Antimicrobials in the Management of Post-Irradiation Infection

I. Brook, T.B. Elliott, M.O. Shoemaker, and G.D. Ledney
Radiation Medicine Department
Armed Forces Radiobiology Research Institute
Bethesda, MD USA 20889-5603

e-mail: brook@afrri.usuhs.mil

ABSTRACT

Ionizing radiation depresses host defenses and enhances susceptibility to local and systemic infection due to endogenous or exogenous microorganisms. Giving mice a lethal dose of ionizing ^{60}Co-gamma radiation induces a dose-related reduction in the number of both aerobic and anaerobic bacteria from 10^{10-12} to 10^{4-6} per gram of stool within four days. Although the number of anaerobic bacteria remains low, measured by per gram of stool bacteria increases significantly, up to 10^9 per gram of stool by the twelfth day following irradiation. This increase is associated with the bacterial translocation of Enterobacteriaceae and fatal bacteremia. Treatment with metronidazole suppressed the anaerobic stool flora and facilitated the increase in the number of Enterobacteriaceae, thus promoting earlier fatal bacteremia. The use of quinolones in the animals was effective in controlling systemic endogenous Gram-negative infection following irradiation. Supplementation with penicillin prevented treatment failures caused by Streptococcus spp. and increased survival. Quinolones given for 21 consecutive days also was effective in managing systemic exogenous infections due to orally ingested Klebsiella pneumoniae and Pseudomonas aeruginosa. The effectiveness of quinolones may be attributed to the inhibition of exogenous microbial growth within the gut lumen while preserving the anaerobic gut flora, and to their systemic antibacterial activity. Based on these findings, the antimicrobial agents recommended for therapy of infection following radiation exposure are ciprofloxacin, levofloxacin, ceftriaxone, cefepime, or gentamicin with or without amoxicillin or vancomycin (to cover gram-positive bacteria), given for 21 days.

1.0   INTRODUCTION

The threat of accidental or hostile exposure to ionizing irradiation is of great concern. Susceptibility to systemic infection from endogenous and exogenous organisms increased following exposure to ionizing radiation [Kaplan 1958, Brook 1986]. A quantitative relationship exists between the degree of neutropenia and the increased risk of infection. Profound neutropenia of fewer than 1.0×10^8 neutrophilic granulocytes/L is the maximum risk factor of infection. Other factors include reduction in the bactericidal function of the granulocytes and macrophages, changes in the endogenous microbial flora, acquisition of potentially pathogenic bacteria, changes in the defensive barrier in the mucus surfaces and skin, and general health status.

The prevention and management of infection are the mainstays of therapy of irradiation victims. However, no controlled studies of therapeutic intervention in humans are available. Furthermore, experience in treating in-

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fections in neutopenic patients that develop immunosuppression following chemotherapy or total body irradiation cannot be utilized in guiding therapy for infection following exposure to ionizing radiation. This is because the infection and other pathology noted after exposure to ionizing radiation is unique [Kaplan 1958, Brook 1986].

This review presents our research in an animal model that established the pathogenesis and the basis for the prevention and treatment of post-irradiation sepsis. This research provides guidance regarding the selection of proper antimicrobials for therapy of sepsis in humans.

2.0   RESEARCH OF POST-IRRADIATION SEPSIS

The source of most post-irradiation infections is the gastrointestinal tract, which normally is colonized by aerobic and anaerobic bacteria [Brook 1986]. Following irradiation with an LD_{50} in mice, a decrease from $10^{10\text{-}12}$ to $10^{4\text{-}6}$ bacteria per gram stool occurs in the number of aerobic and facultative anaerobic bacteria in the ileum of mice. That decrease starts 2 days after irradiation and is maximal 9 days following ^{60}Co-gamma photon irradiation [Brook 1988a].

However, after day 9, the number of *Enterobacteriaceae* increases and returns to the previous number within 3–5 days, but the number of anaerobes stays low. The increase in the *Enterobacteriaceae* numbers coincides with the appearance of endogenous *Escherichia coli* and *Proteus mirabilis* in the blood, spleen, and liver of the animals and the emergence of mortality [Brook 1988a, Brook 1984]. Another potential source of serious infection in the irradiated host is an exogenous organism, such as *Pseudomonas aeruginosa* or *Klebsiella pneumoniae*. Animals exposed to ^{60}Co-gamma radiation become susceptible to colonization and systemic infections with these organisms, starting 2 days after irradiation.

Mortality in mice given 10-Gy ^{60}Co-gamma irradiation and treated with metronidazole, alone or in combination with gentamicin, occurs earlier than in the controls (P < 0.001) [Brook 1988b]. Microorganisms are recovered from the blood, spleen, and liver of the metronidazole-treated mice earlier than from other groups. The predominant organisms recovered from these animals were *Enterobacteriaceae*.

As compared to untreated mice, a rapid decrease (by 8.8 logs) in the number of anaerobic flora occurred in the mice treated with metronidazole 5 days after irradiation. This change preceded a rapid increase in the number of aerobic organisms, which coincides with the earlier mortality in this group. These data suggest that antimicrobial agents that decrease the number of the strict anaerobic component of the gut flora enhance systemic infection by aerobic or facultative anaerobic bacteria, and contribute to the mortality after irradiation.

Polymicrobial intra-abdominal infection involving such aerobic and anaerobic bacteria as *E. coli* and *Bacteroides fragilis* can occur following irradiation associated with intra-abdominal trauma. Previous studies have illustrated the importance of administering antimicrobials that are effective against both of these organisms for the successful management of such infections [Solomkin 1984]. However, treatment of mixed aerobic-anaerobic infections in irradiated hosts may be complicated by the adverse effects following the use of antimicrobials that are capable of reducing the number of the anaerobic gut flora [Brook 1988a].

Therapy for mixed aerobic and anaerobic infections reduces the number of anaerobic gut flora, allows overgrowth of the aerobic flora, and results in increased mortality due to sepsis with *Enterobacteriaceae*.

3.0 USE OF ANTIMICROBIAL AGENTS TO PREVENT AND TREAT INFECTIONS IN ANIMALS

Therapy for systemic infection due to Gram-negative bacteria in the immunocompromised host generally involves the use of an aminoglycoside in combination with a beta-lactam antibiotic [Hathorn 1987]. An additional approach in the prevention of such infection is the selective decontamination of the gastrointestinal tract by using agents that spare the anaerobic gut flora while inhibiting *Enterobacteriaceae*.

Several recently developed quinolone compounds exhibit high *in vitro* bactericidal activity against most Gram-negative bacteria [Andriole 1999]. These agents also can be administered orally and are relatively free of serious side effects. Quinolones also are effective in the management of septic episodes in neutropenic patients [Rozenberg-Arska 1985, Liang 1990]. Furthermore, selective decontamination of the gut with orally administered quinolones is used to prevent sepsis in immunocompromised hosts [Rozenberg-Arska 1985, Liang 1990].

Selective decontamination of the bowel using antimicrobial agents, which are effective against only the aerobic and facultative anaerobic flora, is aimed at eliminating these bacteria while preserving the anaerobic bowel flora. The use of quinolone antimicrobial agents in the treatment of these infections in irradiated mice is effective in controlling systemic endogenous Gram-negative infection following irradiation [Brook 1991a].

Supplementation of quinolone therapy with penicillin prevents treatment failures due to streptococci, and increases survival after non-lethal doses of ^{60}Co-gamma irradiation [Brook 1991b]. Quinolones also are effective in managing systemic exogenous infections due to orally ingested *K. pneumoniae* and *P. aeruginosa* [Brook 1990a, Brook 1990b]. A 21-day course of therapy for *K. pneumoniae* infection is superior to a 7-day course of therapy [Brook 1992]. The effectiveness of quinolones in the management of these infections may be attributed to local inhibition of the exogenous organism's growth within the gut lumen while preserving the anaerobic gut flora and their systemic antibacterial activity [Brook 1991c].

Administration of antimicrobial agents effective against anaerobic bacteria may be required for the management of aerobic-anaerobic polymicrobial infections. Supplementing anti-anaerobic therapy with a quinolone can control the Gram-negative bacterial component of the infection and prevent *Enterobacteriaceae* translocation and mortality [Brook 1994a].

The availability of an oral and a parenteral route of administration, the advantage of achieving selective inhibition of potential pathogens in the gut, and the ability to treat systemic infection make the quinolones promising agents for the therapy of endogenous and exogenous infections following irradiation [Verhoef 1993]. However, growing antimicrobial resistance by potential pathogens against these and other antimicrobial agents warrants careful and controlled use [Schaeffer 2002].

Trimethoprim-sulfamethoxazole also was used for selective decontamination in immunocompromised individuals [Brook 1994b]. However, this agent has been known to cause idiopathic marrow suppression and may be detrimental in irradiation injury.

4.0 PREVENTION OF INFECTIONS IN HUMANS

Initial care of medical casualties with moderate and severe radiation exposure should include early institution of measures to reduce pathogen acquisition from the environment, with emphasis on food with low microbial content, clean water supplies, frequent hand washing (or wearing of gloves), and air filtration.

Prophylactic use of selective gut decontamination with antibiotics that suppress aerobes but preserve ordinarily commensal anaerobes is recommended. Antibiotic prophylaxis should be considered only in afebrile patients who are at the highest risk for infection because of exposure to a high dose of radiation over 1.5 Gy. The quinolones (e.g., ciprofloxacin, ofloxacin) are used for selective decontamination. However, the use of pefloxacin for selective decontamination or therapy of post-irradiation sepsis is not recommended because its use in irradiated mice increases their mortality rate due to suppression of granulocyte-macrophage progenitor cells [Patchen 1993]. The disadvantage of using quinolones for selective decontamination is that they are absorbed and distributed throughout the body. This may generate systemic side effects and promote antimicrobial resistance [Schaeffer 2002]. The development of such resistance may interfere with the potential use of the quinolones if a systemic infection develops. An alternative approach is the use of non-absorbable antibiotics such as polymyxin, neomycin, and bacitracin. Because these agents are not used for therapy, their use for prophylaxis does not generate resistance.

Measures that help prevent infections of an alimentary tract source (mouth, esophagus, and intestines) following exposure to irradiation include the maintenance of gastric acidity (avoidance of antacids and H_2 blockers). This measure may prevent bacteria from colonizing and invading the gastric mucosa and may reduce the frequency of nosocomial pneumonia due to their aspiration. The use of sucralfate or prostaglandin analogues can prevent gastric hemorrhage without decreasing gastric activity.

To maintain the immunologic and physiologic integrity of the gut, an early oral immunoincompetent diet is preferred to intravenous feeding. A subcutaneously tunneled central venous catheter may be needed to allow frequent venous access, but meticulous attention to proper care is necessary to reduce catheter-associated infections, which could become life-threatening.

5.0   RECOMMENDATION FOR ANTIMICROBIAL THERAPY

The management of established or suspected infection following exposure to radiation (characterized by neutropenia and fever) is similar to that used for other febrile neutropenic patients. However, important differences between the two conditions exist [Verhoef 1993]. For example, although individuals exposed to irradiation otherwise may be healthy, they have no protection of selected parts of their body such as the gastrointestinal tract. And the response of irradiated animals to antimicrobial therapy is sometimes unpredictable, as was evident in some of our work where metronidazole [Brook 1988b] and pefloxacin [Patchen 1993] therapies were detrimental.

Antimicrobial agents that decrease the number of the strict anaerobic component of the gut flora (i.e., metronidazole) generally should not be given because they may enhance systemic infection by aerobic or facultative anaerobic bacteria, thus facilitating mortality after irradiation [Brook 1988b]. The patient that develops neutropenia after radiation is susceptible to irradiation damage to other tissues, such as the lungs and the central nervous system. These patients may require therapeutic interventions not needed in other types of neutropenic patients.

An empirical regimen of antibiotics should be selected, based on the pattern of bacterial susceptibility and nosocomial infections in the particular area and institution and the degree of neutropenia. Broad-spectrum empirical therapy (see below for choices) with high doses of one or more antibiotics should be initiated at the onset of fever.

These antimicrobials should be directed at the eradication of Gram-negative aerobic organisms that account for more than three-fourths of the isolates causing sepsis. Because aerobic and facultative Gram-positive bac-

teria (mostly alpha-hemolytic streptococci) cause sepsis in about a quarter of the victims, coverage for these organisms may be necessary in the rest of the individuals.

A standardized plan for the management of febrile, neutropenic patients must be devised in each institution or agency. Empirical regimens must contain antibiotics broadly active against Gram-negative bacteria. Antibiotics directed against Gram-positive bacteria need to be included in instances and institutions where infections due to these organisms are prevalent.

These are the antimicrobial agents we recommend for therapy of infection following exposure to irradiation:

- **First choice:** ciprofloxacin (a second-generation quinolone) or levofloxacin (a third-generation quinolone) +/– amoxicillin or vancomycin. Ciprofloxacin is effective against Gram-negative organisms (including *Pseudomonas* species) but has poor coverage for Gram-positive organisms (including *Staphylococcus aureus* and *Streptococcus pneumoniae*) and some atypical pathogens. Levofloxacin has expanded Gram-positive coverage (penicillin-sensitive and penicillin-resistant *S. pneumoniae*) and expanded activity against atypical pathogens.

- **Second choice:** ceftriaxone (a third-generation cephalosporin) or cefepime (a fourth-generation cephalosporin) +/– amoxicillin or vancomycin. Cefepime exhibits an extended spectrum of activity for Gram-positive bacteria (staphylococci) and Gram-negative organisms, including *Pseudomonas aeruginosa* and certain *Enterobacteriaceae* that generally are resistant to most third-generation cephalosporins. Cefepime is an injectable and is not available in an oral form.

- **Third choice:** gentamicin or amikacin (both aminoglycosides) +/– amoxicillin or vancomycin (all injectable). Aminoglycosides should be avoided whenever feasible due to associated toxicities.

The second and third choices of antimicrobials are suitable for children because quinolones are not approved for use in this age group.

The use of these agents should be considered in individuals exposed to doses above 1.5 Gy, should be given to those who develop fever and neutropenia, and should be administered within 48 hours of exposure. An estimation of the exposure dose should be done by biological dosimetry whenever possible and by detailed history of exposure.

If infection is documented by cultures, the empirical regimen may require adjustment to provide appropriate coverage for the specific isolate(s). When the patient remains afebrile, the initial regimen should be continued for a minimum of 7 days. Therapy may need to be continued for at least 21–28 days or until the risk of infection has declined because of recovery of the immune system. A mass casualty situation may mandate the use of oral antimicrobials.

Modifications of this initial antibiotic regimen should be made when microbiological culture shows specific bacteria that are resistant to the initial antimicrobials. The modification, if needed, should be influenced by a thorough evaluation of the history, physical examination findings, laboratory data, chest radiograph, and epidemiological information. Antifungal coverage with amphotericin B may need to be added, if indicated, for those who remain persistently febrile for 7 days or more on antimicrobial therapy in association with clinical evidence of infection or if they have new fever on or after day 7 of antimicrobial therapy. If resistant Gram-positive infection is evident, vancomycin should be added. If diarrhea is present, cultures of stool should be examined for enteropathogens (i.e., *Salmonella, Shigella*, *Campylobacter*, and *Yersinia*). Oral and pharyngeal mucositis and esophagitis suggest *Herpes simplex* infection or candidiasis. Either empirical antiviral or antifungal therapy or both should be considered.

6.0   CONCLUSION

The administration of proper antimicrobial therapy is essential for the prevention and treatment of systemic infection from endogenous and exogenous organisms that can occur following exposure to ionizing radiation. The management of these patients includes also the use of specific and non-specific biological response modifiers or immunomodulators. Care must be taken of any conventional injuries, and affected organ systems. Future research may lead to enhancement of the survival of the patients by the concomitant use of specific and non-specific biological response modifiers or immunomodulators.

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