Microbiological sampling has limited value in managing acute postoperative bacterial endophthalmitis: a multicentre study in the United Kingdom

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Synopsis

Microbiological sampling has limited value in managing acute postoperative bacterial endophthalmitis resulting from any intraocular procedure in a large cohort of patients from across the United Kingdom.

Abstract

Aims: To determine whether microbiological testing impacts clinical management in acute postoperative endophthalmitis.

Methods: Multicentre retrospective cohort study encompassing five tertiary centres in the United Kingdom. Patients presenting with acute postoperative endophthalmitis with at least four weeks follow-up were included. The main outcome was the proportion with a change in management (defined as further intravitreal antibiotic therapy and/or further surgical intervention within four weeks of the initial treatment) and the rationale for this change.

Results: 190 eyes of 189 patients were included. Patients presented at a median of five days postoperatively (IQR 3-10). Sampling was predominantly obtained via vitreous tap alone (80/190, 42%) or with both vitreous and anterior chamber tap (84/190, 44%). Over half were culture-positive (107/190, 56%), and only bacterial pathogens were isolated. Culture-positive cases with available antibiotic sensitivity data demonstrated in vitro sensitivity to at least one of the empirical intravitreal antibiotics administered. Seventy-six eyes (40%) had a change in management within four weeks of the initial treatment. These additional procedures took place within 48 hours of initial treatment in 46% (35/76) of patients. The main reasons were a lack of clinical improvement (46/76, 61%) or clinical deterioration (18/76, 24%); none of these changes were prompted or guided by culture or sensitivity results.

Conclusions: Microbiological sampling was of limited clinical utility in this series. In patients presenting with suspected acute bacterial endophthalmitis, if microbiological sampling might pose any delays to treatment, consideration should be given to immediate intravitreal antibiotic treatment without sampling to optimise visual outcomes.

What is already known on this topic - summarise the state of scientific knowledge on this subject before you did your study and why this study needed to be done

- Endophthalmitis cases are commonly managed with “tap and inject”
- There is little evidence on the optimal management of endophthalmitis after the initial “tap and inject”
- Vitreous culture results from cases of endophthalmitis secondary to intravitreal anti-VEGF injections or cataract surgery from a single centre in the USA had a limited effect on subsequent management

What this study adds - summarise what we now know as a result of this study that we did not know before

- Microbiological sampling did not influence the management and course of acute postoperative bacterial endophthalmitis from **any** intraocular procedure, in a large cohort of patients from across the UK
- Instead, additional treatment (e.g. vitrectomy, further intravitreal antibiotics) tended to be guided by clinical signs

How this study might affect research, practice or policy - summarise the implications of this study

- In patients with suspected acute bacterial endophthalmitis without atypical features, if attempting taps might pose any delays to treatment, immediate intravitreal antibiotic treatment without sampling should be considered to optimise visual outcomes.
- This is particularly important for patients presenting outside standard working hours or to peripheral units without ophthalmology cover, where delays are likely.

Introduction

Exogenous endophthalmitis is a rare but visually devastating complication that may result from any penetrating intraocular procedure. Although treatment protocols vary, sampling intraocular fluid for microbiological testing invariably forms a key part of initial management, alongside empirical intravitreal antibiotics. Guidelines from institutions such as the Royal College of Ophthalmologists in the United Kingdom (UK) and the European Society of Cataract and Refractive Surgery (ESCRS) recommend performing aqueous fluid or vitreous sampling in such cases.[1,2]

Vitreous taps are preferred to anterior chamber (AC) taps, as the latter have a lower yield and a lower sensitivity and specificity, although they may serve as a helpful adjunct.[3,4] Obtaining a vitreous sample can be painful in an already inflamed eye, and challenging in eyes without liquefied vitreous, resulting in 'dry' vitreous taps if simple needle aspiration without cutting is attempted. In addition, microbiological yield is only positive in approximately half of successful taps (range: 18-62%).[5–9] While pars plana vitrectomy (PPV) may provide a larger volume for microbial testing and theoretically improve yield, evidence for this assumption is limited and PPV is not commonly performed first-line (if vision is better than perception of light) due to a lack of consensus about the risks versus benefits.[10]

At the same time, there are no established treatment protocols regarding the subsequent management of endophthalmitis after the initial 'tap and inject' procedure. The general (and currently non-evidence based) consensus is to consider further intravitreal antibiotics or PPV if there is no improvement or clinical deterioration 48 hours after initial treatment.[11] This typically occurs before culture results become available.

This raises the question: is microbiological sampling actually useful for the management of acute postoperative endophthalmitis? Do the results affect clinical practice? Studies from a single eye hospital in the United States (US) have suggested that vitreous culture results had a limited effect on clinical outcome in cases related to intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections or cataract surgery.[12,13] In this study, we aimed to explore whether and how microbiological sampling affects the subsequent management of patients presenting with acute postoperative endophthalmitis resulting from any intraocular procedure in the United Kingdom (UK).

Methods

This was a multicentre retrospective study involving five large geographically distant tertiary eye centres in the UK: Oxford Eye Hospital, Sunderland Eye Infirmary, Moorfields Eye Hospital, Royal Hallamshire Hospital, and Southampton General Hospital (Figure 1). The study was registered as a clinical audit and was exempt from formal ethics approval.[14]

Patient Selection

All consecutive patients presenting with acute postoperative endophthalmitis from January 2016 to July 2022 were identified. This was defined as severe intraocular inflammation due to infection occurring within six weeks of any intraocular surgery or procedure.[15] The initial diagnosis was made clinically, based on typical signs and symptoms such as pain, redness, loss of vision, hypopyon, intraocular inflammation, hazy media, supported by adjunctive B-scan ultrasonography.[2,5] Exclusion criteria are detailed in Supplementary S1.

Endophthalmitis Management

Initial management included a ‘tap and inject’ procedure (sampling of intraocular fluids followed by intravitreal antibiotic injection) detailed in Supplementary S2.

A change in clinical management was defined as further intravitreal antibiotic therapy and/or further surgical intervention within four weeks of the initial treatment. The decision to institute these changes were made by the treating clinician.

Data Extraction and Outcomes

Pseudonymised data were extracted from the local departmental electronic medical record system or paper records. This included patient demographics (age at presentation, gender, comorbidities); clinical characteristics (aetiology, initial management, microbiological results, change in clinical management with rationale); visual acuity (VA) at baseline, presentation, and final follow-up; and final outcomes including complications.

Logarithm of the minimum angle of resolution (logMAR) VA was used to facilitate analysis. VA recorded in Snellen fractions were converted to the appropriate logMAR equivalent. In accordance with the convention utilized by the National Ophthalmology Database audit, counting fingers (CF), hand movements (HM), perception of light (PL), and no perception of light (NPL) were assigned logMAR equivalents of 2.1, 2.4, 2.7, and 3.0 respectively.[16]

Statistical Analysis

All data were collected and recorded in a standardized Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, WA). Data analysis was performed using R version 4.4.0 (R Core Team, 2024). Outcomes were considered statistically significant at a level of $p<0.05$.

Continuous data were described with the median and interquartile range (IQR). The χ^2 test was employed to conduct univariate analyses for categorical data, and the Mann-Whitney U test for non-parametric continuous data after confirming a non-normal distribution with the Shapiro-Wilk test. Pre-specified sensitivity analyses were conducted

compare patients with missing antibiotic sensitivity results and those with recorded sensitivities.

Multiple logistic regression was employed to evaluate the predictors of a poor visual outcome, defined as logMAR 1.0 or worse according to the World Health Organisation's definition for severe visual impairment,[17] and of developing a retinal detachment (RD). Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated, and the final models were assessed for fit with area under receiver operating characteristic curve (AUROC).

Results

Patient cohort

We identified 190 eligible eyes (189 patients) presenting with acute postoperative endophthalmitis across five tertiary eye centres (Figure 1; Supplementary Figure 1). The median age was 76 years (IQR 64-82). The cohort comprised more female (106/189, 56%) patients. Patients presented at a median of five days postoperatively (IQR 3-10), after being symptomatic for a median of one day (IQR 1-3). Intravitreal injections accounted for most cases (110/190, 58%), followed by cataract surgery (42/190, 22%) and vitreoretinal procedures (23/190, 12%), while cases from other subspecialty procedures were less frequent (Figure 2A).

Initial management

All patients underwent a ‘tap and inject’ procedure (sampling of intraocular fluids followed by intravitreal antibiotic injection). Sampling was predominantly obtained via both vitreous and AC tap (84/190, 44%), followed by vitreous tap alone (80/190, 42%), PPV with vitreous biopsy (13/190, 7%, all in eyes with HM vision or worse), and AC tap only in cases of unsuccessful vitreous taps (13/190, 7%). Of the 164 eyes that underwent a vitreous tap, the majority were sampled by needle aspiration (145/164, 88%) and the remainder by mechanical cutter (19/164, 12%) (site-specific protocol).

In terms of intravitreal antibiotics, 65% (124/190) received vancomycin and ceftazidime. The remainder received vancomycin and amikacin - this comprised all patients treated at Moorfields Eye Hospital according to local protocols, and three patients at the other sites who were allergic to penicillin or cephalosporins.

Microbiological results

Microbiological analysis demonstrated that approximately half of the cases were culture-positive (107/190, 56%), of which the majority were gram-positive organisms (93/107, 87%). *Staphylococcus epidermidis* was the most commonly isolated organism (n=36), followed by coagulase-negative *Staphylococcus* (n=13) and *Staphylococcus aureus* (n=10). *Pseudomonas aeruginosa* (n=6) and *Serratia marcescens* (n=5) were the most common gram-negative organisms.

For culture-positive cases, antibiotic sensitivity results were available for 80% (86/107). There were two cases of *Staphylococcus epidermidis* endophthalmitis which were resistant to vancomycin but sensitive to amikacin (the other intravitreal antibiotic given empirically at presentation), and one of *alpha-haemolytic streptococcus* resistant to amikacin but sensitive to vancomycin. Overall, all cases were sensitive to at least one empirically chosen antibiotic administered intravitreally at presentation. Antibiotic sensitivity data was unavailable for the remaining cases (21/107, 23%). Sensitivity analyses demonstrated no statistically significant difference between cases with and without recorded antibiotic sensitivity results, in terms of demographic characteristics, precipitating procedure, VA at presentation, final VA, or whether a change in management occurred (Supplementary S3).

Change in clinical management

Seventy-six eyes (40%) had a ‘change in management’, defined as further procedures (such as further intravitreal antibiotic therapy or surgical intervention) within four weeks of initial empirical treatment. The median time between initial treatment to further procedure was three days (IQR 2-5), with 46% (35/76) of procedures occurring within two days of presentation.

The majority had PPV with intravitreal antibiotics +/- AC washout (49/76, 64%). Another 30% (23/76) had a repeat intravitreal antibiotic injection of vancomycin, ceftazidime, or amikacin, of which six had further procedure(s) after the repeat injection - one penetrating keratoplasty for corneal melt, one AC washout, and four further PPV with intravitreal antibiotics. Four cases (5%) required other procedures related to complications of endophthalmitis or the precipitating procedure (one each of revision of leaking scleral flap, scleral patch graft for scleral melt, evisceration for uncontrolled inflammation and pain, and evisceration for scleral perforation) within the four-week period after initial treatment (Figure 2B).

Changes in management were primarily prompted by lack of clinical improvement and/or the presence of severe inflammation (46/76, 61%), or clinical deterioration (18/76, 24%). In six cases (8%), a clinical decision was made to administer further treatment to clear vitreous debris and/or speed up recovery despite some clinical improvement. In four cases (5%), surgery was required to manage the complications of endophthalmitis or precipitating procedure, as detailed above. The rationale for treatment was unavailable for the remaining two cases. Culture and sensitivity results were not a factor in the decision-making process prompting these further procedures.

Visual outcomes

The median VA was 2.40 logMAR (IQR 1.78-2.40) at presentation, with 57% (109/190) presenting with HM vision or worse. The median VA improved to 0.90 (IQR 0.32-2.10) at final review. Patients who underwent a change in management had worse VA at initial presentation (2.40 logMAR, IQR 2.40-2.40 vs. 2.40, IQR 1.30-2.40; p=0.0005) than those who did not. These patients continued to have poorer final VA (1.00 logMAR, IQR 0.60-2.40 vs 0.78, IQR 0.30-1.32, p=0.007).

Positive microbiological cultures were associated with worse final VA (p=0.004) as well as a poor visual outcome (defined as logMAR 1.0 or worse) (p=0.023) on univariate analysis. However, in a multivariate regression model which adjusted for other potentially relevant explanatory variables such as age, gender, primary causative procedure, presenting VA, and microbiological yield, worse presenting VA was the only predictor for a poor visual outcome (OR 3.1, 95%CI 1.6-5.6, AUROC 0.732).

Complications

There were 22 cases of RDs (22/190, 12%), of which five were total RDs. For the 164 eyes that underwent vitreous taps at presentation, there was a non-significant trend towards higher rates of RDs with needle aspiration compared to mechanical cutter biopsy (n=22/145, 15% vs n=0/19, 0%, p=0.156). In a multivariate regression model which adjusted for other potentially relevant explanatory variables including age, gender, primary causative procedure, microbiological yield, further intravitreal antibiotics and further PPV within four weeks (for clinical reasons related to the endophthalmitis rather than a RD), undergoing a further PPV was the only predictor for developing a RD (OR 3.3, 95% CI 1.2-9.5, AUROC 0.767).

Overall, five patients underwent evisceration.

Discussion

Intraocular fluid sampling had minimal impact on clinical management in this cohort. Changes in management were based on clinical findings rather than microbiological results, and positive bacterial cultures demonstrated in vitro sensitivity to at least one of the empirical intravitreal antibiotics administered.

Microbiological testing remains the gold standard for many ocular infections. Not obtaining these samples may therefore seem counterintuitive for many clinicians; however, it is important to examine the evidence behind this practice.

The arguments for microbiological testing

Initial management of acute postoperative endophthalmitis appears to have followed on from the Endophthalmitis Vitrectomy Study (EVS), a landmark randomised multicentre trial conducted between 1990-1994 comparing 'tap and inject' versus early PPV for post-cataract surgery endophthalmitis.[10,15]

Further arguments for microbiological sampling include maintaining intraocular pressure (IOP) control by performing AC or vitreous taps to mitigate the anticipated increase in vitreous volume following intravitreal antibiotic injection, medico-legal protection as sampling remains conventional practice in many countries, rare cases of microbial resistance to empirical antibiotic treatment or non-bacterial pathogens, epidemiological surveillance of microbial trends, or source control in the context of outbreaks.[1]

In addition, microbiological sampling may potentially be of prognostic value in approximating final visual outcomes. We found that cases with positive cultures tended to have poorer visual outcome on univariate analysis, as did other studies in the literature.[12,13] However, in our study, we have additionally performed multivariate

regression analysis to account for other potentially explanatory variables, and found that positive cultures were no longer associated with a poorer visual outcome.

The argument against microbiological testing

There are potential arguments against this approach. Vitreous taps were unsuccessfully attempted ('dry' taps) in 7% of patients in our cohort, ranging up to 18% in the literature.[18] Although these patients tend to undergo AC taps to complete microbiological testing, this means that they may be subjected to an often uncomfortable procedure for limited gains. Our microbiological yield of 56% is in line with literature from the past decade (range 18-64%),[5–9] meaning that approximately one in two cases are culture-negative, negating the utility of microbiological testing in guiding clinical management in half the cases tested. Culture-negative cases should not be misattributed to sterile or non-infectious endophthalmitis (although this remains a differential), as the causative organism may simply be unculturable, fastidious, or slow-growing.[19] Novel methods such as next generation sequencing (NGS) can potentially increase the diagnostic yield and speed of diagnosis from intraocular fluid samples to some degree, albeit with costs and equipment availability as limiting factors.[20] In addition, a further research focus may be to improve diagnostic techniques or optimize aspects of the sampling and processing workflow, such as minimizing the time from sample collection to laboratory inoculation, or considering direct inoculation into the culture media to increase microbiological yield.

Antibiotic sensitivity data was available for 80% of culture-positive cases in our cohort, which were sensitive to at least one empirical intravitreal antibiotic administered at presentation. Sensitivity analyses comparing patients with and without antibiotic sensitivity data did not reveal any significant differences in baseline or outcome measures between both groups. Large studies of bacterial endophthalmitis isolates have

found that 99.6-100% were sensitive to vancomycin, 91.5-100% to ceftazidime, and 93-100% to amikacin in countries such as Canada, Australia, the US, and Taiwan,[21] with lower sensitivity rates in other countries such as India.[22] Given that approximately half are culture-negative in general, the numbers of taps required to identify a single case of bacterial endophthalmitis resistant to empirical treatment is much smaller. This is relevant if vitreous taps carry inherent risks.

Vitreous aspiration can theoretically induce an iatrogenic retinal break and detachment. We found a trend towards higher rates of RDs in patients who underwent vitreous needle aspiration at presentation compared to mechanical cutter biopsy. However, the small numbers and lack of statistical significance suggests that this hypothesis should be tested in larger cohorts, particularly as cutter biopsies are standard practice in only one of the five units here. Previous studies found a trend towards higher rates of RDs in those undergoing a ‘tap and inject’ (vitreous needle aspiration and intravitreal antibiotics) compared to intravitreal antibiotics only (5% vs 0%), although this was similarly not statistically significant.[12,13,18] Where vitreous taps are unsuccessful, mechanical biopsy via a vitreous cutter may be helpful. A post-hoc analysis of the EVS cohort did not find a statistically significant difference in microbiological yield or RD rates between biopsies obtained through needle aspiration or mechanical cutting with a 20G vitrector.[10,23] It is unclear whether the advent of small-gauge vitrectomy or different inciting procedures other than cataract surgery will impact this.

In addition, mechanical cutter biopsy often necessitates securing an operating room, which may further delay treatment initiation. This also has important implications for patients presenting outside standard working hours, or those presenting to peripheral or remote units without surgical facility, where transfer to tertiary centres delay microbiological sampling and treatment, which can compromise visual outcomes.[24] An

animal model of *Bacillus cereus* endophthalmitis demonstrated poorer retinal function when treatment was initiated over four hours after onset.[25] Following the incubation phase, the patient starts developing symptoms of inflammation during the acceleration phase, wherein inflammatory mediators within the eye can contribute to local destructive effects, retinal injury and vitreoretinal proliferation.[2] Organisations such as ESCRS have therefore issued recommendations that acute postoperative endophthalmitis should be considered a medical emergency, with initial management initiated within an hour of presentation.[2]

There is no consensus on management after the initial 'tap and inject' procedure. We found that changes in management were primarily prompted by lack of clinical improvement and clinical deterioration, often within 48 hours of initial management, before microbiological results with antibiotic sensitivities typically become available. Whether this ultimately affects visual and anatomical outcomes cannot be determined, and studying this on a prospective basis is difficult given the rarity of the condition. A cross-sectional survey of vitreoretinal specialists in the US found that 87% attempt to obtain vitreous samples at least half the time, but that for 78%, these results influenced further management less than half the time. For many, signs of clinical deterioration were an important motivator for recommending PPV with intravitreal antibiotics.[11] Again, this reinforces how changes in management appear to be based on clinical findings rather than microbiological results in clinical practice, corroborating our findings.

The arguments for and against performing taps are summarised in Figure 3.

Strengths and limitations

Strengths of this study include the multicentre coverage encompassing a population of approximately 10 million (15% of the UK population), providing a broad overview of practice patterns and enhancing generalisability. The retrospective design necessitated by the rarity of the condition brings inherent limitations, such as incomplete sensitivity data reflecting disjointed electronic medical record systems and data sharing between peripheral units and tertiary care. Nevertheless, sensitivity analyses did not demonstrate a significant difference in patients with missing antibiotic sensitivity data, and data collection was otherwise relatively robust and complete. It is also important to highlight the absence of postoperative fungal endophthalmitis in our and similar cohorts.[12,13] While this likely reflects practice in these countries (the US and UK), it may not necessarily be generalizable to tropical countries such as India, where fungal infections may be more prevalent.[26] Considerations for management of non-bacterial endophthalmitis are discussed in Supplementary S4.

An alternative strategy?

Considering the limited value of microbiological testing and the risks of delaying treatment to obtain these samples, an alternative initial management of suspected bacterial acute postoperative endophthalmitis should be considered. In cases where sampling means delays in initiating treatment, consideration should be given to early intravitreal antibiotic injections with AC paracentesis for IOP control as required. If there is no subsequent clinical improvement, or clear signs of deterioration develop, PPV could then be considered to remove the infected vitreous gel and reduce the microbe burden, from which a generous sample would be sent for microbiological testing. NGS could then be considered to increase the yield and/or turnaround time to aid

management, depending on cost and resource availability. NGS detects both viable and non-viable bacteria as well as cell-free DNA (including fungal DNA), meaning that prior antimicrobial therapy should not impede testing at this stage.[27]

Conclusion

While microbiological sampling may be helpful in guiding treatment rationalization in general, it had limited value in influencing subsequent interventions following the initial presentation of acute postoperative bacterial endophthalmitis in this multicentric cohort of patients who presented after a variety of inciting procedures. In such patients, should procuring microbiological samples risk delays in treatment, we propose that consideration should be given to immediate intravitreal antibiotics without sampling. This can minimise time to treatment and optimise visual outcomes, rather than allow complexities in performing the sampling delay prompt treatment.

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AYO and PCI conceptualized this study. AYO, PCI, and BLT designed this study. AYO, BLT, AM, AT, BF-S, VH, JMF, AM collected data. AYO and BLT analysed the data and drafted the manuscript. All authors interpreted the data, revised the draft ,and approved the final version.

Ethics statement:

The study was registered as a clinical audit and was exempt from formal ethics approval.

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Figure/ Table Legends

Figure 1: Distribution of cases across the five tertiary centres in England by number and by geography.

Figure 2: A) Procedures precipitating acute postoperative endophthalmitis; B) Change in management and secondary procedures performed within 28 days of initial empirical treatment.

Figure 3: Summary of the arguments for and against vitreous sampling.

Supplementary S1: Flow chart depicting cases excluded from analysis and the rationale for exclusion.

Supplementary S2: Typical management of endophthalmitis cases by site.

Supplementary S3: Sensitivity analyses comparing cases with available versus missing antibiotic sensitivity data.

Supplementary S4: Further considerations for non-bacterial endophthalmitis.