

Reverse isolation for neutropenic patients

Srividyalakshmi Seshadri, MD,¹ and Michael A. Baumann, MD^{1,2}

¹Department of Medicine, Division of Hematology/Oncology, Boonshoft School of Medicine, Wright State University, Dayton, OH, and ²Department of Veterans Affairs Hospital, Dayton, OH

Hospitalized patients with neutropenia are commonly placed in reverse isolation intended to protect them from acquiring serious infections. This step often causes confusion and anxiety for patients, families, and health care workers. We reviewed the evidence for efficacy of various types of reverse isolation in select patient groups. Reverse isolation in laminar air flow or high-efficiency particulate air (HEPA)-filtered rooms reduces the incidence of infection and may improve survival for patients receiving allogeneic bone marrow or stem cell grafts. Patients with acute leukemia, aplastic anemia, or other conditions characterized by similarly severe and prolonged neutropenia have also been shown to develop fewer infections when kept in laminar air flow or HEPA-filtered rooms during treatment; however, survival is probably not improved for these patients. Patients receiving chemotherapy for solid tumors or lymphoproliferative diseases who become neutropenic have not been shown to benefit from reverse isolation the way that it is practiced in most hospital settings. Therefore, the practice should be discouraged in the management of these patients.

A 64-year-old man undergoing chemotherapy for small cell lung cancer presents with fever and malaise. A complete blood cell count reveals a white blood cell count of 600/ μ L with an absolute granulocyte count of 100/ μ L. The patient is admitted to the hospital for antibiotic treatment for febrile neutropenia. An order is written by the admitting physician to place the patient under “neutropenic precautions.” He is placed in a standard, private hospital room. The door is kept closed, and a sign titled “Neutropenic Precautions” is posted on the door. The sign states that all visitors should wash their hands upon entering the room and that any visitors with symptoms of a respiratory infection should wear a mask. Gowns, gloves, and masks are placed on a table outside the room.

Despite the wording of the sign, the nursing staff routinely dons gowns, masks, and gloves when entering the room and requires visitors to do so, telling them that this precaution is important for the patient’s safety. Respiratory therapists and other ancillary personnel entering the room also routinely don gowns, masks, and gloves. A medical oncologist enters the room without wearing a gown, gloves, or mask. He washes his hands before examining the patient. After he leaves, the patient’s wife complains to the hospital administration that the oncologist demonstrated disregard for her husband’s safety by failing to wear protective clothing. She demands that the oncologist no longer be involved in her husband’s care.

This clinical vignette is one of several similar episodes that have occurred in two teaching hospitals affiliated with our medical school. It illustrates the confusion that exists regarding the efficacy and procedures of reverse isolation for neutropenic patients. In this article, we will examine the evidence for reverse isolation strategies for defined groups of patients.

The risk of infection in neutropenic patients is related to the degree of neutropenia and its duration. Accordingly, patients at highest risk are those with acute leukemia or aplastic anemia or those who have undergone high-dose chemotherapy in

KEY POINTS

Hospitalized neutropenic patients are often placed in some form of reverse isolation.

There is no evidence of benefit of reverse isolation for most neutropenic patients.

The practice of reverse isolation commonly causes confusion and anxiety for patients, families, and healthcare workers. It should be abandoned for all but a select group of patients in specialized facilities.

Manuscript received June 27, 2008; accepted October 8, 2008.

Correspondence to: Michael A. Baumann, MD, Hematology/Oncology (111W), VA Medical Center, 4100 W. Third Street, Dayton, OH 45428; telephone: 937-268-6511, ext. 1016; fax: 937-267-5310; e-mail: michael.baumann@wright.edu.

Commun Oncol 2008;5:628-632 © 2008 Elsevier Inc. All rights reserved.

preparation for bone marrow transplant or peripheral stem cell grafting. The majority of studies of reverse isolation address these higher-risk patient populations. We examined the available studies for evidence of efficacy in three broad patient groups: patients expected to have prolonged, severe neutropenia, patients receiving bone marrow or stem cell transplants, and patients expected to have severe but transient neutropenia. The latter group includes most patients undergoing treatment for solid tumors or lymphoproliferative diseases. We reviewed only randomized studies, with the exception of a large retrospective review of more than 5,000 cases of allografted patients (Table 1).

Reverse isolation in high-risk patients

In 1973, a study¹ was reported in which 88 patients undergoing induction chemotherapy for acute leukemia were randomized to receive oral nonabsorbable antibiotics alone, a protected environment (laminar air flow, topical antiseptics, nonabsorbable antibiotics, low microbial diet, and sterilization of items entering the patients' rooms), and neither isolation nor antibiotic prophylaxis. There was no apparent benefit of oral nonabsorbable antibiotics alone compared with standard ward care. There was a significant reduction in infections in the protected environment group, with reduced short-term mortality. However, long-term survival did not differ in any group.¹

Another study² randomized 116 patients with acute myelogenous leukemia (AML) to one of four groups: ward care, ward reverse isolation (gowns, glove, and masks) with topical and oral antibiotics, total barrier isolation without antibiotics, or total barrier isolation with topical and oral antibiotics. The latter three groups received low microbial diets. Total barrier isolation included, variably, a plastic tent isolator, a plastic

tent with high-efficiency particulate air (HEPA) filtration, or a room with laminar air flow. Regardless of the type of isolation, there was no direct contact by medical or visiting personnel. The authors reported that there were fewer infections in the barrier-isolated patients after the first 3 weeks. No statistical analysis was provided, except that fewer infections were respiratory in the isolated patients. There was no difference in survival among the groups.²

Schimpff and colleagues³ randomized 64 patients with AML undergoing induction chemotherapy to laminar air flow reverse isolation, oral nonabsorbable antibiotics and a low microbial diet, routine ward care with nonabsorbable antibiotics, or routine ward care alone. The isolation rooms were HEPA-filtered; room surfaces were cleaned with antiseptic solutions daily; and any personnel entering the room wore gowns, gloves, masks, and booties.

Statistically, fewer patients in isolation died as a result of infection than did those in the routine ward care group. Development of infection was delayed in patients in both groups who received oral antibiotics and could tolerate them, but no statistical analysis was presented. The complete remission and overall survival rates were reported to be significantly higher in both groups receiving oral antibiotics than in those in the standard ward care group.³ Interpretation

of the results from these studies is confounded by the fact that none of the trials used a consistent chemotherapy regimen.

The European Organization for Research on Treatment of Cancer⁴ conducted a multicenter, randomized trial in patients with acute leukemia, allocating them to three groups: protective isolation and nonabsorbable antibiotics, protective isolation alone, or routine ward care. Protective isolation entailed either a sterilized plastic enclosure or a laminar flow isolator. All items and food entering the room were sterilized. Persons entering the room used "aseptic techniques" that were not further defined. One hundred-thirty-seven cases were analyzed. There were no significant differences in the occurrence of severe infections between the groups and in the rate of remission or survival. There were significantly fewer respiratory infections in both isolation groups than in the ward care group.⁴

The group at M. D. Anderson Cancer Center in Houston, Texas,⁵ randomized 145 adults with acute leukemia to one of four groups: protected environment and oral antibiotics, protected environment and systemic antibiotics, ward care and oral antibiotics, or ward care and systemic antibiotics. All groups received prophylactic antibiotics. The protected environments were either plastic isolators with glove-box access and HEPA filtration or laminar air flow rooms.

TABLE 1

Summary of evidence for benefit of reverse isolation

Patient group	HEPA filtration or laminar air flow		Reverse isolation in a standard room	
	Reduced infections	Improved survival	Reduced infections	Improved survival
Allogeneic marrow or stem cell graft	Yes	Yes	No	No
Standard treatment of acute leukemia or aplastic anemia	Yes	No	No	No
Chemotherapy of solid tumors or lymphoma	No*	No	No	No

*Unless kept hospitalized for an entire 3 cycles of treatment

HEPA = high-efficiency particulate air

All items that entered the room, including food, were sterilized. The oral antibiotic regimen included a number of nonabsorbable and absorbable drugs given on a rotating schedule. The systemic antibiotics also included several rotating regimens. Patients in protected isolation also applied topical germicidal agents.

There was a significant survival advantage as well as a higher remission rate for patients treated in the protected environment. Fewer infections occurred in the protected environment, and there were significantly fewer fatal infections. There was no significant difference between oral and systemic antibiotics, either in or out of a protected environment.⁵

A European group⁶ randomized 95 patients with a granulocyte count of less than 500/ μ L to receive either reverse isolation with prophylactic oral nonabsorbable antibiotics or routine ward care. All but nine of the patients had acute leukemia or chronic myelogenous leukemia in blast transformation. Of the remaining nine patients, six had aplastic anemia. Reverse isolation entailed a two-chamber unit with HEPA-filtered positive pressured air. A low microbial diet and topical decontamination were used.

There was a statistically significant reduction in the incidence of fever, infections, and deaths due to infections for the patients treated in reverse isolation. There was no difference between the groups in terms of remission rate, duration of remission, or overall mean survival time.⁶

In most settings, the physical facilities and logistical procedures followed in these studies are unavailable or impractical. As a result, reverse isolation techniques that are less stringent were commonly used, with the assumption that they would be of benefit.

Nauseef and Maki⁷ assessed the value of simple protective isolation compared with standard hospital care in 43 episodes of severe neutropenia in 37 patients. Most of the patients

had acute leukemia, and the few who did not had aplastic anemia. The protective isolation group was assigned a private room and toilet. Persons entering the room were required to wear gowns, gloves, and masks. Patients in the "standard care" group were assigned to a two-bed room with a sign on the door reminding those entering to wash their hands. Neither group received nonabsorbable antibiotics, topical disinfectants, or sterilized food.

There was no significant difference in the overall incidence of infection, time to onset of first infection, or days with fever. There was a statistically significant increase in bacteremia for patients in isolation. The reasons for this finding were unknown, but it was speculated that less attention to vascular access devices due to the inconvenience of donning protective clothing might have been a contributory factor. No difference in remission rate or survival between the two groups was noted. Although the group sizes were small, statistical analysis suggested that the study was sufficiently powered to detect a difference of 10% or more between the two groups.⁷

In summary, these trials (the most recent published in 1981) suggest that for patients with acute leukemia or other illnesses characterized by similarly prolonged periods of severe neutropenia, strict reverse isolation in sterilized, protective enclosures with HEPA filtration and/or laminar air flow may reduce the incidence of serious clinical infection related to neutropenia. Whether oral or systemic prophylactic antibiotics are of benefit is not clear, although suppression of endogenous bacterial and fungal colonization could be demonstrated.^{1-4,6,8} Most studies did not show an improvement in remission rate or overall survival.

Reverse isolation in bone marrow transplant patients

The first study of a protective envi-

ronment for marrow transplant recipients randomized 90 patients with either acute leukemia or aplastic anemia who were to receive transplants from human leukocyte antigen (HLA)-matched siblings to undergo either isolation and decontamination or no isolation. Isolation and decontamination included the use of laminar air flow rooms, topical and oral nonabsorbable antibiotics, sterile diets, and sterilization of all items entering patients' rooms. Personnel entering isolation rooms wore gowns, gloves, masks, and booties. For patients who were not in isolation, personnel entering isolation rooms wore only masks. All medical equipment was sterilized, kept in the patient's room, and used for one patient only.

The incidence of clinically significant systemic and local infections was significantly lower in the isolated group. The time until development of the first infection was prolonged in the isolated group. There was no significant difference in survival between the two groups.⁹ A subsequent study of 101 patients receiving allografts for aplastic anemia showed both fewer infections and improved survival for isolated patients.¹⁰

Ninety-nine patients with hematologic malignancies who received allografts from matched siblings were randomized to decontamination, a laminar air flow room, a sterile diet, and prophylactic systemic antibiotics or prophylactic systemic antibiotics in a conventional single-bed hospital room. There were significantly fewer episodes of documented septicemia in the isolated patients. There were no differences in febrile days, length of hospitalization, or survival.¹¹

The same authors conducted a four-arm study of 342 patients comparing no infection prophylaxis in a conventional hospital room and prophylactic systemic antibiotics in a conventional room, isolation in a laminar air flow room with topical and oral decontamination, and lami-

nar air flow isolation/decontamination plus prophylactic systemic antibiotics. There were significantly more episodes of septicemia in the control group than in all three of the other groups and significantly less septicemia in the isolated group that received systemic antibiotics than in the isolated group without systemic antibiotics. There were no survival differences among the groups.¹²

A large retrospective report by the International Bone Marrow Transplant Registry¹³ of 5,065 patients with leukemia from 222 centers receiving allografts from an HLA-identical sibling or alternative related or nonrelated donor compared outcomes for patients in HEPA or laminar air flow (or both) protective isolation with outcomes for those in conventional isolation (single-patient room and any combination of hand-washing, gloves, masks, and gowns). Transplant-related and overall mortality rates in the first 100 days after transplant were significantly lower in the HEPA/laminar air flow group. This finding resulted in a significantly higher 1-year survival rate for patients treated in HEPA/laminar air flow rooms.¹³

In summary, patients with acute leukemia or aplastic anemia who receive high-dose chemotherapy and allografting may benefit from the use of reverse isolation in HEPA or laminar air flow rooms, with a reduced incidence of serious infection and perhaps a reduced rate of mortality.

Reverse isolation in patients receiving chemotherapy for lymphoma or solid tumors

There are few studies of reverse isolation in patients receiving chemotherapy for lymphoma or solid tumors, and they were conducted at one institution, using isolation procedures that were previously described for leukemic patients.⁵ Fifty-eight patients with lymphoma were randomized to receive treatment with 3 cycles

of standard-level chemotherapy in either a protected environment with prophylactic antibiotics or without reverse isolation. There was no difference between the groups in terms of response rate or duration. There were significantly fewer infections in the isolated group.¹⁴

Another study¹⁵ randomized 51 patients with advanced malignant sarcoma to undergo the same method of reverse isolation or hospitalization without isolation throughout 3 cycles of escalating-dose chemotherapy. The response rate, response duration, and survival were similar between the groups, but the isolated patients had significantly fewer infections.¹⁵

A third study¹⁶ tested whether there would be a benefit to escalating conventional doses of chemotherapy in patients with advanced breast cancer. The 33 patients were randomized to receive the first 3 cycles of chemotherapy either in a laminar air flow room with topical decontamination and prophylactic oral antibiotics or in a standard hospital room. There was no difference in response rate, time to disease progression, survival, or even in the incidence and severity of infection between the two groups. The authors concluded that a protective effect of isolation was not apparent, due to the brief duration of severe neutropenia in these patients.¹⁶

The same authors reported a subsequent study¹⁷ in which 59 patients with advanced breast cancer were randomized to receive their first 3 cycles of chemotherapy either at doses 100%–260% higher than standard doses administered in the same protected environment reported previously or standard doses of chemotherapy given on an outpatient basis. Once again, there was no difference in response rate or duration or in survival between the two groups. The high-dose group experienced substantially more toxicity, including more infections, than did the standard-dose group. The utility of the protected

environment in this study cannot be comparatively assessed, because the two groups received substantially different chemotherapy treatments.¹⁷

The previous studies suggest that it may be possible to reduce the incidence of infection in patients receiving myelosuppressive chemotherapy for solid tumors or lymphoproliferative diseases, provided that they remain in a protected environment throughout at least the first 3 cycles of their treatment. There are no studies assessing the value of reverse isolation in patients who have received standard-dose chemotherapy for solid tumors or lymphomas and are later admitted to the hospital either with or without evidence of infection and are found to be neutropenic. However, in most hospital settings, this is the most common reason for using reverse isolation procedures.

Discussion

The interpretation of studies of reverse isolation in neutropenic patients is complicated by the small sample sizes of most of the studies. There are also problems related to the heterogeneity of antitumor treatment received by patients in many studies. The studies are largely 20–30 years old, and supportive care has evolved considerably since then. The common use of indwelling venous access devices and hematopoietic growth factors are just two developments that were not available during many of the studies. The use of a low microbial diet, employed in many of the cited studies and often used in general hospital settings for neutropenic patients,¹⁸ has not been independently studied in a rigorous fashion and is therefore of unclear value.¹⁹

The evidence suggests that management of patients with leukemia or aplastic anemia who are receiving allografts in laminar air flow or HEPA isolation rooms can reduce morbidity and possibly mortality. Similar treatment of patients receiving conven-

tional chemotherapy for acute leukemia or other illnesses characterized by comparably severe and prolonged neutropenia may reduce infectious complications but probably has little effect on remission rates or survival.

For patients receiving myelosuppressive conventional chemotherapy for solid tumors or lymphoproliferative diseases, reverse isolation in laminar air flow or HEPA rooms can arguably reduce the incidence of infections, provided the patients remain hospitalized in isolation throughout at least the first 3 cycles of treatment. However, few investigators would argue that the cost and inconvenience of this approach are worth the benefit, and it is unlikely that survival is improved.

The evidence does not support the use of reverse isolation in hospital settings in which laminar air flow or HEPA-filtered rooms are not available. No data support the use of reverse isolation of any type for patients with solid tumors or lymphoproliferative diseases who are receiving conventional doses of chemotherapy and are later admitted to the hospital with neutropenia, although this is the most common clinical situation in which reverse isolation is used in most hospitals. The use of reverse isolation procedures should be discouraged in the management of these patients, because they are unlikely to be of benefit and commonly cause anxiety and confusion for patients, their families, and healthcare workers.

References

1. Levine AS, Siegel SE, Schreiber AD, et

al. Protected environments and prophylactic antibiotics: a prospective controlled study of their utility in the therapy of acute leukemia. *N Engl J Med* 1973;288:477-483.

2. Yates JW, Holland JF. A controlled study of isolation and endogenous microbial suppression in acute myelocytic leukemia patients. *Cancer* 1973;32:1490-1498.

3. Schimpff SC, Greene WH, Young VM, et al. Infection prevention in acute nonlymphocytic leukemia: laminar air flow room reverse isolation with oral, nonabsorbable antibiotic prophylaxis. *Ann Intern Med* 1975;82:351-358.

4. Dietrich M, Gaus W, Vossen J, van der Waaij D, Wendt F. Protective isolation and antimicrobial decontamination in patients with high susceptibility to infection: a prospective cooperative study of gnotobiotic care in acute leukemia patients. I: clinical results. *Infection* 1977;5:107-114.

5. Rodriguez V, Bodey GP, Freireich EJ, et al. Randomized trial of protected environment—prophylactic antibiotics in 145 adults with acute leukemia. *Medicine (Baltimore)* 1978;57:253-266.

6. Ribas-Mundo M, Granena A, Rozman C. Evaluation of a protective environment in the management of granulocytopenic patients: a comparative study. *Cancer* 1981;48:419-424.

7. Nauseef WM, Maki DG. A study of the value of simple protective isolation in patients with granulocytopenia. *N Engl J Med* 1981;304:448-453.

8. Storrang RA, Jameson B, McElwain TJ, Wiltshaw E. Oral non-absorbed antibiotics prevent infection in acute non-lymphoblastic leukaemia. *Lancet* 1977;2:837-840.

9. Buckner CD, Clift RA, Sanders JE, et al. Protective environment for marrow transplant recipients: a prospective study. *Ann Intern Med* 1978;89:893-901.

10. Navari RM, Buckner CD, Clift RA, et al. Prophylaxis of infection in patients with aplastic anemia receiving allogeneic marrow transplants. *Am J Med* 1984;76:564-572.

11. Petersen FB, Buckner CD, Clift RA, et al. Infectious complications in patients undergoing marrow transplantation: a prospective randomized study of the additional effect of decontamination and laminar air flow isolation among patients receiving prophylactic systemic antibiotics. *Scand J Infect Dis*

1987;19:559-567.

12. Petersen F, Thornquist M, Buckner C, et al. The effects of infection prevention regimens on early infectious complications in marrow transplant patients: a four arm randomized study. *Infection* 1988;16:199-208.

13. Passweg JR, Rowlings PA, Atkinson KA, et al. Influence of protective isolation on outcome of allogeneic bone marrow transplantation for leukemia. *Bone Marrow Transplant* 1998;21:1231-1238.

14. Bodey GP, Rodriguez V, Cabanillas F, Freireich EJ. Protected environment—prophylactic antibiotic program for malignant lymphoma: randomized trial during chemotherapy to induce remission. *Am J Med* 1979;66:74-81.

15. Bodey GP, Rodriguez V, Murphy WK, Burgess A, Benjamin RS. Protected environment—prophylactic antibiotic program for malignant sarcomas: randomized trial during remission induction chemotherapy. *Cancer* 1981;47:2422-2429.

16. Hortobagyi GN, Buzdar AU, Bodey GP, et al. High-dose induction chemotherapy of metastatic breast cancer in protected environment: a prospective randomized study. *J Clin Oncol* 1987;5:178-184.

17. Hortobagyi GN, Bodey GP, Buzdar AU, et al. Evaluation of high-dose versus standard FAC chemotherapy for advanced breast cancer in protected environment units: a prospective randomized study. *J Clin Oncol* 1987;5:354-364.

18. Smith LH, Besser SG. Dietary restrictions for patients with neutropenia: a survey of institutional practices. *Oncol Nurs Forum* 2000;27:515-520.

19. Moody K, Charlson ME, Finlay J. The neutropenic diet: what's the evidence? *J Pediatr Hematol Oncol* 2002;24:717-721.

ABOUT THE AUTHORS

Affiliations: Dr. Seshadri was a fellow in hematology/oncology, Boonshoft School of Medicine, Wright State University, at the time this article was written. Dr. Baumann is Professor of Medicine, Boonshoft School of Medicine, Wright State University and Chief of Hematology/Oncology, Dayton Veterans Affairs Hospital, Dayton, OH.

Conflicts of interest: None to disclose.