JOURNAL OF CLINICAL MICROBIOLOGY, Oct. 1986, p. 625–628
0095-1137/86/100625-04$02.00/0

Vol. 24, No. 4

Outbreak of *Candida parapsilosis* Endophthalmitis after Cataract Extraction and Intraocular Lens Implantation

EUGENE McCRAY,[1]* NANCY RAMPELL,[1] STEVEN L. SOLOMON,[1] WALTER W. BOND,[1] WILLIAM J. MARTONE,[1] AND DENIS O'DAY[2]

Hospital Infections Program, Center for Infectious Diseases, Centers for Disease Control, Atlanta, Georgia 30333,[1] and Department of Ophthalmology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232[2]

Received 30 April 1986/Accepted 20 June 1986

Between November 1983 and January 1984, 13 cases of *Candida parapsilosis* endophthalmitis occurred in Florida, Georgia, and Tennessee in patients who had had an intraocular lens implantation (IOLI) or cataract extraction with an IOLI. This outbreak followed the introduction in July 1983 of a new brand of balanced salt solution (BSS) used as an intraoperative ophthalmic irrigating solution. This product was subsequently recalled because of intrinsic fungal contamination. A retrospective cohort study including 704 ophthalmology patients at risk for exposure to this brand of BSS revealed that definite exposure to that product was a significant risk factor for *C. parapsilosis* endophthalmitis ($P < 0.001$, Fisher exact test). A retrospective case control study including 203 control patients with definite exposure to BSS suggested that exposure to systemic steroids ($P = 0.007$, Fisher exact test) was an additional risk factor for *C. parapsilosis* endophthalmitis. Treatment modalities among the 13 patients included topical, intraocular, or systemic antifungal therapy (or a combination of these modalities) in 13 patients and vitrectomy in 10 patients. No patient had systemic symptoms or complete visual loss. Laboratory investigations showed a 6.7% overall contamination of the product with *C. parapsilosis*. After recall of the product by the manufacturer, no patients having a cataract extraction or IOLI at the institutions studied are known to have developed *C. parapsilosis* endophthalmitis.

Fungal endophthalmitis is an uncommon complication following intraocular lens implantation (IOLI). With the exception of two cases reported in 1962 (2) and a cluster of 13 cases reported in 1980 (6), recent published reports identify only individual cases of fungal endophthalmitis (3, 4, 8, 10). This report describes the nationwide epidemiologic investigation of the first documented epidemic of postoperative *Candida parapsilosis* endophthalmitis.

In September and October 1983, a cluster of cases of *C. parapsilosis* endophthalmitis occurred in California. An investigation was conducted by private consultants and officials of the state and local public health departments and the U.S. Food and Drug Administration (9a). During this investigation, it was determined that some unopened bottles of a new brand of eye irrigating solution, balanced basic salt solution (GBR-BSS) (lot 16738; Maurry Biological Co., Los Angeles, Calif.), may have been contaminated with *C. parapsilosis*. GBR is a brand name and should not be confused with the generic product, glutathione-bicarbonate-Ringers, a different solution sometimes referred to as GBR in the ophthalmology literature (1). Further laboratory investigations by the Food and Drug Administration and California state health authorities showed that GBR-BSS (lot 16738) was intrinsically contaminated with *C. parapsilosis*. On 11 November 1983, the distributor voluntarily initiated a recall of the product.

From October to December 1983, several patients in Tennessee, Florida, and Georgia who had undergone an IOLI or cataract extraction with an IOLI developed *C. parapsilosis* endophthalmitis. All the patients had been exposed to the same irrigating solution, GBR-BSS (lot 16738), before the recall notice on 11 November 1983 (4a). An epidemiological investigation was initiated to determine the clinical and public health impact of this product contamination.

MATERIALS AND METHODS

Active surveillance for cases. From a list of user accounts supplied by the distributor of GBR-BSS, all wholesale drug companies, hospitals, ambulatory clinics, and physicians that received the contaminated lot of the product from the distributor were identified. Each health care institution and practitioner in the southeastern states that had received GBR-BSS was contacted, and the following information was obtained: (i) the number of bottles of GBR-BSS of the implicated lot received, (ii) the number of bottles of GBR-BSS used, (iii) the number of bottles of GBR-BSS returned to the distributor following the recall notice, (iv) the number of patients exposed to GBR-BSS, and (v) the number of patients with *C. parapsilosis* isolated from ocular fluid after ophthalmological surgery.

Case definition and ascertainment. We defined a case as infection in any patient who had *C. parapsilosis* isolated from the aqueous or vitreous humor of the eye. Site visits were made to three institutions in Tennessee, four in Florida, and one in Georgia that had used GBR-BSS. At the institutions in Tennessee, microbiological records were reviewed from 1 January 1982 to 10 January 1984 for all isolates of *C. parapsilosis*. Ophthalmological surgery at these institutions was performed as an inpatient hospital procedure. At the institutions in Florida and Georgia, microbiological records were not reviewed because ophthalmological surgery was performed in ambulatory surgery clinics that did not have facilities for processing microbiological specimens. At these clinics, the specimens were sent to reference laboratories for processing, and patients with suspected *C. parapsilosis* endophthalmitis were referred to other institutions for diagnosis and treatment. The institutions to which patients with suspected postoperative en-

* Corresponding author.

TABLE 1. Distribution and utilization of GBR-BSS in California the southeastern United States, May to November 1983

State	No. of institutions	U of GBR-BSS received	U of GBR-BSS used[a]	U of GBR-BSS returned to distributor
Tennessee	3	288	179	109
Florida	4	306	180	91
Georgia	3	148	70	78
California	2	63	24	Unknown
Alabama	1	36	20	16
South Carolina	1	2	2	0

[a] The sum of units of GBR-BSS used and units of GBR-BSS returned to the distributor may not equal units of GBR-BSS received because some institutions did not return unused units of GBR-BSS to the distributor.

dophthalmitis were referred and the microbiology laboratories to which cultures were sent were contacted to verify the diagnosis of *C. parapsilosis* endophthalmitis.

The medical records of all case patients were reviewed for the following: age; sex; diagnosis; receipt of parenteral nutrition, intravenous therapy, antibiotics, eye irrigating solutions during surgery, and immunosuppressive therapy; date of ophthalmological surgery; location of surgery; type of surgical procedure; type of intraocular lens inserted during surgery; volume of eye irrigating solution used; recent history of nonophthalmological surgery (≤6 months); signs and symptoms of fungal endophthalmitis on follow-up examinations; diagnostic procedures; antifungal chemotherapy; and clinical outcome.

Cohort study. To test the association of cases with exposure to GBR-BSS, all patients who had an IOLI or cataract extraction with an IOLI during the period 8 June through 11 November 1983 were studied. At each cooperating institution, all patients who were potentially exposed to GBR-BSS were identified. Patients were categorized as having had definite, probable, or possible exposures to GBR-BSS according to the following criteria. (i) A patient had definite exposure if the billing or operative record documented the use of GBR-BSS during eye surgery or if the eye surgery was performed during a period when GBR-BSS was the only irrigating solution available at that institution and the operative record documented the use of an eye irrigating solution. (ii) A patient had a probable exposure if there was a miscellaneous billing charge for an unspecified eye irrigating solution during a period when another BSS with a unique billing number and GBR-BSS were both available at the institution. (iii) A patient had a possible exposure if eye surgery was performed which usually requires the use of an eye irrigating solution but for which there was no documentation.

Patients were considered ill if they met the case definition. Patients were considered not to be ill if they had no signs or symptoms of a fungal endophthalmitis or were symptomatic but had a negative aqueous or vitreous humor culture for *C. parapsilosis*. Five symptomatic patients who did not have cultures done were excluded from the analysis; all five were from the definite exposure group.

Case control studies. To identify risk factors for developing *C. parapsilosis* endophthalmitis among the group of patients with definite exposure to GBR-BSS during ophthalmological surgery, we selected as controls 203 patients with definite exposure to GBR-BSS during an IOLI or cataract extraction with an IOLI during the period 8 June through 8 November 1983, with neither signs nor symptoms suggestive of endophthalmitis. Potential risk factors sought in the case control study included the following: age; sex; medical illnesses; recent surgical procedure(s) (≤6 months before illness); receipt of parenteral nutrition, intravenous therapy, antibiotics, and immunosuppressive therapy, volume of GBR-BSS used; intraoperative complications; and type of intraocular lens inserted during eye surgery.

To determine whether patients having eye surgery during the outbreak period were comparable with patients operated on before GBR-BSS was available, we did a second case control study with historical controls. Four historical controls were chosen for each case patient based on the institution of the case patient. A total of 52 patients who had an IOLI or cataract extraction with an IOLI in the 6-month period prior to the use of GBR-BSS at each institution and who did not develop signs or symptoms of endophthalmitis were compared with the 13 case patients. These 52 patients were randomly selected from the surgery log at the corresponding institution for case patients. Cooperating institutions with no cases were not included in this analysis. We reviewed the charts of historical controls in the same manner as the charts for the first case control study.

Laboratory investigations. To confirm that GBR-BSS lot 16738 was intrinsically contaminated with *C. parapsilosis* and to estimate the overall contamination rate of the single production lot, we collected, in a statistically random manner, 246 bottles of GBR-BSS from the manufacturer and the Department of Health Services, Food and Drug Section, Los Angeles, Calif. A total of 42 of the 246 bottles were collected from a sample of 542 bottles of GBR-BSS at the California state facilities. The remaining 204 bottles were collected from a sample of 5,572 bottles of GBR-BSS stored in the warehouse of the manufacturer. Bottles of GBR-BSS stored at the California state facilities had been preselected by the manufacturer because they were reported turbid on macroscopic inspection (high-risk bottles). The rest of the bottles (low-risk bottles) had remained in storage at the warehouse. Each of the 246 bottles of GBR-BSS we selected was examined macroscopically at the Centers for Disease Control, Atlanta, Ga., for turbidity, and 25 ml from each bottle was cultured qualitatively for microorganisms by aseptic procedures. A quantitative pour plate assay was performed on each bottle with turbidity or sediment on macroscopic examination. *C. parapsilosis* was identified by standard methods (9).

RESULTS

Surveillance for cases. Sales and sample distributions of the product were made in five southeastern states and in California between 31 May and 11 November 1983. GBR-BSS was manufactured as a sterile irrigating BSS by Maurry Biological Co. of Los Angeles, Calif., for sale by a single distributor. All bottles manufactured were from lot 16738.

According to the manufacturer, 7,425 bottles were produced, and 7,232 were forwarded to the distributor. The product was distributed to 14 institutions in California and the southeastern United States (Table 1). Approximately 95% of the GBR-BSS shipped by the distributor was sent to Florida (39%), Tennessee (37%), and Georgia (19%); 95% of the GBR-BSS that was actually used on patients in the southern United States was used in Florida (40%), Tennessee (40%), and Georgia (15%).

Case ascertainment and description of patients. A total of 13 patients fulfilled our case definition; 8 in Tennessee, 4 in Florida, and 1 in Georgia (Fig. 1). All 13 cases had an IOLI or cataract extraction with an IOLI between 19 July and 8 November 1983 and developed symptoms between 1 Octo-

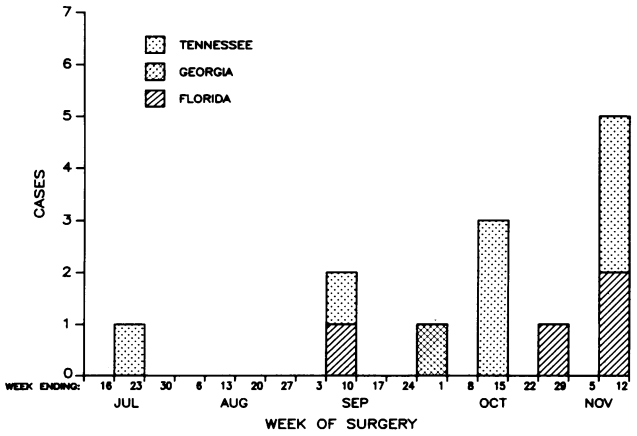

FIG. 1. Cases of *C. parapsilosis* endophthalmitis, by week of surgery and state, 11 July to 13 November 1983.

ber and 23 November 1983. The length of time from the date of surgery to date of onset of the first symptom ranged from 2 to 97 days, with a mean of 20.2 days (median = 9 days).

At the institutions investigated in Tennessee, Florida, and Georgia, all patients with potential exposure to the GBR-BSS had been contacted by their ophthalmologists after 11 November 1983 and were asked to return for a follow-up ophthalmological examination to look for signs of infection. This represented an unusual ascertainment by the ophthalmologists because these additional examinations would not routinely have been performed in all patients. Case patients reported the following symptoms: decreased vision (62%), eye pain (62%), red eye (54%), and visual floaters (15%). The most commonly documented signs identified by physicians were anterior chamber cells and flare (100%), keratic precipitates (85%), and ciliary injection (54%). Clinical signs of vitreous cells and vitreous "snowballs" were reported in five (38%) and four (31%) of the cases, respectively.

Treatment modalities varied among the 13 cases. All cases received topical steroids, six cases received subconjunctival or subtenons steroids, and only two cases received systemic steroids. Of the 13 cases, 11 received some type of antifungal therapy; intraocular amphotericin B was used in 11 cases, topical amphotericin B was used in 5 cases, and oral ketoconazole or flucytosine was used in 10 cases. A partial or extended vitrectomy was performed on 10 of the 13 cases.

Complications following therapeutic interventions for *C. parapsilosis* endophthalmitis included decreased visual acuity in six cases documented by ophthalmological examinations, retinal detachment in one case, and glaucoma in one case. The five remaining patients had no significant postoperative visual deterioration. At the time this investigation concluded, no patients had systemic symptoms or complete loss of vision in the affected eye. There was no sex predominance among cases; seven patients were male, and six patients were female.

TABLE 2. Likelihood of exposure in cases of *C. parapsilosis* endophthalmitis and patients exposed to GBR-BSS from 8 June to 11 November 1983

State	No. of institutions	No. of cases[a]	No. of patients exposed to GBR-BSS		
			Definite	Probable	Possible
Tennessee	3	8	104	51	171
Florida	4	4	200	0	21
Georgia	1	1	34	0	128

[a] All cases were in the definite exposure group.

TABLE 3. Risk factors for *C. parapsilosis* endophthalmitis in patients exposed to GBR-BSS in Tennessee, Florida, and Georgia from 8 June to 11 November 1983

Risk factor	No. of cases (%) (n = 13)	No. of controls (%) (n = 203)	Odds ratio	P^a
Receipt of systemic steroids[b]	6 (46)	28 (14)	5.4	0.008
Implantation of lens type 1	3 (23)	13 (6)	4.4	0.05

[a] Fisher exact test, one-tailed test.
[b] No data were available on two control patients.

Cohort study. In Tennessee, Florida, and Georgia, 338 patients were identified with definite exposure, 51 patients with probable exposure, and 320 patients with possible exposure to GBR-BSS (Table 2). All patients were at risk for exposure during the period 8 June through 11 November 1983, the time when GBR-BSS was available at the various institutions. The ophthalmological surgical procedures during which exposure occurred were IOLIs or cataract extractions with IOLIs. At the institutions studied, a group of patients undergoing the same ophthalmological surgical procedures who were definitely not exposed to GBR-BSS during the period of risk could not be identified for two reasons. (i) Several cooperating institutions used only GBR-BSS when it was available. (ii) Institutions using GBR-BSS and another BSS rarely documented which BSS was used during surgery. A total of 13 (3.9%) of 333 patients with definite exposure to GBR-BSS developed *C. parapsilosis* endophthalmitis, compared with none of 371 patients with only possible or probable exposure to GBR-BSS ($P < 0.001$, Fisher exact test, one-tailed).

Case control studies. In the first case control study, exposure to perioperative systemic steroids ($P = 0.007$, Fisher exact test, one-tailed) and exposure to lens type 1 ($P = 0.05$, Fisher exact test, one-tailed) were significantly associated with development of *C. parapsilosis* endophthalmitis (Table 3). In the second case control study, cases and historical controls did not differ in their exposure to perioperative systemic steroids and lens type 1.

Laboratories studies. Results of laboratory studies are shown in Table 4. All 35 turbid bottles revealed pure cultures of *C. parapsilosis* with a mean titer of 2.3×10^4 organisms per ml (range, 1.2×10^4 to 3.8×10^4 organisms per ml). Of the remaining 211 clear bottles, only 1 bottle (in the low-risk group) grew *C. parapsilosis* when cultured. Thus, when this sample was used for extrapolation to the entire production

TABLE 4. Intrinsic contamination rate of GBR-BSS with *C. parapsilosis*

Bottles examined (n)	Positive for *C. parapsilosis*	
	No. of bottles	% of total
Low-risk[a] bottles (204)	2	1.0
Turbid (1)	1	100
Clear (203)	1	0.5
High-risk[b] bottles (42)	34	81
Turbid (34)	34	100
Clear (8)	0	0

[a] Reportedly clear on macroscopic inspection by the manufacturer.
[b] Reportedly turbid on macroscopic inspection by the manufacturer.

lot, the overall contamination rate with *C. parapsilosis* was 6.7% (95% confidence intervals, 4.5 to 8.9%).

DISCUSSION

Epidemic postoperative fungal endophthalmitis is extremely uncommon. In the only previous report of epidemic fungal endophthalmitis, *Paecilomyces lilacinus* was isolated from the ocular fluid of 11 of 13 patients with suspected fungal endophthalmitis who had had previous cataract surgery with an IOLI (3). A total of 8 of the 13 infected eyes eventually required enucleation. The source of contamination was traced to a single production lot of sodium bicarbonate neutralizer used to rinse the intraocular lens before implantation.

In this outbreak, we showed a statistical association between definite, as opposed to probable or possible, exposure to GBR-BSS lot 16738 during eye surgery and subsequent development of *C. parapsilosis* endophthalmitis. GBR-BSS lot 16738 was found by the Food and Drug Administration and subsequently confirmed by our studies to be contaminated with *C. parapsilosis*. The intrinsic rate of contamination for GBR-BSS lot 16738 was estimated to be 6.7%. The ultimate source of the contamination of GBR-BSS lot 16738 during manufacture was not identified.

Other associated risk factors for *C. parapsilosis* endophthalmitis were identified in the first case control study. These were exposure to perioperative systemic steroids and exposure to lens type 1. Perioperative systemic steroids were given to patients only in institutions A and C in Tennessee, where 6 of the 13 cases occurred. Previous reports have shown that exposure to systemic corticosteroids is a predisposing factor for fungal endophthalmitis (5, 7). Systemic steroids may attenuate the host response, making the host more susceptible to infections by microorganisms of low virulence. In contrast to systemic steroids, which were used only at two institutions, topical steroids were administered to all case patients and all controls. With regard to the statistical association of *C. parapsilosis* endophthalmitis with lens type 1, it is unlikely that contamination of this lens type is responsible for this outbreak of *C. parapsilosis* endophthalmitis because only 3 of 13 case patients had this lens implanted and because this lens was used at only one institution.

The association between receipt of steroids and placement of lens type 1 was not maintained in the case control study in which case patients were compared with historical controls. Therefore, we believe that these factors may have been associated with cases only in conjunction with the microbiological insult of intraoperative contamination from the eye irrigating solution.

Problems encountered in delineating the extent of this outbreak were the indolent nature of the infections and the low infection rate. In most cases, the signs of inflammation were mild and nonspecific and had a gradual onset. Most patients had initial improvement on local steroid therapy, which led many ophthalmologists to suspect an aseptic uveitis, a condition that occurs after IOLI. In addition, physicians assume that products purchased as sterile are sterile. When infections occur with a low frequency following the use of a contaminated commercial product, a single physician may see only one or two cases. Unless infection control surveillance identifies a temporal cluster of infections in patients under the care of different physicians in different institutions, a single case may be interpreted as a known complication of the surgical procedure or as a problem in surgical technique, rather than an intrinsic contamination of a product.

The case control study with the historical control group was hampered by selection bias because patients whose surgery was performed while GBR-BSS was in use received additional follow-up ophthalmological examinations that would not have been performed routinely. Of the 13 patients with *C. parapsilosis* endophthalmitis, 5 (38%) appeared to have been detected by increased follow-up; i.e., the first sign or symptom of endophthalmitis was not documented in the medical records until after the opthalmologist was aware of the possible intrinsic contamination of GBR-BSS.

The frequent performance of a low-risk procedure that usually has a good outcome can have the effect of reducing the likelihood that health care professionals will easily be able to identify specific routine activities or interventions as risk factors for clusters of illness. As is true in other outbreaks, this fact underscores the need for assiduously detailed record keeping about treatment and procedures and for good infection control surveillance at the hospital level. Since the withdrawal of GBR-BSS, no patients operated on at the insitutions studied are known to have developed *C. parapsilosis* endophthalmitis.

ACKNOWLEDGMENTS

We thank Janice Haney-Carr, Betty W. Holland, and W. Ruth Pruitt for their laboratory assistance, John W. White for statistical support, and Irene Cason-Tucker for secretarial support.

LITERATURE CITED

1. **de Jong, P. T., and C. Strous, and J. P. Fildt Kok.** 1983. Glutathione bicarbonate Ringers intraocular irrigation fluid. Prospective double-blind study. Ophthalmologica **186**:35–40.
2. **Francois, J., E. De Vos, M. Hanssens, and M. Elewant-Rijsselaere.** 1962. Mycoses intraoculaires. Ann. Ocul. **145**:97–119.
3. **Gilbert, C. M., and M. A. Novak.** 1984. Successful treatment of postoperative Candida endophthalmitis in an eye with an intraocular lens implant. Am. J. Ophthalmol. **97**:593–595.
4. **Mosier, M. A., B. Lusk, T. H. Petit, D. H. Howard, and J. Rhodes.** 1977. Fungal endophthalmitis following intraocular lens implantation. Am. J. Ophthalmol. **83**:1–8.

4a. **O'Day, D. M.** 1985. Value of a centralized surveillance system during a national epidemic of endophthalmitis. Ophthalmology **92**:309–315.

5. **Painter, B. G., and H. D. Isenberg.** 1973. Isolation of *Candida parapsilosis*: report of two cases. Am. J. Clin. Pathol. **59**:62–65.
6. **Pettit, T. H., R. J. Olson, R. Y. Foss, and W. J. Martin.** 1980. Fungal endophthalmitis following intraocular lens implantation: a surgical epidemic. Arch. Ophthalmol. **98**:1025–1039.
7. **Ray, T. L.** 1980. Fungal infections in the immunocompromised host. Med. Clin. North Am. **64**:955–968.
8. **Samples, J. R., and P. S. Binder.** 1984. Contamination of irrigating solution used for cataract surgery. Ophthalmic Surg. **15**:6.
9. **Silva-Hutner, M., and B. H. Cooper.** 1980. Yeasts of medical importance, p. 562–576. *In* E. H. Lennette, A. Balows, and W. J. Hausler, Jr. (ed.), Manual of clinical microbiology, 3rd ed., American Society for Microbiology, Washington, D.C.

9a. **Stern, W. H., E. Tamura, R. A. Jacobs, V. G. Pons, R. D. Stone, D. M. O'Day, and A. R. Irvine.** 1985. Epidemic postsurgical *Candida parapsilosis* endophthalmitis. Clinical findings and management of 15 consecutive cases. Ophthalmology **92**:1701–1709.

10. **Stransky, T. J.** 1981. Postoperative endophthalmitis secondary to *Candida parapsilosis*. A case treated by vitrectomy and intravenous therapy. Retina **1**:179–185.