example, almost 100% mortality occurred in rats given both 2.5 Gy of gamma radiation (no mortality when given alone) and a burn wound over 33% of their body surface area (50% mortality when given alone).[16]

A role for endogenous microorganisms in deaths following combined injury has been established by determining survival in germ-free rats and conventional rats

undergoing combined radiation exposure and wound injury.[17] No mortality was seen in germ-free rats exposed to 8.0 Gy of total-body radiation compared to 55% mortality in conventional rats. If a 3-cm wound was also inflicted, mortality was 17% and 100% in germ-free and conventional animals, respectively.

As suggested in Figure 5-1, opportunistic infections do not occur until days or weeks after the injury. A chart from a Chernobyl victim (Figure 5-2) shows that elevated temperature, indicating infection, was not recorded until more than 3 weeks after injury. In laboratory animals given lethal radiation, infections are detected at about 9 days after exposure, and death occurs between days 11 and 15.[18]

FACTORS PREDISPOSING TO POSTIRRADIATION INFECTIONS

Impaired Inflammatory Response

Postirradiation infections are associated with neutropenia. In normal persons, inflammatory responses control many microorganisms that penetrate normally sterile tissues (Figure 5-3). Humoral components of inflammation, such as complement, interact with the microbial antigens and become activated to induce cellular responses, such as vasoconstriction and exudation of polymorphonuclear leukocytes. These cells phagocytose and kill many microorganisms. Later, macrophages enter the inflammatory site where they contribute to the removal of microorganisms and debris, and secrete factors that promote tissue repair.

Microorganisms are also removed from the circulation by the reticuloendothelial system (RES). In the presence of proper opsonins, RES macrophages, such as those in the liver and spleen, sequester and kill microorganisms and also secrete mediators that help augment host defenses. Failure in systemic host defenses after trauma may be caused in part by a deficiency of circulating opsonic protein (plasma fibronectin). The infusion of this substance into persons depleted by trauma has been associated with enhanced RES activity.[19] Since macrophages are relatively long-lived, they can be used to augment the host's resistance to infection after radiation exposure.

In traumatized subjects, an adequate inflammatory response is often not achieved because of immunosuppressive factors and the loss of functional cells. For example, the mortality rate from infection varies directly with the degree of granulocytopenia. Dogs given gentamicin plus granulocytes survived longer and cleared *P. aeruginosa* better than dogs given the antibiotic alone.[20] Although granulocytes are undoubtedly important in controlling gram-negative sepsis, it is questionable whether transfusion with these cells is essential for effective therapy. Antibiotics are available, and safer and more realistic agents are being developed for use in mass-casualty situations.

Other cells and humoral agents are also lost due to trauma and radiation exposure. Fibronectin and immunoglobulin G are depleted in trauma victims, and lymphocytes are directly injured by irradiation. In addition, some injuries (such as burns) produce immunosuppressive factors that may impair the function of macrophages or other surviving cells.[21]

There are several examples of increased susceptibility to systemic infection after irradiation. When mice were challenged with *K. pneumoniae,* the LD_{50} was 1 x 10^6. Radiation alone reduced the LD_{50} to 1 x 10^3, and radiation plus a 3-cm dermal wound reduced the LD_{50} still further to 1 x 10^2. Similarly, the inoculation of *E. coli, S. aureus,* or *S. pyogenes* into muscles of mice exposed to 6.5 Gy of gamma radiation resulted in increased numbers of microorganisms in their tissues 5 days later, compared to normal mice. When *S. aureus* was injected into the local wounds of mice exposed to 7.0 Gy of gamma radiation, fewer bacteria were required to produce a lesion or death than in nonirradiated animals.[22]

Postirradiation infections are often polymicrobial, and it has recently been found that the complexity of infection in mice increases with increasing doses of radiation.[23] While *S. aureus* was more often recovered at 9.0 Gy and below, *E. coli* and anaerobes were isolated most frequently in mice receiving a dose of 10 Gy.

Changes in Resident Microbial Populations

Various deficiencies in host defenses can increase the susceptibility to infection, but changes in the microbial populations on body surfaces are also important. Such population shifts can occur when protective coatings on epithelial cells are lost and when indigenous flora, which resist colonization by exogenous pathogens, are reduced in number. These events allow pathogens to colonize mucosal surfaces, from which they may spread to ordinarily sterile sites in the body.

Recent evidence suggests that epithelial surfaces in the oropharyngeal cavity of trauma victims can lose cell-surface fibronectin and become prone to attachment by gram-negative bacteria, such as *P. aeruginosa.*[24] This may also occur after irradiation and may enhance the possibility that pathogens will successfully colonize the host.

Microorganisms in the intestine increase in numbers distally and provide a focus for abnormal colonization, which can lead to overwhelming infections when systemic host defenses have also been compromised. This phenomenon can be found in rats given sublethal or lethal radiation exposures.[25] The ileum of a normal rat is colonized by unusual bacteria, known as segmented filamentous microflora (SFM), which cannot be cultivated but whose numbers can be easily discerned with scanning electron microscopy. These organisms are intimately associated with the epithelium of the intestine. Their precise role in the intestine is

unknown; however, because they are associated with well-being, SFM can be used as indicator organisms, demonstrating that an injury (which could alter bacterial populations) has occurred in the intestine. Twenty-four hours after sublethal exposure to 5 Gy of gamma radiation, SFM disappeared from the rat ileum. However, by day 4, SFM populations were back to normal. In rats given a lethal radiation dose (10 Gy), SFM did not return at day 4 and were still absent from the ileum at day 11. Potential opportunistic pathogens, measured by the cultivation of dilutions of intestinal homogenates, declined in numbers shortly after exposure to 5-10 Gy. At the lower radiation dose, their numbers began to increase after the return of SFM, but they were still subnormal at day 11. In contrast, rats given 10 Gy showed increasing numbers of facultative flora after the first few days following irradiation, and by day 11 these organisms had colonized the ileum in numbers far above normal. This event correlated with systemic infection and preceded death.

It is apparent that an event associated with exposure to higher doses of radiation is responsible for abnormal colonization preceding infection. Little is known about the pathophysiology of this injury. Intestinal epithelial cells are almost as sensitive to radiation as are marrow cells, and even doses of radiation below the gastrointestinal-subsyndrome level can cause injuries that affect bacterial colonization.

Since most intestinal microorganisms are found in the 450-micron mucin layer at the epithelial surface, any injury that produces changes in this structure can contribute to significant alterations in patterns of microbial colonization in the intestine. Evidence for the loss of the intestinal mucous barrier has been found in mice that received 10 Gy of cobalt-60 radiation.[26] When procedures were used that stabilized the mucous gel for electron microscopy, a progressive loss of this material was observed between irradiation and day 3 (Figure 5-4). Prior to irradiation, villi were not visible beneath the mucus, but by day 3, major sections of villi were completely uncovered.

Loss of the mucous barrier and other ecological and immunological changes in the intestine enable opportunistic pathogens to overgrow on the mucosal surface and subsequently to translocate to other tissues. Translocation from the intestine has been well correlated with conventional disturbances of mucosal ecology and also systemic trauma.[27] This process can lead to infections when defense mechanisms are also suppressed.

MANAGEMENT OF INFECTIONS

Opportunistic infections that are a consequence of trauma in conventional warfare have been difficult to control. This will also be true in persons with radiation injuries or combined injuries. In seriously injured Chernobyl victims (Table 5-3), the number of patients with radiation and thermal burns was greater with higher radiation doses, and mortality rose with the severity of combined injuries. Of the

twenty-nine deaths, most were directly attributable to infectious complications. It is clear from the Chernobyl experience that bone-marrow transplants in persons who received uneven radiation exposures (in whom stem cells may have survived) can be dangerous.

If bone-marrow transplantation is not practical in treating radiation victims, the management options are those used in conventional injury: antibiotics, surgery, and supportive therapy.

Antibiotics

New antibiotics are continually being developed. Figures 5-5 and 5-6 describe the different groups of antibiotic agents and indicate their usefulness against different kinds of infections. Some newer antibiotics, such as ceftazidime or the quinolones, may be useful as monotherapy, but most antibiotics seem more effective when used in synergistic combinations. Today, the effectiveness of some antibiotics may be enhanced by the use of inhibitors of bacterial enzymes (such as clavulanic acid) which inhibit betalactamase activity and thereby preserve the function of penicillin derivatives.

Antibiotic effectiveness may also be enhanced by ensuring that therapy is directed against all components of an infection. For example, *Bacteroides* species and facultative gram-negative microorganisms often occur together. One of these organisms may produce capsular material that protects the other organism from phagocytosis, as well as beta-lactamase for protection against antimicrobial therapy. Also, one organism could create an anaerobic environment that is essential to the other organism, or could produce nutritional growth factors. Many slowly growing and fastidious pathogens, which are important in infections of severely compromised patients, may still be unrecognized. Further studies of these organisms will be necessary for better selection of antimicrobial therapy.

It is important that initially avirulent bacterial populations may become more virulent if allowed to persist in mixed infections. Nonabscess-forming cultures, when inoculated into mice along with capsular material or other pathogens, may convert to encapsulated populations that are capable of establishing abscesses on their own.[28]

Antibiotics can also be used to reduce the colonization of intestinal mucosa by opportunistic pathogens. Total intestinal decontamination is difficult to achieve, and it creates further vulnerability to colonization by antibiotic-resistant pathogens. However, selective decontamination with oral antibiotics has already been tested clinically, and it offers promise for the management of mass casualties who have been exposed to midlethal radiation. The oral administration of specific antibiotics eliminates opportunistic pathogens but leaves intact the relatively benign intestinal flora.[29,30] These benign flora increase resistance to colonization by occupying binding sites and creating an environment that is inhospitable to

pathogens. This approach eliminates the need for elaborate methods of isolation. In patients with aplastic anemia, leukemia, or burns, selective decontamination with antibiotics (such as oral nalidixic acid, cotrimoxazole, or amphotericin B) significantly reduces the number of infectious episodes.

The importance of the presence of colonization-resistant flora after irradiation and the hazard of using systemic antibiotics are indicated by experimental studies in mice. After exposure to 10 Gy of gamma radiation, mice treated with metronidazole, which reduces the intestinal anaerobe population, died about 5 days earlier than did the untreated irradiated mice.[31] In contrast, gentamicin did not affect colonization-resistant flora in the intestine and did not shorten the survival times.

Antimicrobial therapy was reasonably effective against infections in those Chernobyl victims who suffered from ARS only, but was not as effective if the ARS was complicated by burns, radiation enteritis, or acute secondary illness due to bone-marrow transplantation. Patients were treated prophylactically with a selective decontamination procedure that called for the daily administration of six tablets of biseptol 480 and 5 x 10^6 units of nystatin.

If fever appeared, the Chernobyl victims were given intravenous therapy with two or three antibiotics, including an aminoglycoside, cephalosporin, or semisynthetic penicillin with antipyocyanic action. If no effect was seen after 24-48 hours, intravenous gamma globulin (Sandoglobulin) was given in three or four doses of 6 grams every 12 hours. If the fever persisted after 1 week, amphotericin B (1 mg/kg/day) was administered.

A number of Chernobyl patients became infected with herpes simplex. In these cases, acyclovir was used as a topical treatment.

Supportive Therapy

Antibiotics will undoubtedly be a basic part of any infection management after radiation exposure. This supportive therapy, in combination with fluids and platelets, has been shown to increase resistance to infection. Dogs receiving this treatment showed an $LD_{50/30}$ (LD_{50} at 30 days after exposure) increase from 2.6 to 3.3 Gy after exposure to cobalt-60, and from 1.5 to 1.8 Gy after exposure to mixed neutron-gamma radiation.[32] These increases in resistance to radiation are significant, considering the steepness of the survival curve between an LD_5 and an LD_{95} dose of radiation.

Another supportive therapy that may be useful against gram-negative infections in irradiated persons is immunoglobulin. Immunoglobulin will act against some portion of the LPS component of the cell wall of gram-negative bacteria. Most experience with anti-LPS antibody preparations has been in nonirradiated research models.[33-35] Clinically, antiserum prepared from the J5 mutant of *E. coli*

has been used to reduce deaths from 39% to 23% in patients with bacteremia, and from 77% to 44% in those with profound shock.[33] Various immunoglobulin preparations have been used to protect experimental animals against infection.[34]

The development of human monoclonal antibodies opens new possibilities for passive immunization against microbial infections. Passive antibody therapy was widely used in the pre-antibiotic era to treat infectious diseases. Although this therapy may be effective in specific instances, appropriate stocks of specific antibodies with high-affinity constants are expensive and difficult to prepare in large amounts by conventional methods. Further, since such antibodies are usually obtained from animals, particularly horses, humans often have immune reactions to the injection of these immunoglobulins. This results in serum sickness, which prevents further use of the specific therapy in that patient. The new technique of producing antibodies *in vitro* by somatic cell fusion (hybridoma technology) has the potential of generating the desired amounts of high concentrations of pure human-specific antibody preparations, which can be used against opportunistic pathogens in host tissues.

Active vaccination against specific antigens of gram-negative bacteria does not appear to be a good option for controlling infection. It is questionable whether an immunosuppressed person can evoke or maintain an immune response. Moreover, the large number of potential opportunistic pathogens makes it unlikely that a sufficient number of different vaccines can be developed in the near future.

Surgery

In combined-injury victims, surgery is expected to be an important adjunct to supportive therapy, but will be complicated by impairments in wound healing that are manifested shortly after exposure to radiation. In contrast to trauma without radiation, the period of opportunity for reparative surgery following irradiation is very short (1 to 2 days), followed by a period of several weeks in which surgery should not be attempted if it can possibly be avoided (Figure 5-7).

As indicated in Figure 5-1, the closure of wounds can eliminate late immunosuppression and other synergistic effects of combined injury. This is illustrated by experiments conducted in mice.[36] Exposure to 5.1 Gy of radiation resulted in 26% mortality, and the same exposure combined with an open wound resulted in 90% mortality. When the wound was closed, the percentage of mortality dropped and was similar to that from radiation alone. This suggests that a deleterious signal or mediator was interrupted. Unfortunately, excision and closure are not always easily achieved. Closure, if done prematurely, will promote the occurrence of systemic sepsis from microbial colonization of necrotic tissue or detritus. Early debridement should be followed by an inspection of the wound 48 hours later, and if the wound seems free of infection or nonliving material, closure can be considered.

Although this approach has not been fully tested for radiation victims, surgical experience suggests that full-thickness burns should be primarily excised and grafted, and partial-thickness burns should probably be treated by aggressive topical therapy and avoidance of nosocomial sepsis. Prophylactic topical management of burn wounds may be accomplished with mafenide acetate (sulfamylon) or silver sulfadiazine (silvadene).[37] Antibiotics are used for prophylaxis only in traumatic cutaneous wounds, selective decontamination, and early surgery.[38]

SUMMARY

A number of conditions may allow opportunistic infections to occur (Table 5-4). Changes in epithelial cell surfaces can enhance colonization of the oropharyngeal-respiratory tree. Frequently, wound contamination, first by skin flora and later by gram-negative flora from the intestine, can also lead to overwhelming infections. Antibiotic-resistant pathogens in the environment can be particularly troublesome if they colonize wounds on vulnerable mucosal surfaces. Artificial invasive devices also subject susceptible surfaces to colonization by pathogens. Finally, if all these events are accompanied by decreased host defenses, then uncontrolled multiplication by opportunistic pathogens can quickly lead to shock and death.

It should be noted that more virulent organisms can also be a problem after a nuclear detonation. Mild immunosuppression in nonhospitalized personnel working in an environment with poor hygiene can lead to epidemics of respiratory and enteric infections.

General principles of patient management (Table 5-5) and current technology can be used in treating postirradiation infections.

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