

Safety and Efficacy of Liposomal Amphotericin B Compared with Conventional Amphotericin B for Induction Therapy of Histoplasmosis in Patients with AIDS

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Background: In patients with moderate to severe histoplasmosis associated with AIDS, the preferred treatment has been the deoxycholate formulation of amphotericin B. However, serious side effects are associated with use of amphotericin B.

Objective: To compare amphotericin B with liposomal amphotericin B for induction therapy of moderate to severe disseminated histoplasmosis in patients with AIDS.

Design: Randomized, double-blind, multicenter clinical trial.

Setting: 21 sites of the U.S. National Institute of Allergy and Infectious Diseases Mycoses Study Group.

Patients: 81 patients with AIDS and moderate to severe disseminated histoplasmosis.

Measurements: Clinical success, conversion of baseline blood cultures to negative, and acute toxicities that necessitated discontinuation of treatment.

Results: Clinical success was achieved in 14 of 22 patients (64%) treated with amphotericin B compared with 45 of 51 patients (88%) receiving liposomal amphotericin B (difference, 24 percentage points [95% CI, 1 to 52 percentage points]). Culture conversion rates were similar. Three patients treated with amphotericin B and one treated with liposomal amphotericin B died during induction ($P = 0.04$). Infusion-related side effects were greater with amphotericin B (63%) than with liposomal amphotericin B (25%) ($P = 0.002$). Nephrotoxicity occurred in 37% of patients treated with amphotericin B and 9% of patients treated with liposomal amphotericin B ($P = 0.003$).

Conclusion: Liposomal amphotericin B seems to be a less toxic alternative to amphotericin B and is associated with improved survival.

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* For a list of study investigators and numbers of patients enrolled, see Appendix.

In endemic areas, 5% to 20% of HIV-infected persons develop disseminated histoplasmosis (1–3). Amphotericin B is the therapeutic agent of choice for induction therapy of moderate to severe disseminated histoplasmosis (1), whereas noncomparative studies show that itraconazole (4) and fluconazole (5, 6) are effective for induction and consolidation treatment of milder disease. Treatment of severe disease with amphotericin B, however, has not produced optimal results (3).

Liposomal amphotericin B achieves high concentrations in the reticuloendothelial system (7) and is less nephrotoxic. It achieves higher blood concentrations and exhibits reduced clearance compared with deoxycholate amphotericin B and other lipid preparations (8). In addition, it achieves the highest concentrations in the brains of rabbits (9). Central nervous system involvement indicates poor outcome in patients with AIDS and disseminated histoplasmosis (2, 10). We compared the safety and efficacy of liposomal amphotericin B with deoxycholate amphotericin B for treatment of moderate to severe disseminated histoplasmosis in persons with AIDS.

METHODS

Study Design

After we obtained informed consent, patients with AIDS and moderate to severe disseminated histoplasmosis were randomly assigned in a 2:1 ratio (liposomal amphotericin B—amphotericin B) in this multicenter double-blind trial. Randomization blocks of size 3 were used, and the research pharmacist at each site randomly assigned patients using the closed-envelope (security) technique. Disseminated histoplasmosis was diagnosed by culture of *Histoplasma capsulatum*, by histopathologic examination, or by urine or serum antigen levels determined by enzyme immunoassay (11, 12). Patients were excluded from the trial if they had a serum creatinine level greater than twice the upper limit of normal; had other uncontrolled opportunistic infections or malignant disease; or had been treated for 3 or more days with ketoconazole, itraconazole, fluconazole, or amphotericin B.

Medication Administration

Patients received daily doses of liposomal amphotericin B (AmBisome, Fujisawa Healthcare, Deerfield, Illinois), 3.0 mg/kg of body weight, or amphotericin B, 0.7 mg/kg, for 2 weeks. Medication was administered in a blinded fashion by intravenous infusion over 2 hours. Patients in whom induction therapy was successful received itraconazole for 10 weeks as consolidation therapy. Premedication was not allowed before the first dose. For later doses, premedication could be used and infusion times could be modified depending on side effects.

Monitoring

Before random assignment, a history and physical examination was performed and hematologic and serum

Context

Amphotericin B is the preferred initial treatment for moderate to severe disseminated histoplasmosis. Because amphotericin B has many serious side effects, alternative treatments are needed.

Contribution

This double-blind, multicenter trial compared liposomal amphotericin B with regular amphotericin B in patients with disseminated histoplasmosis and AIDS. Liposomal amphotericin B had a higher treatment response (88% vs. 64%) and lower mortality rates (2% vs. 13%). It also had fewer infusion-related side effects (25% vs. 63%) and less nephrotoxicity (9% vs. 37%).

Implications

Although expensive, liposomal amphotericin B is better than regular amphotericin B for treating severe disseminated histoplasmosis.

—The Editors

chemistry values, serum and urine samples for detecting *H. capsulatum* antigen levels, quantitative lysis centrifugation blood cultures, and a chest radiograph were obtained. Samples were drawn for blood cultures and serum and urine antigen testing for *H. capsulatum* on days 4, 7, and 14 and at weeks 4, 8, and 12 (or when a patient withdrew from the study). Samples were analyzed at the Histoplasmosis Reference Laboratory in Indianapolis, Indiana.

Response Criteria

Clinical and mycologic successes were the primary efficacy end points. A successful clinical response to induction therapy was defined as a maximum daily temperature lower than 37.8 °C for 72 hours; no increase in severity of signs, symptoms, or laboratory abnormalities attributable to histoplasmosis; and the resolution of at least one of the signs or symptoms of histoplasmosis that qualified the patient for enrollment in the trial. A clinical success could be declared after as few as 7 days of induction therapy, at which time itraconazole therapy could be started. A successful clinical outcome after consolidation therapy was defined as resolution or reduction in clinical severity of symptoms and signs attributed to histoplasmosis compared with baseline. Survival was compared for the two treatments. Early discontinuation of induction therapy due to drug toxicity was the primary end point for safety.

Secondary end points were time to defervescence; mycologic efficacy, defined as rate of blood culture conversion; change in *H. capsulatum* antigen levels in urine and serum at week 2; and rates of acute infusion toxicities and nephrotoxicity (increase in serum creatinine level to more than twice the baseline level).

Statistical Analysis

The accrual target was 75 patients. Positive baseline blood cultures were estimated at 80%. The response rate for both therapies was expected to be 70%. Outcome analysis was performed on an intention-to-treat basis. Treatment groups were compared by using the Kruskal–Wallis test for ordered measurements (13) and the Fisher exact test for categorized measurements with corresponding exact 95% CIs (14). Mantel–Haenszel methods were used in a post hoc analysis to assess the impact of enrolling-site differences on clinical outcome (15). The Kaplan–Meier method was used in survival and defervescence analyses, and the treatment groups were compared by using the log-rank test (16). We used StatXact 4 for Windows (Cytel Software, Cambridge, Massachusetts) for efficacy comparisons that involved exact methods. We used SAS software,

Figure 1. Flow of patients through the study.

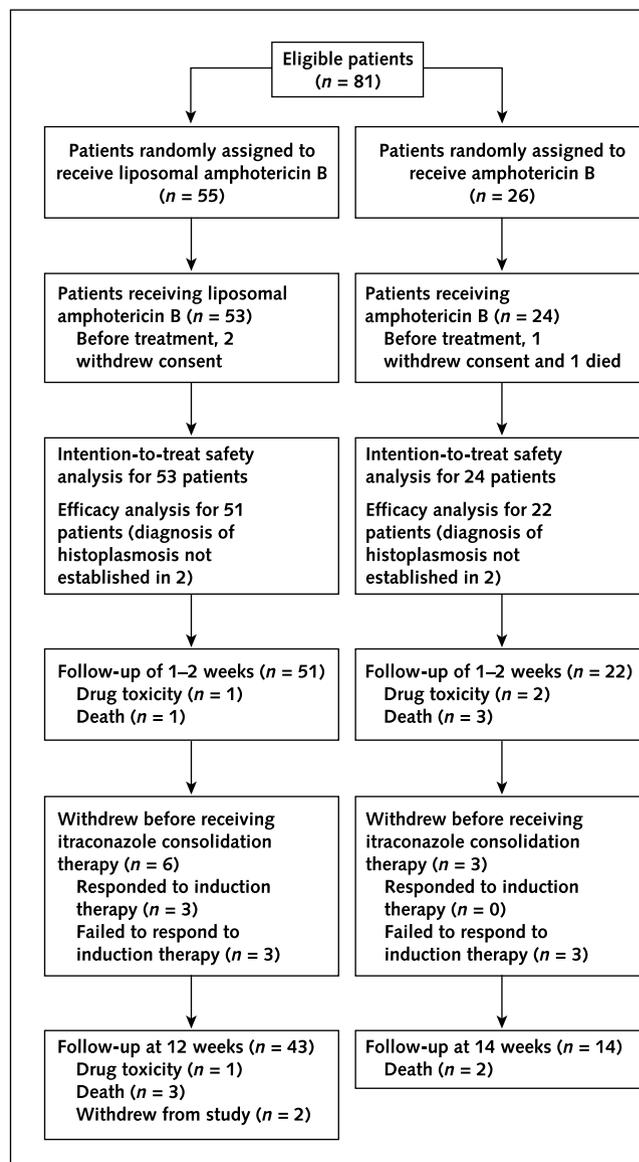


Table. Characteristics of Patients with Progressive Disseminated Histoplasmosis and AIDS, according to Treatment Group

Variable	Liposomal Amphotericin B Group (n = 51)	Amphotericin B Group (n = 22)	P Value
Median CD4 cell count (range), $\times 10^9$ cells/L	0.018 (0.001–0.182)	0.018 (0.004–0.094)	>0.2
Median lactate dehydrogenase value (range), U/L	10.34 (0.10–111.17)	16.82 (2.39–124.58)	0.14
Positive blood cultures for <i>Histoplasma capsulatum</i> , n (%)	37 (73)	17 (77)	>0.2
Positive bone marrow cultures for <i>H. capsulatum</i> , n (%)	8 (16)	3 (14)	>0.2
Positive levels of serum histoplasmosis antigen, n/n (%)*	38/46 (83)	18/19 (95)	>0.2
Positive levels of urine histoplasmosis antigen and other laboratory findings of histoplasmosis at baseline, n/n (%)*	39/45 (87)	20/21 (95)	>0.2
Only a positive level of urine histoplasmosis antigen at baseline, n/n (%)*	4/45 (9)	4/21 (19)	>0.2
Temperature $\geq 39^\circ\text{C}$, n (%)	28 (55)	13 (59)	0.19
Hypotension (systolic blood pressure <90 mm Hg), n (%)	6 (12)	4 (18)	>0.2
Hypoxia (≤ 70 mm Hg), n (%)	4 (8)	3 (14)	>0.2
Lost >5% of total body weight	33 (65)	5 (68)	>0.2
Karnofsky performance status score <70, n (%)	30 (59)	9 (41)	0.08
Bone marrow suppression, n (%)†	31 (61)	14 (64)	0.20
Liver function abnormalities, n (%)‡	14 (27)	10 (45)	0.07
Central nervous system, gastrointestinal, or adrenal histoplasmosis	4 (8)	2 (9)	>0.2
Coagulopathy, n (%)	5 (10)	1 (5)	>0.2
Albumin level <35 g/L, n (%)	13 (26)	6 (27)	>0.2

* Antigen levels were determined by using enzyme immunoassay.

† Bone marrow suppression was defined as follows: hemoglobin <100 g/L, absolute neutrophil count <1.0 $\times 10^9$ cells/L, or platelet count <100 $\times 10^9$ cells/L.

‡ Liver function abnormalities were serum levels of alanine and aspartate aminotransferase >2.5 times normal or bilirubin levels >2 times normal.

version 6.12 (SAS Institute, Inc., Cary, North Carolina) for all other analyses.

Role of the Funding Source

This study was supported by a research grant from the National Institute of Allergy and Infectious Diseases (NIAID) and the National Center for Research Resources, and by Gilead Sciences, Inc. The NIAID assisted in the collection, analysis, and interpretation of the data and in the decision to submit the paper for publication. The National Center for Research Resources assisted with data collection at sites with a General Clinical Research Center. Gilead Sciences, Inc. had no direct role in the conduct of this study.

RESULTS

Eighty-one patients were enrolled by 21 sites. Flow of patients through the study is shown in **Figure 1**. Of 55 patients randomly assigned to receive liposomal amphotericin B, 2 withdrew consent before receiving the study medication and were ineligible for the efficacy and safety analyses and 2 were excluded from the efficacy analysis because they did not have disseminated histoplasmosis. Of 26 patients randomly assigned to receive amphotericin B, 1 died and 1 withdrew consent before receiving any medication. These 2 patients were excluded from the efficacy and safety analyses. Another 2 patients did not have histoplasmosis and were excluded from the efficacy analysis. Overall, 73 patients were evaluated for efficacy and 77 patients were evaluated for safety in an intention-to-treat analysis.

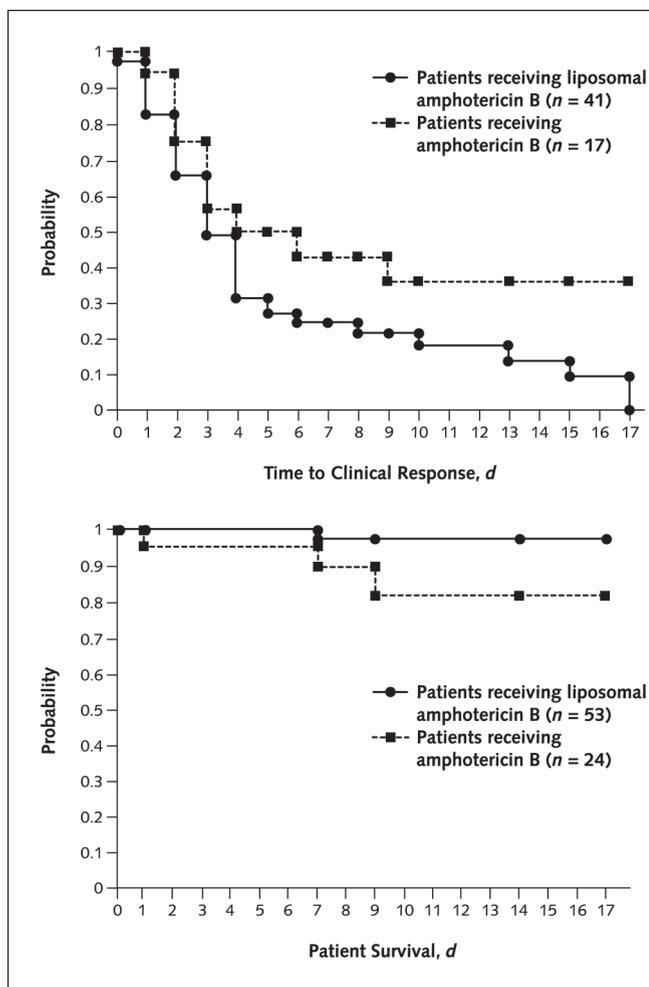
The two treatment groups did not differ significantly in any baseline characteristics tested, including clinical features of severe disease (**Table**). The median age of patients was 33 years (range, 16 to 68 years), and approximately

88% of the 73 patients were men. Fifty-two percent were African American, 32% were white, 15% were Hispanic, and 1% were Asian. Baseline blood cultures were positive in 74% of patients.

The overall clinical efficacy of induction therapy differed between groups. Clinical success was achieved in 45 of 51 patients (88% [95% CI, 77% to 96%]) treated with liposomal amphotericin B compared with 14 of 22 patients in the other treatment group (64% [CI, 42% to 83%]) ($P = 0.014$). The difference between groups was 24 percentage points (CI, 1 to 52 percentage points). Twenty-eight of 51 patients (55% [CI, 40% to 69%]) treated with liposomal amphotericin B and 7 of 22 patients (32% [CI, 14% to 55%]) treated with amphotericin B successfully completed therapy before 14 days (difference, 23 percentage points [CI, -2 to 48 percentage points]). The median time to defervescence was 3 days for both therapies (**Figure 2, top**). By day 14, however, patients receiving liposomal amphotericin B were less likely to have fever than those receiving amphotericin B (13% vs. 36%; $P = 0.09$ [log-rank test]).

Among the 57 patients receiving itraconazole for consolidation therapy, 89% had a clinical response. Consolidation therapy was successful in 38 of 43 patients (88% [CI, 76% to 96%]) treated with liposomal amphotericin B and 13 of 14 patients (93% [CI, 66% to 99%]) treated with amphotericin B (difference, 5 percentage points [CI, -25 to 35 percentage points]) ($P > 0.2$). There was no significant difference in time to negative cultures ($P > 0.2$). After 2 weeks of therapy, 89% of all patients had negative cultures, regardless of type of treatment. Of the 54 patients with a baseline blood culture positive for *H. capsulatum*, 74% responded to induction therapy and received

Figure 2. Kaplan–Meier analysis.



Top. Time to clinical response, as defined by defervescence, for patients with a temperature higher than 37.8 °C 1 day before or at baseline. *P* value for clinical response, defined by defervescence, was 0.09 using the log-rank test. **Bottom.** Survival during induction therapy. *P* value for survival during induction therapy was 0.04 using the log-rank test.

consolidation therapy. There was no statistically significant difference in negative cultures between the two groups at the end of consolidation therapy. *Histoplasma capsulatum* antigen clearance was also similar between the treatment groups. To control for potential investigator bias in outcome responses, data for 42 patients from eight sites were evaluated by using Mantel–Haenszel methods. The odds ratio for clinical response at 2 weeks, comparing liposomal amphotericin B with amphotericin B, was 2.44 (CI, 0.52 to 12.82; *P* > 0.2). Clinical outcomes and mycologic outcomes could not be analyzed at 12 weeks because data for outcomes by regimen were sparse at most of the sites.

Patient survival during induction therapy is shown in the bottom panel of Figure 2. One of 53 patients (2%) treated with liposomal amphotericin B died of bacteremia caused by *Staphylococcus aureus* compared with 3 of 24 patients (13%) in the amphotericin B treatment group who died of progression of disseminated histoplasmosis

(difference, 11 percentage points [CI, 6 to 37 percentage points]) (*P* = 0.04 [log-rank test]). Of the 57 patients who completed itraconazole consolidation therapy, 5 additional patients died (*P* = 0.11). In the amphotericin B treatment group, one patient died of histoplasmosis at day 17 and another died suddenly, possibly of hypokalemia that occurred at day 38. In the liposomal amphotericin B treatment group, one patient died at day 29 of progression of histoplasmosis, one nonadherent patient died of progression of disseminated histoplasmosis at day 120, and one patient died of opportunistic infections.

Overall, acute infusion-related toxicities occurred in 13 of 53 patients (25%) treated with liposomal amphotericin B and 15 of 24 patients (63%) treated with amphotericin B (*P* = 0.002). Nephrotoxicity occurred in 5 of 53 patients (9%) treated with liposomal amphotericin B and 9 of 24 patients (37%) treated with amphotericin B (*P* = 0.003). Protocol therapy was discontinued because of toxicity in one patient in the liposomal amphotericin B treatment group and two patients in the amphotericin B treatment group (*P* = 0.19).

DISCUSSION

This study demonstrates the clinical efficacy of liposomal amphotericin B compared with amphotericin B for induction treatment of moderate to severe disseminated histoplasmosis in patients with AIDS. The time to defervescence for both treatment groups was rapid, showing a trend toward an earlier response to liposomal amphotericin B (*P* = 0.09). Persistent fever did not seem to be caused by febrile responses to amphotericin B. Mycologic responses to induction therapy were similar for both treatment groups. The rate of blood culture clearance was substantially faster in our study than in a previous study of empirical treatment of mild to moderate disseminated histoplasmosis with itraconazole. In that study, 47% of 30 patients had negative cultures after 14 days of therapy (5; Wheat LJ. Personal communication).

Mortality rates during induction were higher in patients treated with amphotericin B than in those receiving liposomal amphotericin B. Liposomal amphotericin B was better tolerated. Fewer infusion-related side effects and less nephrotoxicity were found in the liposomal amphotericin B treatment group. These results are similar to those of a study of empirical therapy with liposomal amphotericin B and amphotericin B in patients with cancer and neutropenia (17). We performed a sensitivity analysis to account for the possibility that observed outcomes varied among centers. The odds ratio (2.44) of the center-stratified analysis was attenuated when compared with the unadjusted odds ratio (4.29), but it still favored liposomal amphotericin B rather than amphotericin B. Because only 42 of 73 of our patients were included in the stratified analysis, statistically significant differences were difficult to detect.

This randomized, double-blind comparative trial of li-

posomal amphotericin B for the treatment of disseminated histoplasmosis in patients with AIDS shows the superiority of a lipid formulation of amphotericin B compared with the deoxycholate formulation for invasive mycosis. Despite its higher cost, intravenous liposomal amphotericin B is an attractive alternative for moderate to severe disseminated histoplasmosis in patients with AIDS because of superior efficacy, lower toxicity, and decreased mortality rates.

APPENDIX: NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES MYCOSES STUDY GROUP

Study Investigators and Numbers of Included Patients

Karsten Witt, Gilead Pharmaceuticals, Boulder, CO; Jim Schnieders, Fujisawa Healthcare, Inc., Deerfield, IL; Robert Baker, Community Hospital, Indianapolis, IN (1 patient); David M. Bamberger, MD, University of Missouri–Kansas City, Kansas City, MO (8 patients); John Black, Methodist Hospital, Indianapolis, IN (5 patients); Robert Bradsher, University of Arkansas, Little Rock, AK (2 patients); Patricia Demarais, Cook County Hospital, Chicago, IL (5 patients); Mitchell Goldman, Indiana University School of Medicine, Indianapolis, IN (5 patients); Elliott Goldstein, University of Kansas City Medical Center, Kansas City, MO (1 patient); Richard Greenberg, University of Kentucky, Lexington, KY (1 patient); David Haas and Steve Dummer, Vanderbilt University, Nashville, TN (1 patient); Harold Henderson, University of Mississippi, Jackson, MS (1 patient); Richard Hamill, Houston VA Medical Center, Houston, TX (3 patients); Anna Huang, University of Louisville, Louisville, KY (3 patients); Philip C. Johnson, University of Texas–Houston Medical School, Houston, TX (6 patients); Susan Kolerar, Ohio State University, Columbus, OH (5 patients); Dan Lancaster, Methodist Hospital, Memphis, TN (8 patients); David McKinsey, Kansas City, MO (3 patients); W. Peter Pappas, University of Alabama, Birmingham, AL (1 patient); William G. Powderly, Washington University School of Medicine, St. Louis, MO (8 patients); Kenneth Shakan, University of Cincinnati, Cincinnati, OH (1 patient); Patricia K. Sharkey, Audie Murphy VA Hospital, San Antonio, TX (4 patients); John Stansell, University of California, San Francisco, San Francisco, CA (3 patients); and L. Joseph Wheat, Indiana University, Roudebush VA Medical Center, Indianapolis, IN (11 patients).

From the University of Texas–Houston Medical School, Houston, Texas; Indiana University School of Medicine and Roudebush Veterans Affairs Medical Center, Indianapolis, Indiana; University of Alabama at Birmingham, Birmingham, Alabama; Methodist Hospital, Memphis, Tennessee; University of Missouri–Kansas City, Kansas City, and Washington University School of Medicine, St. Louis, Missouri; National Institute of Allergy and Infectious Diseases Mycoses Study Group, National Institutes of Health, Bethesda, Maryland; and Veterans Affairs Medical Center and University of Michigan Medical School, Ann Arbor, Michigan.

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Drafting of the article: P.C. Johnson, L.J. Wheat, G.A. Cloud, W. Dismukes.

Critical revision of the article for important intellectual content: P.C. Johnson, L.J. Wheat, G.A. Cloud, M. Goldman, D. Lancaster, D.M. Bamberger, W.G. Powderly, R. Hafner, C.A. Kauffman, W. Dismukes. Final approval of the article: P.C. Johnson, L.J. Wheat, G.A. Cloud, M. Goldman, D. Lancaster, D.M. Bamberger, W.G. Powderly, R. Hafner, C.A. Kauffman, W. Dismukes.

Provision of study materials or patients: P.C. Johnson, L.J. Wheat, G.A. Cloud, M. Goldman, D. Lancaster, D.M. Bamberger, W.G. Powderly. Statistical expertise: G.A. Cloud.

Obtaining of funding: W.E. Dismukes.

Administrative, technical, or logistic support: G.A. Cloud, R. Hafner, C.A. Kauffman, W.E. Dismukes.

Collection and assembly of data: G.A. Cloud, D.M. Bamberger.

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