



The **ROYAL COLLEGE** of
OPHTHALMOLOGISTS

Ophthalmic Services Guidance

Managing an outbreak of postoperative endophthalmitis

January 2022

18 Stephenson Way, London, NW1 2HD, T. 02037705322

contact@rcophth.ac.uk @rcophth.ac.uk

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Date of review: October 2023

1. Introduction

The aim of this document is to provide advice on the identification and management of an outbreak of post-ophthalmic procedure (post-op) endophthalmitis. The guidance will concentrate particularly on cataract surgery, but the principles and much of the detail are applicable to other intraocular procedures including intravitreal injections and glaucoma surgery. As much as possible, it is based on published evidence but, in the absence of published high quality evidence for many aspects, expert consensus has been used to make recommendations.

Acute endophthalmitis is a severe intraocular inflammation presumed to be due to entry of microbes into the eye during the perioperative period or later if associated with glaucoma filtering surgery. Post-operative endophthalmitis is usually identified in the first two weeks after surgery and presents as a red painful eye with severe anterior uveitis, often with fibrin and hypopyon, and vitritis. It is not always culture positive. It is one of the most serious postoperative complications of intraocular procedures and, despite treatment, often results in a very poor visual outcome. The incidence in the developed world is low, approximately 0.1-0.08%, with an incidence in the UK (as determined by BOSU in 2004⁵) of 0.14% after cataract surgery and approximately 0.02-0.06% after intravitreal injections.

Bleb-related endophthalmitis is a specific type of post-operative endophthalmitis where the presence of a filtering bleb conveys an enduring risk of infection over the patient's lifetime. The Collaborative Initial Glaucoma Treatment Study demonstrated the calculated risk of bleb-related endophthalmitis to be in the order of 1.1% at 5 years⁶. This is probably similar for glaucoma drainage devices although exposure of the tube increases this risk to approximately 6%⁷. B lebitis is a distinct entity related to bleb-related endophthalmitis, for this document we adopt the classification system proposed by Azuara-Blanco et al⁸ as follows: Stage I bleb involvement with erythema and a turbid bleb, stage II includes stage I but with anterior chamber reaction (can include hypopyon), Stage III denotes vitreous involvement.

Many units may face a possible or actual cluster of cases ("outbreak") of post-op endophthalmitis at some point and a logical method of investigating and tackling this is key to reducing harm to patients and minimising operational disruption to the ophthalmology service.

A summary sheet and check list is included at the end.

2. Sources of causative microorganisms

Most cases of sporadic isolated postoperative endophthalmitis arise from the patient's own commensal bacteria (Staphylococci and Streptococci) and are mainly (60-80%) gram positive cocci. More virulent organisms are seen in bleb-related endophthalmitis which are thought to migrate through thin-walled blebs by the aid of bacterial exotoxins-these include more virulent Streptococcus species and gram-negative organisms.

However, clusters of cases have a greater likelihood of arising from some particular

source of contamination and have a much greater chance of being gram negative bacteria (Coliforms or Pseudomonas) or fungal with potentially worse outcomes.

Sources of contamination in outbreaks include:

- Contaminated intraprocedural solutions both extraocular (e.g. povidone saline) and intraocular (e.g. irrigating fluid, intracameral drugs including antibiotics, anti-VEGF, dyes and viscoelastic). This is the commonest source in clusters
- Contaminated phaco machines including tubing and phaco probes
- Inadequate ventilation systems providing poor air change rate per hour in the operating environment
- Defective sterilisation procedures
- Miscellaneous e.g. defective, contaminated or dirty instruments
- Some have more than one source
- In approximately 20% there is no obvious or identifiable source

3. Routine prophylaxis against endophthalmitis

The low incidence of endophthalmitis makes it difficult to obtain robust evidence of the efficacy of preventative measures in reducing its occurrence. Although this is not a full guideline on how to avoid endophthalmitis^{9, 10}, there are a number of areas where there is general consensus on what is good ophthalmic theatre practice or likely to offer a benefit:

Operating theatre general measures

- Rigorous theatre procedures including thorough hand washing, following strict theatre discipline to maintain sanctity of preparation and sterile areas to avoid contamination, separation of clean and dirty areas and minimization of unnecessary theatre traffic. This can be modified for designated intra-ocular injection rooms deemed fit for the procedure following inspection by the infection control team.
- Proper environmental cleaning.
- Maintain and monitor performance (annual preventive planned maintenance – PPM schedule) of theatre/clean room ventilation/airflow systems to appropriate standards.
- Following manufacturers' guidelines regarding single use of instruments.
- Follow manufacturers' guidelines on cleaning, disinfection and sterilisation of instruments and devices. Ensure theatres and the sterilizing unit comply with appropriate related standards.

Preoperative

- Avoidance of intraocular procedures in patients with significant active non-ocular infections
- Treatment of patients with blepharitis, significant lid malpositions (e.g. entropion with lashes abrading ocular surface), infective conjunctivitis and nasolacrimal infections prior to procedure, where clinically indicated.

- Avoidance of intraocular procedures in patients with significant active non-ocular infections
- Treatment of patients with blepharitis, significant lid malpositions (e.g. entropion with lashes abrading ocular surface), infective conjunctivitis and nasolacrimal infections prior to procedure
- Patients on immunosuppression agents: – no strong evidence based suggestion that patients on immunosuppressants are at greater risk of developing infections post cataract surgery. If patients are on immunosuppressive chemotherapy and/or biologics, they should be continued at current dosage¹¹

During procedure

- Povidone iodine solution 5% instilled into the conjunctival sac prior to commencement
- Skin preparation with povidone iodine or aqueous chlorhexidine 0.1% if allergic to povidone iodine. It is important to inform the patient Chlorhexidine may confer a slightly increased risk of infection as compared to Povidone iodine. Chlorhexidine also requires a longer time period to be effective. Chlorhexidine is an unlicensed product and this should be made clear to the patient.
- Intravitreal injection without povidone Iodine prophylaxis incurs up to a 40-fold increased risk of endophthalmitis. If allergy is self-reported a 'dry-run' or challenge to Iodine could be considered if multiple procedures are likely to be needed as with AMD. Other variations to consider, in the absence of evidence on how best to deal with this, may be prompt and copious wash out of the iodine and avoiding its use on the skin (in favour of an alternative as above)
- Good draping technique to isolate the lid margins and lashes from the surgical field
- Ensuring all equipment, intraocular lenses, viscoelastics, drugs and solutions are from a reliable source
- Rejection of instruments which are damaged, faulty or show signs of poor cleaning such as debris or deposits. Do not clear blocked instrument lumens e.g. of an irrigation-aspiration cannula during the procedure as sterility may then be uncertain.
- Excellent surgical wound construction and good wound closure.
- Avoidance of serious intraoperative complications especially posterior capsular rupture and vitreous loss and avoidance of overly prolonged surgery.
- Prophylactic antibiotics in accordance with the RCOphth (or equivalent) surgery and procedure guidelines where indicated. There is published evidence about the rate of intracameral antibiotics and although there are no Randomised Clinical Trials, the general standard of practice in UK is that intracameral antibiotics is usual.
- Any other procedure shown with good statistical support to be effective and safe.

Preventive measures

Suggested by some authors, but for which there is little consensus or evidence, include:

- Non-touch technique as far as possible, avoiding contaminating the functional end of instruments.
- Rejection of lens implants which have inadvertently contacted the lid margins.
- Wear facemasks in theatre, especially scrub nurses and surgeons.
- Injecting lens implants rather than folding them with forceps, to reduce the possibility of contact with the lid margin.
- Single use/disposable instruments.
- Single use medications.
- Postoperative antibiotic drops (regimens vary but usually one-two weeks).

Special considerations:

- Iodine sensitivity
- Penicillin allergy¹²

4. Treatment of cases

It is beyond the bounds of this document to detail the treatment of endophthalmitis. However, it is important, even if briefly, to mention two important points of principle:

1. This is a condition where time is of the essence. It is crucial that cases are diagnosed early and treated as an emergency. If there is enough clinical suspicion of endophthalmitis, treatment should not be delayed waiting for microbiological confirmation or the effects of a trial of steroids.
2. All units or surgeons undertaking intraocular surgery or intravitreal injections, whether within the NHS or independent sector, have a duty to ensure their patients can access emergency assessment and treatment of endophthalmitis. All patients should be warned what to look out for postoperatively, and given clear information on where to go or whom to call if they are concerned. There should be clear agreed pathways for care if a provider of the procedure is not able to offer emergency post-procedure care.

It is also worth noting other considerations arise when treating endophthalmitis after glaucoma filtering surgery. Visual outcomes are generally poor due to involvement with more virulent organisms. Some have suggested a pars plana vitrectomy should be considered at an earlier juncture although high quality evidence to support this is lacking. Furthermore, in the presence of a glaucoma drainage device, debate exists as to whether the device should be removed immediately. A recent literature review suggested early removal can be associated with a lower rate of evisceration/enucleation although visual acuity outcomes were no better¹³. Evidence is lacking regarding the incidence and management of endophthalmitis in the presence of MIGS (minimally invasive glaucoma surgery) either when performed in isolation or in combination with cataract surgery. Currently these presentations should be managed on a case-by-case approach until more evidence is forthcoming.

Post intravitreal injection endophthalmitis is generally treated in the same as that post cataract surgery.

5. Active monitoring of incidence and investigation of isolated cases

Postoperative endophthalmitis cases should be reported to the hospital risk management team usually via the incident reporting system. All incidents reported locally are normally shared nationally with the National Reporting and Learning System to detect national trends.

For cases of endophthalmitis that have arisen at another unit, the ophthalmic clinical lead and the operating consultant of the source unit must be informed about the case by the receiving/treating unit so that they can incident report and investigate. In the unfortunate event that the source unit does not seem to reply/act/engage, whether NHS or independent, the commissioner should be notified directly.

Ophthalmology audit or clinical governance meetings should include a regular complications and morbidity slot, which should consider any cases of endophthalmitis and examine any predisposing factors or areas for action, learning or improvement.

Electronic patient records can facilitate continuous audit and surveillance, and identify even a small rise in endophthalmitis cases or other complications, which might not otherwise be evident.

Incidence should be regularly monitored, either via electronic patient records, incident reporting or both. Departments should have a system for identifying and acting upon any rise in incidence or cluster of cases.

Report to the Medicines and Healthcare products Regulatory Agency, and to the manufacturers, any problems with drugs or devices.

6. How many cases comprise an outbreak?

This is a difficult question to answer as random clusters mimicking an outbreak may occur from time to time. With such a low background incidence, even one or two extra events during a short time frame can raise concerns but may turn out not to be significant and may be followed by an unusually long period with no cases so that the frequency over a longer time frame may be within acceptable limits.

It is important to consider the possibility that more than one case in a short time frame may have arisen from a preventable and recurring cause.

7. What should raise particular concerns?

- Analysis of the cases demonstrate a common organism especially an unusual organism
- Analysis of the cases demonstrates the same apparent underlying cause or concern
- Analysis of the cases demonstrates the cases related clearly to only one team member, one surgeon, one theatre/site, one session in the week (for all of these especially if significantly out of proportion to the relevant share of surgical activity), a particular instrument or consumables batch number
- Two or more cases have arisen during the same theatre list
- A rate that is significantly over that expected in the modern era; in cataract surgery this might perhaps be >0.4% and above; and a rate that is >0.8% should be taken extremely seriously
- Cluster occurring over a very short period e.g. days to weeks
- Some have used statistical methods or charts to ensure a sensible balance between complacency and overkill. There are a number of methods (see references). It is wise to involve the local microbiologist in determining the best local method for this and even wiser to have done so proactively before any suspected cluster rather than reactively after concerns have been raised.

8. Actions once suspicions have been raised

The degree of action will of course depend on both the rate of occurrence, any suspicious factors and whether the problem persists. Operational factors must be considered, but the first duty is to minimise patient harm.

Keep detailed records of all action taken and minute any meetings.

The decision as to whether or not there is an outbreak (see above) based on frequency, possible statistical analyses and identification of common factors in the cases.

9. Notification and involvement of others, raising awareness, detecting cases

- Alert colleagues: make them aware of the cases so far, ask if there are other cases not yet reported, advise a high degree of suspicion and to report any further cases
- Ensure incident reports are completed for any cases
- Alert the lead clinician, clinical director and the medical director
- If receiving multiple cases from another provider, their clinical lead and medical director must be notified, and take action. If their response is deemed inadequate, contact their commissioner

- Involve the hospital consultant microbiologist and hospital infection team at an early stage
- Involve the risk team and consider notifying commissioners
- With risk team notify MHRA and manufacturers if devices or drugs are clearly implicated
- Consider establishing a multidisciplinary team to manage and investigate (ophthalmologists, nurses, theatre staff, managers, risk, microbiology, infection control)
- Verify that patients are fully aware of postoperative danger symptoms
- Consider resuming day two or day three follow-up if this is not normally undertaken
- Ask neighbouring units if they also have noticed an increased incidence of endophthalmitis

10. Immediate actions to improve prophylaxis/prevent further cases

- Ensure that established agreed theatre procedures and preventative measures are robust and being followed and remind staff about them
- Cease bilateral simultaneous cataract surgery where performed
- Temporary closure of theatre(s) or provision of the procedure: give serious consideration to cessation of all intraocular surgery in the interests of patient safety whilst investigating the cause

11. Investigation

1. Review cases urgently and examine:

- Patient/surgical risk factors such as blepharitis, nasolacrimal disease, immunosuppression/diabetes, concurrent systemic infection etc, vitreous loss, duration of surgery, postop wound leak, non-compliance with prescribed drops.
- Surgeon or injector factors surgical and draping technique
- Common hospital factors such as draping and procedural technique, antibacterial prophylaxis, surgeon, nursing staff and other personnel, theatres, solutions, drugs, viscoelastics, intraocular lenses, disposable and non-disposable equipment, which autoclave used, on which day of the week, which position on the list and at what time of day patients were operated. Track batch numbers of solutions, drugs, disposables and lenses.
- Ensure there is appropriate documentation of practices, instrumentation and drugs.

2. Note any procedure or environment that coincided with or recently preceded the outbreak.

3. Microbiological analysis of intraocular tap samples, looking for a common organism or subtype - fully subtype any organisms (investigation methods to determine the source of these outbreaks use a combination of phenotypic [routine culture, biochemical profiles of the organism, antibiotic susceptibility patterns 43, 45, 51 (44, 46, 52)] and molecular [e.g. 16s PCR polymerase chain reaction in culture negative specimens/tap]).
4. Environmental considerations: building works in or nearby, poor condition of estates, level of cleanliness, clutter and ergonomics, separation of dirty and clean areas and condition of equipment. Confirm that the ventilation/ air-flow is appropriate and tested in consultation with the infection control team. Check what other cases (e.g. dirty cases) are being performed in the theatre or nearby from theatre records.
5. Microbiological sampling: may include microbiological sampling/culture from irrigating solutions, extra and intracameral solutions and drugs, viscoelastics. Sample phaco sets (tubing, phaco and I/A hand pieces) and phaco machine, air filters and ventilation units, and environmental swabbing of theatre areas.
6. Review theatre practices: independent observation of practices such as door closures, staff movements, facemasks, drugs and instrument prep and use, solution and drug handling etc.
7. Review surgical techniques, equipment and IOL handling.
8. Assess that all equipment and disposables are functional and used according to manufacturer's instructions, are in date and appropriately serviced. Confirm single use where instruments are so designated.
9. Assess efficacy of cleaning and sterilization processes, in particular examine how reusable hollow bore equipment lumens are rinsed or cleaned. Arrange for professional assessment of the hospital sterilizing service. Look actively by examining instruments for damage or debris and blocked lumens.

Address the specific cause if found.

Actions when a specific cause cannot be found

- Review and revise current prophylaxis protocol and re-examine and, if possible, improve any other relevant preop, intraoperative and postoperative care and theatre activities
- Consider introducing extra prophylaxis measures (see above) e.g. intracameral antibiotics
- Consider an external review by a neighbouring unit or The Royal College of Ophthalmologists

12. Summary

Units should have robust protocols for endophthalmitis prevention, and methods to monitor the incidence. It is important to identify a significant rise in incidence, analyse and learn from sporadic cases. The discovery or suspicion of an outbreak of endophthalmitis should prompt a rapid, systematic and open investigation to attempt identification and remedy of any possible cause. Patient safety is paramount and may involve temporary cessation of intraocular procedures.

13. Flow chart - coping with a cluster of postoperative endophthalmitis



14. Unusual or uncommon scenarios

While it is not possible to cover every eventuality in different clinical settings, three additional items may be of relevance to the timing of this updated document.

1. The use of face masks: Patel et al⁶⁶ have analysed more than 500,00 intravitreal injections between Oct 2019 and July 2020, comparing practices where both patient, staff and injector wore a mask with those where masks were by none. There was no statistical difference in the rate of post injection endophthalmitis reported between the 2 groups. The authors acknowledge some of the study limitations including its retrospective design, inconsistent or incomplete data, and the heterogeneity of the injection techniques, to name some. This is relevant given the evolving practices in the light of the COVID pandemic. However, this new area of clinical interest will likely remain controversial for some time due to evidence suggesting opposing views, in this case the risk of infection to the patient posed by the patient wearing a facemask during the injection^{66 (67)}.

2. Immune suppressed patients: With increasing prevalence of different cancers and patients living longer with cancer, the risk of post injection endophthalmitis in this sub-group is a cause for concern. No evidence was found to suggest that patients who are immunosuppressed are at greater risk of developing infections post-ocular surgery or injections at the time of publishing this document. However, current practice is more cautious in these patients with the use of modified protocols in the hope that this maintains the same low risk of infection in those who are not immune suppressed. This too will be an uncommon scenario where evidence is lacking.

3. The use of mobile units ([Surgicube](#) and Toul Operio): Despite these being present before the COVID pandemic, their use has gained additional interest as a way of dealing with the backlog of patients needing both surgery and/or injections. At the time of writing this document, no UK based unit has been identified using this system, to share their experience using either of these units. A British Ophthalmological Surveillance Unit (BOSU) study may answer further questions about their use if undertaken.

15. Appendix 1 Vitrectomy for post-cataract extraction endophthalmitis

Since its publication in 1995, the Endophthalmitis Vitrectomy Study (EVS) ¹⁴ has been widely cited and used as the gold standard reference for all treatment protocols of postoperative endophthalmitis in the UK and around the world. The main findings of the study was that vitrectomy and intravitreal antibiotics injection (VIT) had no advantages over vitreous tap and intravitreal injection of antibiotics (TAP) except in patients with presenting visual acuity of light perception (LP).

That study, however, had several limitations, including that nearly all patients had extracapsular cataract extraction and patient populations were exclusively those who had endophthalmitis after cataract extraction or secondary lens implantation.

Also, with regards to secondary outcomes, the VIT group of the EVS study, had 3-fold increase in obtaining 20/40 visual acuity compared to the TAP group (33% vs 11%). Moreover, although the study showed no significant difference in complications, 5%-6% of patient in the TAP group subsequently had vitrectomy and 1-2% had enucleation¹⁵.

The above limitations and the difference in secondary outcome, combined with the technical improvement in vitrectomy machines, namely the advent of the wide-angle viewing systems, improved fluidics, the introduction of small gauge and high cut rate probes, the availability of endolaser, etc, that have improved the safety profile of surgery, have led some authors to maintain that VIT should be instated as the mainstay for treatment.

Role of TAP and timing of VIT

Initial TAP remains the mainstay of treatment in patient with PCEE. Although controversial, early vitrectomy i.e. within 72 hours of presentation, for those presenting with no fundal view, has since been shown in several retrospective studies to result in good visual outcome. (Reference: Mason LB, Mason JOI, Friedman DA, Mason JOI. Postoperative bacterial endophthalmitis: tap/inject versus sutureless vitrectomy. *Med Res Archives*. 2017. Available from: <https://journals.ke-i.org/mra/article/view/999>. Accessed, 2020. [Google Scholar] ^{16,17, 18}. It is worth noting however that the timing of vitrectomy remains a matter of debate because of the lack of level 1 evidence.

Proposed advantages of vitrectomy

- It reduces the number of micro-organisms inside the eye,
- It de-bulks the inflammatory debris together with the inflammatory and bacterial toxins,
- It allows more effective delivery of the antibiotics to the target tissues.
- It helps obtain more adequate samples from the vitreous, thus increasing the culture yield and this will help with the timely introduction of specific antimicrobial agents
- It helps in controlling the bacterial growth when silicone oil is used as a tamponade^{19, 20}.

Proposed management of acute PCEE

Documentation

Adequate clinical and photographic documentation is paramount in PCEE as patients often end up being looked after by multiple clinical teams.

TAP at presentation

The results from the EVS and subsequent largely retrospective studies [14, 15](#) indicate that a large proportion of patients (20-40%) would have either sterile endophthalmitis or respond well to intravitreal antibiotics. It would therefore be reasonable for TAP to be the initial step in managing patients with PCEE.

After TAP & prior to VIT

Attempts should be made to clear up the inflammatory debris and membranes from the anterior chamber to help get a clear fundus view. Evidence exists regarding the utility of tissue plasminogen activator (TPA) in helping to clear the view in patients with severe fibrinous uveitis and endophthalmitis [21, 22, 23](#). A dose of 10-20micrograms should be used and injected at least 4-6 hours prior to surgery. This may be combined with intensive topical steroids.

Clinical review should be scheduled soon after TAP i.e. within 24-48 hours:

- If the condition appears to be deteriorating i.e. visual acuity or fundus view is worsening, vitrectomy should be considered.
- If the condition remains stable, repeating intravitreal antibiotic injection may be considered (after checking the initial culture and antibiotics sensitivity results and changing the antibiotics accordingly).

VIT surgery

Surgical approach should be modified as per the clinical and microbiological findings as well as to visual prognosis.

The role of vitrectomy in different categories of endophthalmitis are included in the appendix.

VIT in cases of endophthalmitis other than PCEE

Endophthalmitis after intravitreal injections

Because the majority of cases are culture-negative or sterile (presumed toxic reaction)[24](#), vitrectomy would be indicated only in patients presenting with or developing severe vitritis obscuring the fundus view despite treatment with intravitreal antibiotics. Later on, vitrectomy would be necessary to remove post-inflammatory debris causing visually disabling floaters.

Chronic endophthalmitis (>6 weeks)

These patients often respond adequately to TAP²⁴. Vitrectomy indication is limited to patients showing resistance to intravitreal antibiotics treatment or in those suspicious to have an unusual microbial cause e.g. gram negative rods or fungi or those with visually significant vitreous debris.

Endophthalmitis after pars plana vitrectomy

Endophthalmitis occurs rarely after pars plana vitrectomy. The incidence has been estimated to be 0.039% to 0.07%^{27, 28, 29}, making it one of the lowest after all other intra-ocular procedures.

TAP and intravitreal antibiotics should be tried first and vitrectomy considered in patient with fundus-obscuring inflammation.

Endophthalmitis after trabeculectomy

Those patients often present several months or years after surgery. Therefore, the above recommendations for chronic endophthalmitis would be applicable.

Special consideration has to be given to patients with blebitis as vitrectomy is rarely indicated and the condition often respond adequately to topical treatment e.g. with systemic and topical fortified antibiotics drops. Care must be taken not to compromise the bleb site e.g. by attempting to aspirate from it.

Endophthalmitis after penetrating trauma

Trauma is often associated with severe infections and virulent organisms, often more than one species. Early vitrectomy therefore is often required and has been shown to be associated with improved visual outcome.³⁰

Endophthalmitis associated with corneal infection and after keratoplasty and kerato-prosthesis

The majority of endophthalmitis cases associated with keratitis are predominantly caused by bacterial agents, including pseudomonas, staphylococcus and streptococcus species. However, fungal infection, including filamentous fungi and fusarium species, have been reported in some cases.

Penetrating keratoplasty and the use of kerato-prosthesis are associated with higher incidence of endophthalmitis compared to other intraocular procedures (0.1%-0.5% vs 0.025%-0.08%)^{31, 32, 33}.

Unlike patients with keratoplasty or kerato-prosthesis, who commonly need early vitrectomy, TAP management should be the initial management step in patients with keratitis unless the view becomes compromised with severe inflammation.

Endogenous endophthalmitis

This seems to be the second most common type of endophthalmitis, presenting in 7-40% of cases^{34, 35}. The presentation varies significantly depending on the causative organisms and the immune statue of patients.³⁶ Fungal agents (commonly candida and aspergillus species) and gram negative organisms are the most common reported causative agents in the majority of patients.

Although fungus inflammation can be treated with systemic and intravitreal anti-fungal agents as well as intravitreal steroids, patients with suspected gram negative infection would benefit from early vitrectomy^{38, 38}.

Viral retinitis & panuveitis

In patients with viral retinitis, vitrectomy is required mainly in patients who develop retinal detachment or post-treatment significant vitreous floaters.

Endophthalmitis in children

This occurs commonly after penetrating trauma or intraocular surgery. Gram positive cocci is the most common causative organisms, including streptococcus and coagulase negative staphylococci.

Early vitrectomy in those cases was found to be associated with better and virulent organisms with worse visual outcome.^{37,38}

16. Authors

- 2021 review authors: Mr Samer El-Sherbiny (South Warwickshire NHS Foundation Trust), Miss Archana Pradeep (University Hospitals of Leicester NHS Trust), Mr Richard Stead (Nottingham University Hospitals NHS Trust), Dr Karina Spiess & Mr Mostafa Elgohary (Kingston Hospital NHS Foundation Trust)
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