# Letters to the Editor

## More on the Outbreak of Invasive Aspergillosis Among Allogeneic Bone Marrow Transplants at Roswell Park Memorial Institute

**To the Editor:**

The editorial by Rhame, commenting on the paper by Rotstein, et al (*Infection Control,* Vol. 6, No. 9, 1985) stated that "It is hard to escape concern that a scientific submission was modified to reduce the impact of pending litigation." Rhame is right to raise such concerns.

Our transplant unit was open for less than a year. The first few cases of Aspergillosis made us wary, but did not raise alarms, because we had seen such cases before in transplant patients and in patient undergoing remission induction for acute leukemia. The last five cases had, unfortunately, all undergon marrow ablative treatment before the first of this subgroup developed *Aspergillus*. Since all were housed on the unit, in this subgroup cross-contamination was a distinct possibility, despite measures taken to avoid such.

At this point, Rotstein and I closed the unit. Since we had failed to demonstrate a source of contamination (although we also suspected the heavy construction and the (retrospectively) inadequate air filtration system) Rotstein chose to begin a case control study. The tabulation of data had been essentially completed, and the conclusions reached, by the fall of 1983. A "paper trail" does exist, demonstrating that the case control study was conceived of and in essence completed prior to the bringing of the suits. The long delay in its appearing in press was related to the usual: submissions, revisions, and re-submissions to different journals.

From a scientific standpoint, I doubt that anyone would question the fact that *Aspergillus* organisms were finding their way to the patients; their source was never proven. The tentative findings that patients with the underlying diagnosis of chronic myelocytic leukemia and patients who had been conditioned withr regimens containing standard dose cytosine arabinoside by infusion were more likely to develop Aspergillosis should not be dismissed lightly; there are possible therapeutic implications here.

I have not been associated with Roswell Park Memorial Institute since January 1984 and am no longer concerned with its numerous difficulties. However, I would hate to see anyone retain the suspicion that Rotstein would participate in any attempt to modify a scientific submission for nonscientific reasons. He is one of the most honest and careful investigators that I have met, and does not deserve even an implied slight on his character as a scientist or a physician.

**Donald J. Higby, MD**
Chief, Hematology/Oncology Service
Professor of Medicine
Tufts University School of Medicine
Boston, Massachusetts

**To the Editor:**

We were quite disturbed to read Dr. Rhame's editorial[1] about our article "An Outbreak of Invasive Aspergillosis Among Allogeneic Bone Marrow Transplants: A Case-Control Study," which appeared in the September 1985 issue of *Infection Control.*[2] We found Rhame's commentary to be marred by inaccuracies and unsupported innuendos.

Rhame implies that we excluded facts in order to abbreviate our analysis. We feel this is unfounded and inappropriate. We included as many variables as possible in our analysis, as well as the environmental setting in which these events took place. It was not within the scope of our analysis to provide the reader with an historical perspective on the events which occurred surrounding the closure of the Bone Marrow Transplant Unit (BMTU) at Roswell Park Memorial Institute. The discrepancies which he claims exist between our account and that of the New York State Department of Health (NYSDH)[3] report raise doubts regarding our honesty in reporting the data. On no occasion did we modify the facts; nor did we selectively report data in order to influence the impact of pending litigation. We would like to emphasize that our analysis was completed prior to the initiation of any litigation. Such litigation was launched against New York State, which operates Roswell Park Memorial Institute.

Rhame criticizes our article for its failure to consider the air filtration system as an explanation for the increased rate of aspergillosis observed among BMT recipients housed on the BMTU. If the air filtration system can truly be implicated as the major cause, resulting in the development of this outbreak among the BMT recipients in the BMTU, why then did transplant recipients

**TABLE**
**ASSOCIATION BETWEEN ROOM AIR CHANGES PER HOUR; PERCENTAGE OF PATIENTS WITH CML TREATED IN A GIVEN ROOM; AND THE ATTACK RATE OF ASPERGILLOSIS IN A GIVEN ROOM ON THE BMTU**

| Room Number | Percentage of Patients Developing Aspergillosis (Attack Rate) | | Air Changes Per Hour | | % CML Patients | | No. of Patients with CML Developing Aspergillosis |
|---|---|---|---|---|---|---|---|
| 4305 | 1/5 = 20% | 5* | 2.3 | 3 | 1/5 = 20% | 5 | 0/1 |
| 4308 | 4/5 = 80% | 1 | 7.6 | 1 | 3/5 = 60% | 1 | 3/3 |
| 4309 | 2/6 = 33.3% | 3.5 | 1.4 | 4 | 2/6 = 33.3% | 2.5 | 1/2 |
| 4312 | 1/3 = 33.3% | 3.5 | 1.0 | 5.5 | 1/3 = 33.3% | 2.5 | 1/1 |
| 4315 | 0/3 = 0% | 6 | 1.0 | 5.5 | 0/3 = 0% | 6 | 0/0 |
| 4316 | 2/4 = 50% | 2 | 2.5 | 2 | 1/4 = 25% | 4 | 1/1 |

**Rank of the six rooms of each variable indicated by the numbers in red.*
*Spearman-Rank Correlations: Attack rate and air changes per hour = 0.76*
*Attack rate and % of CMLs = 0.83*

housed in the satellite building during the same period, with the same filtration system, not have similar attack rates of aspergillosis? We acknowledge, in two separate locations in our article (page 347, and again, on page 354), that inadequate data were available to implicate or exclude a common environmental source for the increased occurrence of aspergillosis, and as a result, the primary focus of our investigation was on the characteristics of patients which predisposed them to develop aspergillosis.

In support of his assumption that a low efficiency air filtration system had to be the explanation for the outbreak of aspergillosis on the BMTU, Rhame points out that the NYSDH report implicated treatment location as the overriding factor influencing the occurrence of aspergillosis in BMT patients.[3] The editorial presents data included in this report which showed a significant correlation between the number of air changes per hour in a room and the attack rate of aspergillosis in those rooms on the BMTU. However, what Rhame fails to consider is the fact that the attack rate per room on the BMTU is actually more strongly correlated with patient diagnosis [chronic myelogenous leukemia (CML) versus other diagnoses] than it is with the number of air changes per hour in a specific room (See the Table where we combine the data on air changes per room from the NYSDH report with the number of CML patients transplanted in each room and the number of patients developing aspergillosis). He also fails to point out that the correlation between the number of air changes and the attack rate per room is non-linear. It should be emphasized that there is no evidence to support the hypothesis that the rate of air changes in a room is related to exposure to *Aspergillus* spores, which was presumed by the NYSDH. The air sampling data collected on the BMTU and reported in our article are not consistent with the conclusion that the more air changes present in a room, the greater the patient's exposure to *Aspergillus* spores. Also, the conditions in the rooms on the BMTU may have been very different when it was opened, compared to when the environmental assessments were completed by the NYSDH consultant 6 months after the BMTU had been closed. Thus, one cannot be sure whether the environmental assessments included in the NYSDH report accurately reflect conditions present when the BMTU was opened.

Although the editorial states that we did not perform an analysis on the impact of the BMTU location on the development of aspergillosis, on page 353 of our article, we in fact present the results of a multivariate analysis that examined the impact of treatment location on aspergillosis. Results of these analyses showed that underlying disease (ie, CML and aplastic anemia versus other diagnoses) was the single best predictor of *Aspergillus* infection. A logistic regression analysis performed on all 76 BMT patients in which both underlying disease and treatment location were used as predictor variables, showed that underlying disease and treatment location were both significantly related to the occurrence of aspergillosis. "Controlling for treatment location, underlying disease (ie, CML and aplastic anemia versus all other diagnoses) was associated with a 27-fold increased likelihood of aspergillosis. By comparison, treatment on the BMTU was associated with an 11-fold increased likelihood of having aspergillosis when controlling for underlying disease." Clearly, a diagnosis of CML or aplastic anemia appeared to be critical to the increased rate of aspergillosis irrespective of treatment location. We cannot completely rule out, though, the possibility that a change in exposure to *Aspergillus* was a factor in the increased rate of aspergillosis seen among BMTU patients.

Two additional items in the editorial are inaccurate. Neither of the two external reviewers invited by the NYSDH to review the Infection Control Guidelines for the BMTU made any comments about the protocols being out of date. Also, Buffalo General Hospital is situated directly north of Roswell Park Memorial Institute and not to the west of it (as Rhame states); thus, this construction site was not in the path of the prevailing southwest winds.

As mentioned above, Rhame contends that the air filtration system of the BMTU was the major cause of this outbreak of aspergillosis. We would like to submit that underlying disease, with profound granulocytopenia and immunosuppression, emerge as the most important risk factors for the development of aspergillosis in the BMT recipients on the BMTU. Our findings on patient characteristics related to aspergillosis are consistent with an earlier published report which Rhame co-authored.[4] We do agree that additional environmental protection for such patients, in the form of laminar air flow units and HEPA filtered room, as demonstrated by others,[5] is warranted as part of our all-out effort to reduce the incidence of aspergillosis in such patients. Such modi-



https://doi.org/10.1017/S0195941700063852 Published online by Cambridge University Press

fications have been made, or are in progress at Roswell Park Memorial Institute.


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**Coleman Rotstein, MD**
**K.M. Cummings, PhD, MPH**
Roswell Park Memorial Institute
Buffalo, New York
**Tracy Gustafson, MD**
Bureau of Epidemiology
Texas Department of Health
Austin, Texas


*Dr. Rhame responds to Dr. Rotstein's comments.*

In my September 1985 editorial[1] I expressed concern that Rotstein et al had misleadingly modified a scientific submission[2] to mitigate their medical-legal exposure. I now believe that concern to be unwarranted. In the editorial I listed three items present in the NY State Health Department report[3] on the Roswell Park aspergillosis outbreak which I believed Rotstein et al had omitted: 1) an expansion of the multivariate analysis from the 26 BMTU patients to all 76 Roswell Park bone marrow transplant patients which found the BMTU to be an independent risk factor for aspergillosis, 2) an analysis of room-specific attack rates which showed a correlation between aspergillosis and room air change rates, and 3) a detailed description of the large scale construction events underway during the BMTU outbreak. Of these three discrepancies, only the first was critical. As Rotstein et al point out above their article *did* contain the expanded multivariate analysis. Unfortunately, the manuscript provided to me by *Infection Control*, which I presume was the original submission, contained no multivariate analysis involving more than the 26 BMTU patients. The final version, perhaps revised in response to reviewers' comments, was not provided to me. I aggravated the problem by submitting my editorial close to the deadline making it difficult for the editor to detect the discrepancy.

Perhaps I am overly sensitive to the medico-legal implications of scientific articles. However, I have little doubt that the Rotstein article will figure prominently in any trials involving these events. As an alumnus of the Dalkon Shield wars, I am familiar with the way attorneys use scientific articles. An article presenting a conclusion supporting one side of a dispute will be presented to the jury as the absolute truth. This presentation will be proceeded by a thorough discussion of the peer review process and the purported assurance that truth results. This rationale may well be extracted from the expert witness of the other side. These maneuvers are very effective because jurors perceive the articles to be unbiased in an otherwise highly adversarial proceeding.

Let us now turn to the more important issue: Why did the Roswell Park BMTU aspergillosis outbreak occur? In the letter above Rotstein et al indicate that the satellite building and the BMTU had the same filtration system but not, during the outbreak period, the same aspergillosis attack rate. The original article[2] indicates that the intake for the BMTU was at the 8th floor while that of the satellite building was at ground level. More information about the precise details of the location of these intakes and the construction projects would be useful. Also important are the practices with respect to leaving windows open on the respective stations and other data bearing on air infiltration.

Ultimately, each of us must judge the plausibility that chronic myelogenous leukemia (CML) and aplastic anemia are really as likely to be critical predisposing factors as the Rotstein et al multivariate analysis indicates.[2] Most bone marrow transplant authorities view acute leukemia patients as among the most immunosuppressed and aplastic anemia patients the least, with CML patients arrayed in between according to the phase of their illness. Seven of the eight CML patients transplanted on the BMTU were in the accelerated phase implying a greater degree of immunosuppression than those transplanted in the chronic phase. In two other large series[4,5] of bone marrow transplant recipients subjected to multivariate analysis of risk factors for aspergillosis, no excess risk due to CML was recognized although the number of CML patients in the first series[4] was small (four patients) and in neither series were data presented on underlying disease as an independent risk factor.

It is unlikely that we will ever be able to unequivocally reconstruct the causes of the Roswell Park aspergillosis outbreak. As scientists, we live with ambiguity, probabilities and incomplete resolution, a luxury not permitted courtroom juries. Regardless, the fundamental lesson remains that special efforts to provide relatively spore-free air to bone marrow transplant patients are clearly warranted.


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**Frank S. Rhame, MD**
University of Minnesota
Hospitals and Clinics
Minneapolis, Minnesota


The Editor and Acting Editor apologize to Dr. Rotstein and colleagues and to Dr. Rhame for not sending the revised manuscript to Dr. Rhame prior to preparation of his Editorial.
Richard P. Wenzel, MD
Dieter H.M. Gröschel, MD