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A retrospective review of endophthalmitis due to coagulase-negative staphylococci

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SUMMARY We retrospectively reviewed 28 cases of postoperative endophthalmitis due to coagulase-negative staphylococci. There was an average delay between surgery and the acute presentation of 7·2 days (SD 3·3). All patients were treated with intraocular antibiotics (IOAB) or therapeutic vitrectomy with IOAB. In six of the 28 cases the organisms were resistant to gentamicin as measured by the Kirby-Bauer technique; none was resistant to cephalosporins. Isolates that had been stored by lyophilisation were reconstituted and tested by serial dilution; none was resistant to gentamicin, though two were borderline. The final visual acuity was 6/18 or better in 72% of the eyes.

In 1964 Theodore suggested that *Staphylococcus epidermidis* could be a causative organism in endophthalmitis.[1] Although *S. epidermidis* grew commonly about normal eyes, most physicians did not regard it as a pathogen. This was in spite of a report in 1898 by Gifford who described the abundance, persistence, and accessibility of this bacterium at the time of intraocular surgery.[2] In addition Gifford succeeded in recovering nearly 6/6 vision in a person with endophthalmitis following cataract extraction when he removed the purulent material and cultured *S. epidermidis*. In the modern literature Valenton *et al.* first reported isolation of *S. epidermidis* in 1973 from the aqueous in two cases of endophthalmitis after cataract extraction.[3]

Controversy centres on choices in management.[4–10] Because the organism is of low virulence, administration of periocular antibiotics may be sufficient therapy. When this is true, invasive procedures such as an intraocular injection of antibiotics and vitrectomy may cause more damage than the disease. On the other hand such non-invasive therapy assumes that the aetiological diagnosis can be made without culturing intraocular fluids. We prefer to make the diagnosis based on cultures of the vitreous and aqueous. For eyes judged to have severe inflammation we perform a vitrectomy.

We here retrospectively review the clinical courses of 28 cases referred with endophthalmitis due to coagulase-negative staphylococci after intraocular surgery. We also review four cases of endophthalmitis due to traumatic perforation of the globe. We collected the preserved isolates of coagulase-negative staphylococci and measured their sensitivity to antibiotics.

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Materials and methods

We reviewed all cases of endophthalmitis referred to the Bascom Palmer Eye Institute between 1973 and 1981. In 36 eyes coagulase-negative staphylococci were isolated from the intraocular fluids; however, only 32 records were available. There were 28 postsurgical and four post-traumatic patients. For six of the postsurgical cases we could not obtain the visual acuity six weeks after treatment. Therefore we here retrospectively review the 28 postsurgical cases and present clinical data on 22 cases.

Patients had both aqueous and vitreous samples collected and examined by techniques previously reported.[10–12] During the eight years that these patients were referred, sensitivities to antibiotics were routinely determined by the Kirby-Bauer agar-diffusion technique.[13] Twenty-six of the isolates were stored after lyophilisation. They were reconstituted, grown on blood agar, subcultured, and tested by serial dilution for minimum inhibitory concentrations of antibiotics with commercially available trays.[14]

Patients were managed by different faculty members at the Institute, and vitrectomies were performed by different surgeons. All patients were

treated with intravenous and topical gentamicin and a cephalosporin.

Results

For the 28 postsurgical cases of endophthalmitis there was a predominance (18/28) of intracapsular cataract extractions (Table 1). This reflects the operation of choice during this period of 1973 to 1981. In the last year extracapsular surgery (5/28) became more popular. We cannot calculate the incidence of endophthalmitis or the relative risk of the operations, since the total number of operations of either type performed at the referring hospitals was not available.

The majority (18/27) of patients presented after their initial surgery with a best vision of hand motion. Fewer (5/27) had only light perception. Three had finger counting, and one was 6/21. Where recorded (17/21), there was marked pain, and the vision decreased dramatically over the 24 to 48 hours preceding diagnostic paracentesis. Although the clinical appearance immediately preceding diagnosis was typical for endophthalmitis, most cases had a quiescent or subacute period before becoming acute. Thus there was a delay between the initial surgery or a subsequent separation of the incision and the diagnosis of 7·2 days (SD 3·3), with a range of 2 to 15 days, for 27 postsurgical cases. One exceptional case had a latent period of 139 days. The incision remained intact, and he had no surgery until the diagnostic paracentesis. This long delay is so different from that of all the others that it may represent a separate mechanism of disease. It was therefore arbitrarily excluded from the calculations. For the post-trauma patients the time between the perforation of the eye and the diagnosis was 2·5 days (SD 1·9).

Sixteen patients received one or more prophylactic antibiotics either topically or subconjunctivally at the time of surgery as follows: gentamicin 12, neomycin 8, chloromycetin 6. There were four patients for whom there was no record of treatment with prophylactic antibiotics. For the remaining eight of the 28 postoperative patients the records were not sufficiently complete to determine their perioperative therapy. With these limited, retrospective data there is no significant difference in the delay of presentation between the 16 who received antibiotics (7·9 days, SD 3·8) and the four who did not receive treatment (6·2 days, SD 1·8).

There was no significant difference in the delay from surgery to the diagnosis by culture for those patients who received topical and/or subconjunctival steroids at surgery. For the 17 who received steroids, the quiescent period was 7·8 days (SD 3·8) with a range of 2 to 15 days. For the six who got no steroids the delay was 6·5 days (SD 2·5). There were no data for five patients.

All vitreous specimens that were cultured were positive by criteria previously described.[10-12] However, fewer than half of the concomitant aqueous specimens were positive (Table 2). In no cases did bacteria grow in the aqueous and not in the vitreous aliquots. Likewise a Gram stain of the vitreous was frequently (68%) positive, but the Gram stain of the aqueous was infrequently (17%) positive.

When patients presented, sensitivities for antibiotics were measured for isolates by the Kirby-Bauer technique (Table 3). Only against cephalosporin was there no resistance. Against gentamicin 21% (6/28) were resistant.

The 26 isolates that had been preserved by lyophilisation were tested for their sensitivity to six

Table 1 *Type of surgery leading to endophthalmitis*

Intracapsular cataract extraction	13
Extracapsular cataract extraction	0
Extracapsular cataract extraction with Intraocular Lens	5
Intracapsular cataract extraction with Intraocular Lens	5
Secondary intraocular lens	1
Trabeculectomy/vitrectomy	1
Penetrating keratoplasty	1
Suture removal	1
Radial keratotomy	1
Total	28

Table 2 *Results of Gram stain and cultures of intraocular fluids*

	Number examined	*Number positive*
Gram stain		
Aqueous	12	2 (17%)
Vitreous	19	13 (68%)
Cultures		
Aqueous	21	9 (43%)
Vitreous	32	32 (100%)

Table 3 *Sensitivities to antibiotics measured by Kirby-Bauer technique*

	Number sensitive/ number tested	*Sensitive (%)*
Cephalosporin	28/28	100
Vancomycin	26/27	96
Gantrisin	25/27	93
Bacitracin	24/27	89
Gentamicin	22/28	79
Erythromycin	22/28	79
Oxacillin	20/28	71
Methicillin	17/25	68
Neomycin	14/22	64
Kanamycin	14/25	56
Tetracycline	12/26	46

antibiotics by measuring minimum inhibitory concentrations (MIC). The majority were sensitive (Table 4). Although 79% (22/28) had been sensitive to gentamicin by Kirby-Bauer techniques, by serial dilution all 26 were sensitive to gentamicin with MICs of 4 μg/ml or less. We repeated measurements by Kirby-Bauer on the four available, preserved isolates initially found to be resistant to gentamicin. Two remained resistant, with zones of 7 mm and 8 mm; their MICs were both 4 μg/ml. One was borderline, with a zone of 14 mm; its MIC was 2 μg/ml. A fourth isolate was sensitive with a zone of 25 mm; its MIC was less than 0·5 μg/ml. (SI conversion: μg/ml=mg/l.)

Clinical data for 22 of the 28 postoperative patients appear in Table 5. Six were not included because final visual acuity was not available. The data show that the final vision was 6/18 or better in the majority

Table 4 *Distribution of the 26 isolates as a function of minimum inhibitory concentration for each antibiotics*

	Minimum inhibitory concentration (μg/ml)							
	0·25	*0·50*	*1*	*2*	*4*	*8*	*16*	*>16*
	Sensitive	Resistant						
Ampicillin	19		3	2	2			
Clindamicin	23						1	2
Methicillin	2	13	4	2	3	1	1	0
Erythromycin	21						1	4
Gentamicin		23		1	2			
Chloramphenicol		5	13	1		1. Sensitive	6 Resistant	

Table 5 *Visual outcome, quiescent periods, and therapy for endophthalmitis secondary to surgery for 22 patients with at least six weeks' follow-up*

Final vision	*Initial vision*	*Days from initial surgery to diagnosis*	*Days from symptoms to diagnosis*	*Intravitreal antibiotics*	*Resistance to antibiotics*	*Steroids*	*Vitrectomy*
6/6	20/80	4	1	G,Z		SC,GT	
6/6	HM(2')	10	2	G,L		SC,GT	+
6/6	CF	(52)*					
		3	2	G,L		SC	+
6/9	HM(3')	8	3	G,L		SC	
6/9	HM(2')	14	2		G	PO,GT	
6/12	HM(2')	10	1	G,L		GT	+
6/12	LPP	4	1	G,Z		SC,GT	+
6/12	HM	(54)†					
		8	6	G,Z		GT	+
6/12	HM(1')	8	2	G,Z		PO,GT	
6/12	HM(2')	6	1	G,Z		GT	
6/15	Bare HM	NA	NA	G,L		SC,GT	+
6/15	3/200	9	2	NA		NA	+
6/18	HM	6	1	G,L		SC	
6/18	HM(1')	4	1	G,Z	G	SC	
6/18	HM(1')	9	1	G,L		SC,GT	
6/18	HM	(15)‡					
		3	1	G,L		SC,GT	+
LP	HM(1')	8	1	G,L		SC,GT	+
LP	HM(2')	5	2	G,L		PO	+
LP	CF(1')	139	123	G,Z	G	GT	+
LP	LPP	6	4	G,Z		GT	+
LP	HM(1')	9	1	G,L		SC	
Enucleated							
	Bare LP	4	2	G,Z		SC,GT	+

*Patient was doing well until 40 days after surgery, when he had an episode of vomiting. Vitreous wick was found and removed surgically on day 49.

†Patient was doing well until 46 days after surgery, when a suture was cut.

‡Patient was doing well until 12 days after surgery, when he slept without a shield; a gape in the wound was noted.

NA=not available. L=cephaloridine. Z=gentamicin and cefazolin. G=gentamicin. LP=light-perception. LPP=light-perception with projection. HM=hand motion at (feet). SC=subconjunctival dexamethazone. PO=oral prednisone. GT=drops of prednisolone acetate.

(16/22), yet only three presented with better than hand motion vision. The average delay in days between surgery and diagnosis for those with a final vision of 6/18 or better was 7·1 days (SD 3·2). Apart from the case with the unusually long delay, for those who attained a vision worse than 6/18 the delay was 6·4 days (SD 2·1).

At the time of diagnostic paracentesis steroids were given subconjunctivally (13/21), orally (3/21), and topically (15/21). No eye received intravitreal steroids. These data are insufficient to evaluate any correlation between their use and the visual outcome.

Most patients (13/22) had a therapeutic vitrectomy, and more than half (8/13) recovered 6/18 or better vision. A vitrectomy did not ensure a good final vision. In fact most (5/6) of those whose final vision was light perception or less had had a vitrectomy.

Discussion

The earliest reported case of recovery of 6/6 vision after culture-proved endophthalmitis with *S. epidermidis* was by Gifford in 1898.[2] He reasoned that the source must be the lids or conjunctiva. Therefore he examined various procedures in an attempt to sterilise the operative field. He concluded that it is impossible to eradicate the bacteria; the observation is true today. *S. epidermidis* is the bacterium most commonly found on the extracted lens[15] and is the commonest cause of postsurgical endophthalmitis.[9] Since the threat remains ever present, one must know its characteristics to be able to recognise and treat the infection effectively.

The rarity of endophthalmitis makes the prospective accumulation of cases for scientific investigation difficult. In addition it is hard to randomise treatment in this potentially devastating disease. Each ophthalmologist manages his patients in the way he considers best. We reason that we cannot identify the causative organism without culturing intraocular fluids. To await the results of the cultures for definitive diagnosis before instituting a therapy that has demonstrated effectiveness is to risk the demise of the eye.

A second judgment selects those with the severest inflammation. Because we suspect that they will have progressive damage to intraocular structures by inflammatory cells, or that they may not be sterilised completely by the injected antibiotics, or that they might have a more rapid recovery of vision, we perform a vitrectomy in selected cases based on the severity of the inflammation.[4 16] This treatment contrasts with the series reported by O'Day *et al.*[7] After obtaining intraocular fluids for culturing, they treated 18 consecutive postsurgical cases of endophthalmitis with *S. epidermidis* using combined antibiotic and corticosteroid therapy without intravitreal injection or vitrectomy. Of those, 78% achieved a final vision of 6/15 or better. In our 22 postoperative cases 55% achieved 6/15 or better and 72% obtained 6/18 or better. Of the 13 who also had a therapeutic vitrectomy 61% recovered 6/18 or better vision. This is similar to the results of Pauliafito *et al.*, who reported a final vision of 6/60 or better in three of five cases (60%) treated with both vitrectomy and intraocular antibiotics.[9]

The unusually long subacute phase is consistent with a low virulence and suggests that external factors can temporarily delay its toxic effects.[6] If this is true, one would expect a greater delay from surgery to diagnosis with the use of prophylactic antibiotics. When 16 patients received either topical or subconjunctival antibiotics peroperatively, the overall delay to diagnosis was 7·9 days. In four who received no antibiotics the quiescent period averaged 6·2 days. These delays are not statistically different. For the 17 patients who had steroids preoperatively the average subacute period was 7·8 days. The six who did not get steroids had an average quiescent period of only 6·5 days. The results in two groups are not statistically different.

At surgery there is a deliberate effort to cleanse the eyelids and conjunctiva. This contrasts with the treatment of trauma, where the tissues may harbour copious organisms. Likewise, one finds that the clinical courses for these two situations are different. After surgery the average duration of the quiescent period for all patients is 7·2 days and the final vision was better than 6/18 in 72%. After trauma the quiescent period averaged 2·5 days and all patients had 6/120 or less final visual acuity. These differences are likely related both to the intraocular trauma and to the quantity of bacteria inoculated into the eye.

For the diagnosis of endophthalmitis Forster has recommended culturing the vitreous.[8] Previously he found that 36% of samples of intraocular fluids showed no growth from the aqueous when organisms grew out of the vitreous. In this series of endophthalmitis due to coagulase-negative staphylococci 57% had no growth from the aqueous when the vitreous was positive. In addition the Gram stain of the vitreous demonstrated bacteria four times more often than the aqueous. Sampling the aqueous in suspected endophthalmitis is insufficient; it is important to obtain a vitreous sample.

There was a 21% (6/28) resistance to gentamicin as measured by Kirby-Bauer technique (Table 3). However, when the four available isolates were retested by serial dilution, none was resistant (Table 4). All patients also received a cephalosporin intraocularly,

and no coagulase-negative staphylococci were resistant to a cephalosporin by the Kirby-Bauer technique or serial dilution. Pauliafito *et al.* found that 37% of isolates were resistant by the Kirby-Bauer technique.[9] They did not measure the MIC. For bacitracin, methicillin, and erythromycin they measured percentages of resistant isolates as 16%, 32%, and 37%. This compares with 11%, 32%, and 21% respectively reported here. Multiply resistant coagulase-negative staphylococci can come from the lids, and not all are sensitive to cephalosporins.[17] Since the lids and conjunctiva may be a source of endophthalmitis, they should be cultured when endophthalmitis is suspected.

The resistance observed for these coagulase-negative staphylococci emphasises a need for determining species in isolates. Since subtyping is not normally done in most laboratories and hospitals, most organisms are reported as *S. epidermidis*. Resistance in *S. epidermidis* may be a manifestation of diversity in coagulase-negative staphylococci. In like fashion this lack of subtyping may explain variability in virulence. Here one relatively nonvirulent bacterium had a subacute phase of 139 days. It was arbitrarily excluded from the calculation of the average quiescent period because it was unique. None of these coagulase-negative staphylococci were subtyped.

Because this is a retrospective study, conclusions drawn from the data are not without bias. In addition these are disparate cases treated by multiple physicians employing surgical judgment, and the records are not complete. In spite of these deficiencies this review suggests the following. With endophthalmitis due to coagulase-negative endophthalmitis there may be a subacute period of a week before diagnosis. In trauma the delay may be less than half as long. Cultures of the vitreous are more often positive than those of the aqueous. We recommend culturing both. Antibiotic therapy with intravitreal injection and selected vitrectomy gives results similar to antibiotic therapy with no intraocular injection. Resistance to gentamicin occurs when sensitivity is measured by the Kirby-Bauer technique and not by serial dilution. Because of the possible resistance a cephalosporin is indicated.

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