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Factors Associated With Positive Microbial Culture in Patients With Endophthalmitis Based on Clinical Presentation and Multimodal Intraocular Sampling

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Purpose: The aim of this study was to identify the factors associated with positive culture sample in patients with endophthalmitis based on clinical presentation and multimodal intraocular sampling.

Design: Retrospective review.

Methods: A total of 259 subjects with a diagnosis of endophthalmitis presented to a tertiary ophthalmic referral center between 2006 and 2018. Patient demographics, presenting clinical findings and the results of aqueous and vitreous sampling were analyzed.

Results: Mean age was 64.2 (± 22.6) years with 52.9% female. Endophthalmitis followed cataract surgery in 84 eyes (32.4%) and was the most common precipitant; intravitreal injections were the next common cause involving 60 eyes (23.2%). Mean visual acuity on presentation was hand movements with a hypopyon present 134 eyes (52%). In total, 135 cases (52.1%) were culture positive. Aqueous sampling was performed in 112 eyes [culture positive 36 (32.1%)]; vitreous sample in 122 eyes [positive in 56 (45.3%)]. Vitrectomy was performed in 169 eyes with 149 sent for culture [70 (47.0%) positive]. A positive vitrectomy culture was observed in 14 eyes (36.9%) of 38, despite initial treatment with intravitreal antibiotics. Factors associated with positive culture were aqueous tap [odds ratio (OR) 2.06, $P = 0.02$], vitrectomy (OR 2.86, $P = 0.001$), and absent red reflex (OR 2.73, $P = 0.001$).

Conclusions: A multimodal approach to intraocular sampling should be considered in those presenting with endophthalmitis, with both aqueous tap and vitrectomy associated with an increased probability of achieving a positive culture.

Key Words: aqueous sampling, endophthalmitis, microbiology, vitrectomy, vitreous biopsy

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Infectious endophthalmitis is a potentially blinding disorder due to contamination of the ocular structures after exogenous trauma, including surgical and intravitreal therapies, or hematogenous spread from other infected tissue sites. Early clearance of the affecting organism is required to minimize tissue destruction, whereas identification of the offending organism and its sensitivity patterns allow a tailored approach to those that fail to respond to empiric antimicrobial treatment. However, identifying the pathogenic organism is not always possible with rates of positive culture ranging between 48% and 75% using traditional gram stain and culture methods.[1–3] These findings are primarily based on the results of a vitreous tap or biopsy, which can be difficult to obtain in the acute setting because of the possibility of a dry tap, whereas delays in access to theatre hinder a timely diagnostic and therapeutic vitrectomy. Although the aqueous humor is much easier to sample, the rates of positive culture are significantly lower with only 27% of aqueous specimens culture positive in the Endophthalmitis Vitrectomy Study (EVS).[4]

We have previously reported on the clinical outcomes of patients that presented to a major tertiary referral centre in—with endophthalmitis.[5] The aim of this follow-up study was to identify the factors associated with a positive intraocular culture sample based on clinical presentation and multimodal intraocular sampling.

METHODS

Subject Selection

This study received ethics approval from the review committee and adhered to the tenets of the Declaration of Helsinki. This was a retrospective review of all subjects presenting to a tertiary ophthalmic referral center with presumed endophthalmitis (in one or both eyes), between 1st January 2006 and 31st December 2018. Cases were identified through the admission records, theatre logbooks, and a computerized search of both aqueous and vitreous samples taken during this time period.

Data Collection

The clinical case notes and laboratory findings of all subjects were recorded onto a standard proforma. This included subject demographics, duration of symptoms, etiology (ie, post-injection, perioperative, among others), examination findings, laboratory results and management. Pertinent examination findings included Snellen visual acuity which was converted to LogMAR for the purpose of analysis. Intraocular inflammation was graded using the Standardization of Uveitis Nomenclature (SUN) and the presence/absence of a red reflex was also recorded.[6,7]

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Intraocular Sampling and Treatment

The timing and mode of intraocular sampling methods were recorded. An aqueous sample was obtained via an anterior chamber (AC) paracentesis (25G-30G). A vitreous tap was performed in the procedure room using a 20 to 25G needle located 3.5 to 4 mm behind the corneal limbus, and a vitreous biopsy using a 23 to 25G vitrector at the time of vitrectomy surgery. A vitreous tap (and injection of intravitreal antibiotics) was performed if there are expected delays in getting the patient to theater to perform an immediate (primary) vitrectomy. Patients who received intravitreal antibiotics and then subsequently proceeded to surgery were labeled as having a secondary vitrectomy. All samples were processed by the microbiology laboratory at ADHB where light microscopy examination and microbial culture were performed. Routine culture media included sheep's blood and GC saponin agar, brain heart infusion (BHI), BHI broth with gentamicin, and sabouraud dextrose agar (fungi). Additional media testing was performed if requested by the managing team. A positive growth was reported if the same organism was observed in more than one medium or a confluence of growth on $\geq$1 solid media.

All patients received intravitreal ceftazidime 2.25% and vancomycin 1% after an intraocular sample was taken (aqueous or vitreous) and/or at the conclusion of vitrectomy surgery.

Statistical Analysis

Data were entered into an Excel spreadsheet (Microsoft Corp, Redmond, WA) and analyzed in STATA version 15 (StataCorp 2017, College Station, TX). Continuous data are presented as median [interquartile range (IQR)] and categorical data as n (%). Logistic regression analysis was used to model predictors of positive culture result, examining role of poor best corrected visual acuity (BCVA) at presentation, AC cellular activity and absence of red reflex. All tests were 2-tailed and a P value of <0.05 was considered significant.

RESULTS

259 subjects were included for analysis. Subject demographics are described in Table 1 and causes of endophthalmitis are reported in Table 2. Mean visual acuity was hand movements (IQR 20/400 – HM) with a hypopyon present in 134 eyes (51.7%)

135 cases were culture-positive (52.1%), with 104 gram-positive (77.0%), 23 gram-negative (17.0%), and 8 fungal (5.9%). Culture results are listed in Table 3. *Staphylococcus* species were the most common in 68 cases (50.4%) followed by *Streptococcus* species in 28 cases (20.7%). The culture positive rate was 48.8% for cataract surgery, 41.7% for intravitreal injections, 46.2% for endogenous endophthalmitis, 59.1% for trauma, 42.9% for vitreoretinal surgery, 57.1% for glaucoma surgery, and 81.8% of corneal infections ($P = 0.094$).

Aqueous tap was performed in 112 eyes and positive in 36 (32.1%). Aqueous tap was positive in 36.4% of cataract surgery, 18.5% of intravitreal injections, 16.7% of endogenous, 40.0% of trauma, 37.5% of vitreoretinal surgery, 35.7% of glaucoma surgery, and 83.3% of corneal infections. Poor BCVA at presentation, AC cellular activity, presence of hypopyon, and absence of red reflex were not associated with likelihood of a positive aqueous tap. There was no association between use of topical antibiotics at presentation and the likelihood of a positive aqueous tap (OR 2.00, $P = 0.112$). Of the 135 culture-positive cases, 6 eyes (4.4%) had a positive aqueous tap in the setting of a negative vitreous tap, and 4 eyes (3.0%) had a positive aqueous tap in the setting of a negative vitrectomy. If we consider the vitreous tap as the criterion standard, the positive predictive value for aqueous tap was 83%.

TABLE 1. Patient Demographics and Clinical Findings on Presentation

	N = 259
Age, y	70.0 (IQR 56.9–79.7)
Female	137 (52.9%)
Ethnicity	
White	178 (68.7%)
Maori	28 (10.8%)
Pacific Island people	26 (10.0%)
Indian	13 (5.0%)
Other Asian	10 (3.9%)
African	2 (0.8%)
Latin American	1 (0.4%)
Unknown	1 (0.4%)
Duration of symptoms	2 days (IQR 1–3)
Presenting BCVA	HM (IQR 20/400–HM)
Hypopyon	121 (54.0%)
Anterior chamber cells	
0	4 (1.8%)
0.5	2 (0.9%)
1	14 (6.3%)
2	14 (6.3%)
3	33 (14.8%)
4	156 (70.0%)
Red reflex present	87 (38.5%)

BCVA indicates best corrected visual acuity; HM, hand movements; IQR, interquartile range.

TABLE 2. Etiology of Endophthalmitis

Aetiology	**No.**	**%**
Cataract surgery	84	32.4
Phacoemulsification	81	
ECCE	1	
IOL exchange	1	
IOL removal	1	
Intravitreal injection	60	23.2
Anti-VEGF	50	
IVTA	10	
Endogenous	39	15.1
Trauma	22	8.5
Vitreoretinal surgery	21	8.1
Vitrectomy	19	
Removal of oil	1	
Scleral buckle	1	
Glaucoma surgery	21	8.1
Trabeculectomy	18	
Tube	2	
MIGS	1	
Corneal infection or surgery	11	4.2
Microbial keratitis	5	
Corneal transplant	4	
Corneal melt	2	
Orbital infection	1	0.3

ECCE indicates extracapsular cataract extraction; IOL, intraocular lens; IVTA, intravitreal triamcinolone or triesence; MIGS, minimally invasive glaucoma surgery; VEGF, vascular endothelial growth factor.

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TABLE 3. Culture Results

Culture result	No. (n = 135)	%
Gram positive	104	77.0
Staphylococcus epidermidis	38	28.1
Staphylococcus aureus	9	6.7
Staphylococcus lugdunensis	9	6.7
Staphylococcus oralis	7	5.2
Coagulase-negative staphylococcus	5	3.7
Streptococcus agalactiae	5	3.7
Streptococcus dysgalactiae	4	3.0
Streptococcus Lancefield Group C	4	3.0
Streptococcus mitis	3	2.2
Streptococcus parasanguinis	3	2.2
Streptococcus pneumoniae	2	1.5
Streptococcus pyogenes	2	1.5
Streptococcus salivarius	2	1.5
Streptococcus sanguinis	2	1.5
Streptococcus viridans	1	0.7
Enterococcus faecalis	1	0.7
Corynebacterium Group G	1	0.7
Corynebacterium jeikeium	1	0.7
Clostridium perfringens	1	0.7
Aerobic sporing bacillus	1	0.7
Rothia dentocariosa	1	0.7
Mycobacterium chelonae	1	0.7
Granulicatella adiacens	1	0.7
Gram negative	23	17.0
Haemophilus influenzae	7	5.2
Pseudomonas aeruginosa	5	3.7
Klebsiella pneumoniae	4	3.0
Serratia marcescens	3	2.2
Moraxella morganii	3	2.2
Escherichia coli	1	0.7
Fungi*	8	5.9
Aspergillus fumigatus	2	1.5
Candida albicans	2	1.5
Candida parapsilosis	1	0.7
Candida rugosa	1	0.7
Fusarium solani	1	0.7
Scedosporium apiospermum	1	0.7

*Two cases received vitrectomy plus intravitreal amphotericin, four eyes received systemic antifungals plus tap/inject with intravitreal antibiotics and two eyes received systemic antifungals plus vitrectomy.

Vitreous tap was attempted in 144 eyes but was dry in 22 (15.3%). In those with a successful tap, 56 (45.9%) were culture positive. Vitreous tap was culture positive in 47.2% of cataract surgery, 31.4% of intravitreal injections, 37.5% of endogenous, 50.0% of trauma, 50.0% of vitreoretinal surgery, 70.0% of glaucoma surgery, and 83.3% of corneal infections. On univariate analysis the after were associated with increased likelihood of positive vitreous tap: poor BCVA at presentation [odds ratio (OR) 2.175, $P = 0.009$]; AC cellular activity (OR 2.405, $P = 0.009$); and absence of red reflex (OR 3.875, $P = 0.001$). On multivariate analysis, only absence of red reflex remained significantly associated with positive vitreous tap (OR 2.808, $P = 0.023$).

Vitrectomy was performed in 169 eyes (primary in 77, secondary in 92). Median time to secondary vitrectomy was 24 hours (IQR 17–72). A specimen was sent for culture in 149 eyes and was positive in 70 (47.0%). 47.7% of primary vitrectomy specimens were culture positive and 45.9% of secondary vitrectomy specimens ($P = 0.826$). Specimens were sent for 38 subjects for both vitreous tap and secondary vitrectomy. Of these, 13 (34.2%) were culture negative for both, 11 (28.9%) had positive vitreous tap only, 5 (13.2%) had a positive vitrectomy culture despite negative vitreous tap, and 9 (23.7%) were positive for both vitreous tap and vitrectomy culture. For those who had secondary vitrectomy, median time from vitreous tap and inject to vitrectomy was 24.5 hours (IQR 19–72). The rate of positive vitrectomy culture was 55.6% for those receiving vitrectomy 0 to 12 hours after tap and inject, 62.5% for more than 12 to 24 hours, 16.7% for more than 24 to 48 hours, and 37.5% for >48 hours. On logistic regression analysis, only absent red reflex was associated with an increased risk of positive vitrectomy culture (OR 2.935, $P = 0.006$). There was no association with poor BCVA at presentation or severity of AC activity.

Median time to injection of intravitreal antibiotics was 4 hours (IQR 1–4). Time to injection was shorter if vitreous tap and inject was the primary procedure (median 3 hours IQR 1.6–5.5) compared with if vitrectomy was the primary procedure (median 4.5 hours IQR 2.9–9.4) ($P = 0.002$).

Factors associated with a positive culture from any of the intraocular specimens sent are reported in Table 4. On multivariate analysis, the following were associated with increased likelihood of positive culture: aqueous tap (OR 2.061, $P = 0.020$); vitrectomy (OR 2.864, $P = 0.001$); and absent red reflex (OR 2.732, $P = 0.001$).

DISCUSSION

In our study of 259 eyes with a clinical diagnosis of endophthalmitis, the rate of culture positive samples was 50%. The culture yield through vitreous sampling was 47% which is less than an earlier publication from our institution (63%) and that reported in the EVS (69%).[1,5] However, the rates of positive aqueous culture were similar to the EVS and comparable to more a more recent publication by de Liano et al where 32% were culture-positive.[4,8] The majority of cases were attributed to recent intraocular surgery; however, 23% were post-injection-related

TABLE 4. Clinical Factors and Ancillary Investigations Associated With Positive Culture

	Univariate		Multivariate	
	OR	*P* value	OR	*P* value
Aqueous tap	1.481	0.120	2.061	0.020
Vitreous tap	1.159	0.454		
Vitrectomy	2.829	<0.001	2.864	0.001
AC cells	1.738	0.001	1.289	0.161
Absent red reflex	3.03	<0.001	2.732	0.001
BCVA presentation	1.885	0.001	1.212	0.444

AC indicates anterior chamber; BCVA, best corrected visual acuity; OR, odds ratio.

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which is an increase from our earlier publication (<7%) in keeping with international trends given the rise in number of intraocular injections performed worldwide.[9,10] With the results of a vitreous tap set as the criterion standard, we found that a positive aqueous tap (OR 2.1), vitrectomy/vitreous biopsy (OR 2.8), and absent red reflex were associated with a positive vitreous culture on multivariate analysis.

Although the diagnosis of endophthalmitis is made clinically, identification of the responsible organism through culture methods not only confirms the diagnosis, but allows sensitivity analysis to be performed. This is most useful for patients who fail to improve after initial broad-spectrum intravitreal antibiotics due to atypical or resistant organisms. Furthermore, microbial identification also assists with identifying commonality and possible causes during an outbreak of cases, and guides treatment protocols at a time when antimicrobial resistance is on the rise.[11] A 2018 publication of bacterial sensitivities in the Auckland region found that the majority of Gram-positive bacteria, which constituted 70% of culture-positive cases, were sensitive to Vancomycin in vitro.[12] Although the vast majority of Gram-negative bacteria (including *P aeruginosa*) were sensitive to Ceftazidime, up to 30% of selected isolates of *E coli* and *K pneumoniae* were resistant to the agent.[13] Although the concentration of intravitreal antibiotics is typically 50 times higher than the mean inhibitory concentration for most bacteria, endophthalmitis caused by antibiotic resistant organisms generally have poorer visual outcomes and thus identification of the responsible organism is important.[14,15]

Identifying the causative organism is dependent on a number of factors including the severity of intraocular inflammation, sampling techniques, and microbiological analysis methods. The severity of intraocular inflammation can be graded using clinical signs and ancillary tests.[6,7,16] Despite its simplicity, we found that vitritis sufficient to obscure the fundal red reflex was strongly associated with positive microbial culture on both uni- and multivariate analysis. Although other clinical factors such as presenting visual acuity and duration of symptoms have been shown to correlate with positive culture results, we did not observe these associations in our study.[17]

A vitreous sample has long been considered the criterion standard for identifying the responsible pathogen in endophthalmitis, either via vitreous tap or biopsy.[4] Despite being more accessible, the diagnostic yield from an aqueous sample is lower, with sensitivities of 38% reported in the literature.[8] This is attributed to a lower obtainable sample volume, rapid regeneration time, and a less favorable medium for microbial proliferation compared with the vitreous. From our study, the aqueous sample has a diagnostic in 8% of all positive cases when the vitreous tap or vitreous biopsy was culture-negative. The positive predictive value for aqueous tap in our study was 83%, with similar values reported in other studies (as high as 95%) of post-surgical endophthalmitis, where the majority involved anterior chamber procedures like cataract surgery or corneal infections, as was also noted in our study.[8] In contrast, a vitreous tap can be technically challenging in the acute setting with the possibility of obtaining a dry tap (15% in our study) if the clinician is unable to access a pocket of liquefied vitreous, due to the patient's anatomy (nominal amount of liquefied vitreous present) or poor surgical technique. A vitreous biopsy overcomes this problem and provides a larger diagnostic specimen. Since 2003, we have used the technique described by Russell and Polkinghorne where a sterile tube is used in the aspiration line of the vitrector, which avoids the risks associated with excessive manual aspiration by the assistant surgeon when an undiluted sample is being collected.[18] To avoid the risk of hypotony in this setting, Mura et al[19] described their technique of performing complete vitrectomy under an air infusion. Other authors have advocated culturing the contents of the vitreous cassette after a complete vitrectomy where the causative organism was cultured in 76% to 43% in those who underwent a core biopsy alone.[20] Furthermore, a complete vitrectomy allows the collection of cortical vitreous to provide a much higher cellular count than biopsy of the core alone.[21] Although these earlier studies report on the importance of collecting an undiluted sample, Chiquet et al found no difference in the diagnostic yield between undiluted and diluted samples where both culture and polymerase chain reaction (PCR) amplification of microbial DNA segment techniques were used.[22]

The use of molecular methods such as PCR has been shown to increase the number of samples with a microbiological diagnosis and reduce the wait time for laboratory confirmation. PCR amplification of bacterial (16S rDNA) or fungal (18S rDNA) was historically used for research purposes. However, the diagnostic yield from aqueous humor and vitrectomy samples with traditional culture methods has been demonstrated to increase from 50% to 72% when combined with PCR testing.[23,24] Furthermore, PCR techniques allowed a microbiological diagnosis in 25% of cases that were reported as culture-negative.[24] Although bacterial and fungal PCR is available at our hospital laboratory, it is not routinely performed and reported on for intraocular samples.

Although the rates of positive culture were higher after a vitreous sample, the yield from a vitreous tap or biopsy in our study was comparable at 46% and 47%, respectively, with similar results reported in the literature.[4] Although the EVS found no difference in visual outcomes between tap and inject versus vitrectomy for those with Hand Motions vision or better, a lower re-culture rate was noted in eyes that underwent vitrectomy (13% vs 71%). A vitrectomy not only reduces the bacterial load but removes the inflammatory debris and biofilms, which hinder the passage and action of intravitreal antibiotics otherwise.[25] In our study, we found that 37% of eyes had a positive vitrectomy culture, despite initial treatment with intravitreal antibiotics. Despite the advantages of early vitrectomy, the challenges associated with access to theatre resulted in a longer delay in time to treatment for patients undergoing primary vitrectomy (4.5 hours) compared with those that received intravitreal antibiotics alone (3 hours).

This is the largest study of the etiology, clinical presentation, and culture results of endophthalmitis in New Zealand. We will present the surgical and clinical outcomes of patients within this cohort in a subsequent article. The retrospective nature of our study design limited our ability to assess other signs on clinical presentation, such as an afferent pupillary deficit, which have also been associated with positive culture in previous publications.[17] Furthermore, we were unable to report on microbial sensitivity as these results were either not available or reported for all patients. Routine use of PCR testing may have allowed a microbiological diagnosis in a greater number of cases; however, this was not reported or performed routinely by our laboratory service.

In conclusion, a multimodal approach to intraocular sampling should be considered in patients presenting with

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endophthalmitis. The study highlights that taking an aqueous tap taken at the time of a vitreous sample increases the likelihood of obtaining a positive culture. The routine use of molecular diagnostic techniques in conjunction with traditional culture methods should be employed to improve the probability of identifying the pathogenic organism.

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