ARHAI Scotland

Antimicrobial Resistance and Healthcare Associated Infection

NHS National Services Scotland

Rapid Review of the Literature

Post-cataract surgery endophthalmitis

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Contents

1. Aim

This rapid review was carried out to evaluate the scientific literature and extant guidance to identify infection prevention and control (IPC) measures to prevent and control endophthalmitis following cataract surgery.

2. Introduction

The Cataract Sub-Specialty Delivery Group (SSDG) Centre for Sustainable Delivery (CfSD) was commissioned by the Scottish Government to address the provision of cataract surgery in Scotland. The primary aim of this group being to deliver higher numbers of cataract procedures per list.

The Scottish National Cataract Short Life Working Group (SLWG) was set up in January 2022 to develop a Blueprint for high-volume cataract surgery in Scotland, with the Cataract Sub-Specialty Delivery Group established in August 2022 to support ophthalmic theatre teams across Scotland to implement this Blueprint.

To successfully implement this Blueprint, assurance of patient safety in relation to infection prevention and control (IPC) is key. Although rare, infectious endophthalmitis is a serious sight-threatening complication of cataract surgery.

This rapid review has therefore been developed to identify IPC factors that should be taken into consideration when increasing the throughput of cataract procedures.

3. Objectives

The following research objectives were considered:

- Which organisms are associated with post-cataract surgery endophthalmitis?
- What factors related to infection prevention and control are associated with post-cataract surgery endophthalmitis?
- What guidance is available related to the prevention of post-cataract surgery endophthalmitis?

4. Methodology

A database search was undertaken using two targeted search strategies on Medline and Embase (see Appendix 1). All searches were limited to articles published between 1 January 2010 and 14 April 2023. Hand searching of reference lists and an extensive search of online resources was also carried out to identify grey literature, including guidance documents.

As this was a rapid review, evidence was critiqued by a single reviewer but not formally graded with the use of an appraisal tool. The SIGN50 principles were applied to critically analyse the evidence base.

Exclusion criteria

Studies reporting post cataract surgery cases with negative patient microbial cultures were excluded from this review. This is because it would be impossible to link the cases to environmental, process or IPC factors without a positive culture. Studies were excluded if endophthalmitis was secondary to trauma or a procedure other than cataract surgery. Studies were also excluded if they were not in English language, focused on non-human subjects, intervention bundles, or non-IPC factors such as prophylaxis and other clinical factors (for example surgical prep and intra-operative surgical practice and technique.

5. Results

The database (Medline and Embase) searches yielded 390 papers after deduplication; 109 of these were subjected to full text screen and 44 were judged to be appropriate for inclusion. Eleven papers identified through hand searching were also deemed suitable for inclusion.

Which organisms are associated with post-cataract endophthalmitis?

A total of 49 papers were identified in relation to this research question, two from the UK, [1, 2] seven from elsewhere in Europe [3-9] and 42 from outside Europe. Twenty-one of the studies were case reports/series,[1, 2, 6, 7, 10-26] 10 were outbreak studies,[3, 4, 27-35] and the remainder(18) were retrospective studies.[5, 8, 9, 35-49] Twelve of the included studies,[3, 4, 13, 19, 21, 27, 29-32, 34, 35] identified a possible source of the organism and five of these undertook genetic typing to confirm the genetic relatedness of the patient isolates and the proposed environmental source.[4, 27, 29-31]

This discussion will consider the pathogens reported and the time to presentation of endophthalmitis. The time to presentation after cataract surgery was used instead of time to symptom onset because while some studies reported the latter, the former was consistently reported and deemed more reliable. It is however important to consider variations in symptom severity, medication effects, healthcare systems, and health-seeking behaviours across different countries that can affect this statistic. Extraction of this data was challenging in certain studies, particularly retrospective reviews, as they included cases of endophthalmitis following surgeries other than cataract surgeries or cases without positive microbial culture.

In the included studies, vitreous samples were the most commonly used specimen for microbiological analysis. It was the only sample taken in 22 studies[3, 6-8, 10-13, 15, 16, 19, 21, 22, 25, 28, 30, 31, 34, 38, 39, 46, 47] and taken in combination with aqueous humour in 16 studies.[1, 4, 5, 14, 17, 20, 23, 24, 29, 32, 33, 35-37, 41, 42, 48, 50] Other samples such as vitreous biopsy,[2, 15, 37, 38, 43] anterior chamber membrane,[37] corneal scrapings,[24, 37, 43] scleral abscess,[14] and explanted intraocular lens,[4, 28, 37, 43] were also collected as adjuncts to other samples.

Overall, there were 878 cases captured in this review, 54.5% of which were associated with gram-positive organisms, 23.1% with gram-negative organisms and 20.4% fungal organisms. Outbreak studies and case series typically reported a single organism all of which were either gram-negative or fungi. Retrospective studies however show a range of organisms and are therefore more likely to represent the day-to-day realities of cataract surgery endophthalmitis.

Gram-negative organisms were identified in 23 pieces of evidence (10 of which were either outbreak studies or case series), the majority being *Pseudomonas aeruginosa*[8, 22, 29, 31, 33, 34, 39, 41, 48, 49] followed by *Stenotrophomonas maltophilia*.[21, 35, 39, 41, 49] Other gram-negative organisms identified were *Burkholderia* spp.,[4, 25, 30] *Haemophilus influenza*,[8, 48] *Klebsiella pneumonia*,[39, 42] *Achromobacter xylosoxidans*,[8] *Acinetobacter* spp.,[8, 39, 48] *Enterobacter* spp.,[38, 48] *Escherichia coli*,[42, 48] *Proteus* spp.,[8, 48, 49] *Prevotella* spp.,[2] other species of *Pseudomonas*,[9, 16, 41, 42, 46, 47] *Serratia* spp.,[39, 47] *Moraxella cataralis*,[49] *Sphingomonas paucimobils*[42], *Ochrobactrum anthropic* [19], and *Paenibacillus glucanolyticus*.[49]

Gram-positive organisms were identified in 16 pieces of evidence (10 of which were retrospective studies), chief of which was *Staphylococcus aureus*[8, 39, 41, 42, 47-49] and *Staphylococcus epidermidis*.[5, 26, 39, 40, 42, 47, 48] Also identified were other *Staphylococcus* species,[8, 9, 36, 39, 41, 42, 46, 47, 49] *Enterococcus* spp.,[5, 8-10, 36, 41, 47, 49] *Rothia mucilaginosa*,[6, 13] *Streptococcus* spp.,[5, 8, 9, 36, 39-42, 45-49] *Abiotrophia* spp.,[8] *Clostridium intestinale*,[12] *Gemella morbillorum*, [8]*Nocardia* spp.,[20, 37] *Propionibacterium* spp.,[8, 42, 47] *Peptostreptococcus spp*, [8] *Corynebacterium* spp.,[41] *Bacillus licheniformis*[46] and other diphtheroids.[8]

Fungal endophthalmitis was described in 17 studies with *Fusarium* spp. being the most frequently reported (n = 6).[3, 24, 27, 28, 32] Others included *Aspergillus* spp.,[39, 43, 46] *Candida* spp.,[39, 48] *Curvularia* spp.,[15] *Penicillium citrinum*,[1] *Trichosporon* spp.,[11] *Pseudozyma aphidis*,[17] and *Wickerhamomyces anomalus,*[7] *Acremonium* spp.[46]

Other organisms identified included *Acanthamoeba culbertsoni* and *Mycobacterium* spp.[14, 23] Two studies reported cases where more than one organism was isolated.[8, 41]

The time to presentation after cataract surgery varied widely among different organisms in the included evidence base. It was generally longest for cases where the associated organism was fungal. For example, of the 10 studies with the longest times (or mean times) to presentation,[3, 7, 11, 15, 17, 20, 27, 28, 30, 44] eight of them were of fungal origin. [3, 7, 11, 15, 17, 27, 28] Overall, the reported range of time to presentation for fungal endophthalmitis was four days to seven months. This is in line with existing understanding that fungal endophthalmitis has subacute presentation following an inciting event, with symptoms worsening over days or weeks.[51] *Candida parasilosis* reported by a single case study,[18] had the longest time to presentation (7 months) while *Penicillium citrinum,* reported by one case study[1] and *Fusarium solani,* reported by two studies (a case study[24] and an outbreak study[32]) had the shortest (7 days). The two latter studies had a total of ten patients with a range of four to ten days.[1, 24, 32]

Within the evidence base included, *Stenotrophomonas maltophilia* had the longest mean time to presentation among gram-negative organisms (13.5 days in a 14-patient retrospective review and six days in a three-patient case series), with a range of 1 to 56 days. [21, 35]. *Pseudomonas aeruginosa* consistently had a time to presentation between two to eight days across four studies involving 50 participants.[22, 29, 33, 34] Among the gram-positive organisms, *Nocardia* had the longest reported time to presentation, with a case study reporting 45 days and a retrospective study of 28 patients reporting a median time of 17 days (range: two to 43 days) [20, 37] Additionally, two case studies reported 14 days for *Clostridium intestinale* and 11 days for *Enterococcus faecium,* respectively.[10, 12]

An important limitation of this body of evidence is the potential publication bias as cases reporting unusual organisms or outbreaks with links to a common source are more likely to be published than single sporadic cases. Hence the evidence identified may not represent the true clinical picture in Scotland. This is especially important as only two papers from the UK are included in this review. It is also noted from an expert opinion source, that gram-positive bacteria are responsible for most cases of post-cataract surgery in Western Countries.[52]

In summary, a list of the organisms identified in this review is given below. An asterisk (*) indicates that they were identified in the UK.

- *Abiotrophia* spp.
- *Acanthamoeba culbertsoni*
- *Acinetobacter* spp. *(A. baumannii, A. iwoffi)*
- *Acremonium* spp.
- *Achromobacter xylosoxidans*
- *Alcaligenes xylosoxidans*
- *Aspergillus* spp. *(A. flavus, A. fumigatus, A. nidulans, A. niger, A. terreus, A. flavipes)*
- *Bacillus licheniformis*
- *Burkholderia* spp. *(B. cepacia, B. contaminans)*
- *Candidia* spp. *(C. parasilopsis, C. albicans)*
- *Clostridium intesinale*
- *Curvularia* spp.
- *Corynebacterium* spp.
- *Enterobacter* spp.
- *Enterococcus (E. faecalis, E. faecium)*
- *Escherichia coli*
- *Fusarium* spp. *(F. oxysporum, F. solani)*
- *Gemella morbillorum*
- *Haemophilus influenza*
- *Klebsiella pneumoniae*
- *Moraxella catarrhalis*
- *Mycobacterium* spp.
- *Nocardia* spp. *(N. asteroids, N. brasiliensis)*
- *Ochrobactrum anthropic*
- *Paenibacillus glucanolyticus*
- *Penicillium citrinum**
- *Peptostreptococcus* spp.
- *Prevotella* spp.*
- *Propionibacterium* spp. *(P. acnes, P. granulosen)*
- *Proteus* spp. *(P. mirabilis, P. vulgaris)*
- *Pseudomonas* spp. *(P. aeruginosa, P. maltophilia, P. paucimobilis, P. stutzeri)*
- *Pseudozyma aphidis*
- *Rothia mucilaginosa*
- *Serratia* spp.

- *Sphingomonas paucimobilis*
- *Staphylococcus* spp*. (S. aureus, S. epidermidis, S. hominis, S. lugdunensis, S. warneri)*
- *Stenotrophomonas maltophilia*
- *Streptococcus* spp. *(S. agalactiae, S. constellatus, S. hemolyticus, S. mitis, S. oralis, S. pneumoniae, S. pyogenes, S. salivarius, S. sanguinis, S. viridans)*
- *Trichosporon* spp.
- Unclassified dematiaceous fungi
- *Wickerhamomyces anomalus*

What factors related to infection prevention and control are associated with post-cataract endophthalmitis?

Eight papers were identified in relation to this question, including six outbreak studies,[4, 27, 29-31, 34] one case series[21] and one retrospective case review.[35] Six of the studies reported outbreaks/cases in Asia (three from India,[29-31] one each from China,[35] Iran,[34] and South Korea[27]), two described an outbreak and a case series in Norway[4] and Argentina, respetively.[21] In seven of the studies, the organisms involved were gram-negative (three were *P. aeruginosa*[29, 31, 34] and two each were *S. maltophilia*[21, 35] and *Burkholderia* spp.),[4, 30] while the eighth involved a fungus – *Fusarium* spp.[27]

The settings of the studies varied from small private single physician clinics[4] to small rural facilities[21] to multi-centre outbreaks.[27] Epidemiological typing is an important part of outbreak investigation. It must be noted however that the lack of a match between a patient and source following genotyping does not exclude a potential source. Therefore, studies that demonstrated a strong epidemiological link between patient and environmental samples were included for this analysis – the minimum being isolation of the same species of organism from both patient and environmental samples; proof of genetic relatedness was not necessary for inclusion in this review.

A key limitation of this body of evidence is a potential publication bias as many outbreak investigations are not published, hence the potential infection prevention and control (IPC) factors related to post-cataract endophthalmitis may not have been identified. Another limitation is the potential lack of applicability due to the differences in systems, practice, and standards between countries compared to Scotland.

To establish the source of the outbreaks, five studies employed various techniques to demonstrate genetic relatedness between the organisms isolated from patients and the environment [4, 27, 29-31] These techniques included variants of repetitive element-based PCR (Rep-

PCR) reported by two studies; BOX-A1R-based repetitive extragenic palindromic-PCR (BOX PCR),[30] and Enterobacterial Repetitive Intergenic Consensus Polymerase Chain Reaction (ERIC PCR).[31] Others include direct sequencing,[27] pulsed-field gel electrophoresis (PFGE),[29] multi-locus sequence typing (MLST).[4]

The sources of outbreaks identified within this body of evidence were contaminated ophthalmic solutions and medications (n = 4 studies),[27, 29-31] contaminated surgical instruments (n = 3 studies)[21, 34, 35] and the ventilation system (n = 1 study).[4] Behind some of these were IPC factors such as built environment contamination,[4] ineffective sterilisation procedures[21, 35] or the lack thereof.[34]

Ophthalmic solutions that were expected to be sterile were reported to be the cause of endophthalmitis outbreaks in four studies.[27, 29-31] They included anaesthetic eye drops, ophthalmic viscoelastic devices (OVDs), trypan blue solution, intraocular lens (IOL) suspension solution. These were contaminated by *P. aeruginosa, B. cepacia* and *Fusarium* spp. and were all confirmed to be genetically linked to the organisms isolated from patient samples. In all four studies, the contamination occurred at a batch manufacturing level as samples from unopened bottles yielded growth of the contaminating organisms.[27, 29-31] One of the studies reported a nationwide outbreak in South Korea which was resolved after a nationwide withdrawal of a particular brand of sodium hyaluronate viscoelastic materials.[27]

Contaminated surgical instruments were reported as very likely sources in three studies with a total of 27 cases.[21, 34, 35] The term 'very likely' is used because epidemiologic typing was not performed to establish clonal relatedness between patient and environmental isolates in these studies. However, they demonstrated plausible connections for example the isolates had identical antibiotic susceptibility profiles. The organisms isolated from the surgical instruments were *P. aeruginosa* and *S. maltophilia*. All three studies involved different areas of the phaco machine namely phaco tip[34] and aspiration – irrigation system.[21, 35] Failures in sterilisation were identified as a key factor in the outbreaks with one of the studies suggesting subpar re-sterilisation of the reusable silicon tubes of the irrigation-aspiration handpiece[21] and another reporting that the surgeon used the same phaco probe for over 10 patients without sterilisation between surgeries.[34] All cases in the former study had their surgeries performed in the same time period but by different surgeons and samples from all other surgical instruments and the operating room did not yield positive cultures. In the third study, *S. maltophilia* with identical antibiotic susceptibility to patient isolates was isolated from the liquid in the aspiration tube which had been sterilised for reuse.[35] Further investigation showed that fluid from the aspiration tube could reach the irrigation tube, which was investigated by injecting a dye into the aspiration tube. The authors therefore

hypothesised that the patients may have been exposed to *S. maltophilia* through irrigation fluid that had been contaminated by fluid from the aspiration tube, as the pathogen may have survived re-sterilisation through the formation of a biofilm.[35] Genotyping could have been used to confirm the accuracy of this hypothesis but this was not done.

A contaminated ventilation system was also identified as the source of an outbreak of *B. contaminans* in a private single physician clinic in Norway.[4] Seven of 118 environmental samples taken from the clinic ventilation system yielded bacterial growth that tested positive by *Burkholderia*-specific PCR assay. All seven positive samples were from a particular air intake duct in the ventilation system, one being from pooled standing water and the other six being swabs from biofilms. Multi-locus sequence typing (MLST) analysis showed that all seven isolates had an identical allelic profile, which were also identical to those recovered from patient cultures. It was hypothesised that this contamination occurred due to water pooling in air intake ducts following flooding. However, air sampling was not performed, to further investigate this as a potential source of infection.

In summary, this body of evidence highlights contaminated ophthalmic solutions, surgical instruments, and ventilation systems as associated factors in post-cataract surgery endophthalmitis. Manufacturing-related contamination of solutions, marketed as sterile, was observed in all cases related to ophthalmic solutions. Although most studies did not report the outcomes of the outbreak, two studies noted that the outbreaks ended following the identification and withdrawal of the contaminated products.[30, 31] Issues with sterilisation, including inadequate re-sterilisation procedures and instrument reuse without proper sterilisation, were particularly implicated in the contaminated surgical instruments. The body of evidence is however limited by publication bias and a potential lack of applicability to Scotland, due to factors including differences in policy and practice especially with respect to sterilisation and reuse.

What guidance is available related to the prevention of post-cataract endophthalmitis?

A total of six guidance documents were identified in relation to this question.[52-57] Three were published in the UK,[54-56] the remainder were published in India,[57] Europe,[52] and the United States, respectively.[53] Two documents[52, 57] provided guidance for cataract surgery (with one specific to IPC),[57] another provided guidance for general surgery[55] and another for management of outbreaks.[54] The remaining two were focussed on cleaning and sterilisation of intraocular surgery equipment and environment.[53, 56] Excluding the European guidance published in 2013,[52] the remainder of the guidance documents were published in the last five years (2018 – 2022).

The methods used to develop all the guidance documents were unclear. While one UK guidance document (managing an outbreak of postoperative endophthalmitis) stated that it was based on published evidence and expert consensus, no specific details were provided on the methodology used.[54] The document published in the USA was heavily based on recently published studies that were predominantly led by members of the task force (who were responsible for developing the guidance),[58] which may have introduced bias in the recommendations made.[53] Although the guidance document published in India[57] claimed to have been developed using scientific principles and evidence, it lacked proper referencing for most recommendations. Two guidance documents gave no mention of the guidance formulation process or the source of the recommendations.[56] [55]

The key factors relevant to IPC that were discussed by the guidance documents were: auditing of intra-ocular solutions/topical drops,[54, 57] operating room/theatre design and disinfection,[52, 54, 56, 57] phaco machine management,[53, 57] sterilisation protocols,[52-54, 57] single use of equipment,[52-54] and personal protective equipment (PPE) use.[54-57]

Three guidance documents provide recommendations on preventing infections from intra-ocular solutions and topical drops and they discussed such factors as microbiological testing for each batch, single session use and single use medications.[52, 54, 57]

More recommendations were available for the operating theatre. These recommendations addressed air flow/ventilation systems,[52, 56, 57] separation of clean and dirty areas,[54, 56] cleaning and disinfection[54, 57] and minimisation of unnecessary traffic.[54, 56, 57]

Guidance was also provided around the maintenance and cleaning of phacoemulsification machinery,[53, 54] sterilisation methods, monitoring and processes as well as on the feasibility and safety of re-use of disposable equipment such as phaco tips.[53] Guidance published by the Ophthalmic instrument cleaning and sterilisation taskforce provided recommendations on the sterilisation of instruments used for cataract surgery, providing recommendations regarding sequential same-day reuse and what to do when it is not possible to follow the manufacturer's instruction for use.[53]

Three documents provided recommendations on PPE use, namely masks, gloves, gowns and caps. Overall, there was a lack of consensus regarding the PPE required for use by the surgical team, and by patients.[54, 56, 57] Evidence-based guidance regarding use of PPE can be found in the **NIPCM**.

In summary, the six guidance documents included in this review covered a range of IPC aspects related to the prevention of post-surgery endophthalmitis. The methods of development were unclear and although some authors noted that the recommendations were based on published evidence, expert consensus, scientific principles, and practice, some of these claims could not be validated because of a lack of relevant references. The documents were published within the last five years with the exception of one published in 2013.[52]

6. Conclusion

Overall, this review identified various organisms associated with post cataract surgery endophthalmitis including gram-positive and negative bacteria as well as fungi. Outbreak studies were heavily associated with gram-negative organisms whilst retrospective case reviews were more associated with gram-positive organisms. In the studies identified for this review, these organisms were introduced to patients through contaminated ophthalmic solutions, inappropriately decontaminated surgical instruments and contaminated ventilation systems. These findings must however be interpreted within the context of the review, noting the clear potential for publication bias. There is also a potential lack of applicability of the findings of this review to Scotland because of differences in systems, practice, and standards in the included evidence base.

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Appendix 1 – Search strategy

Database search on post-cataract surgery endophthalmitis

Search performed on April 13, 2023

Ovid MEDLINE

Line	Search Term	Result number
1	*Cataract Extraction/	18984
2	(cataract$ adj4 (surg$ or operat$ or extract$ or aspirat$ or excis$ or remov$ or emulsif$ or implant$)).ti,ab,kf.	33863
3	post?cataract.ti,ab,kf.	225
4	Phacoemulsification/	11634
5	(pha?oemulsif$ or phaco or phako).ti,ab,kf.	10897
6	1 or 2 or 3 or 4 or 5	45205
7	*Endophthalmitis/	6416
8	endophthalmiti$.ti,ab,kf.	9421
9	ophthalmia.ti,ab,kf.	1989
10	7 or 8 or 9	12333
11	exp *Infection Control/	41325
12	exp *Cross Infection/	47255
13	exp *Disease Transmission, Infectious/	45086
14	exp *Decontamination/	3295
15	exp *Equipment Contamination/	7767

16	Postoperative Complications/pc [Prevention & Control]	50789
17	((infect$ or endophthalmiti$) adj3 (prevent$ or control$ or manag$)).ti,ab,kf.	130832
18	(cross infect$ or contamina$ or decontamina$ or sterili$ or disinfect$).ti,ab,kf.	380922
19	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	641568
20	6 and 10 and 19	564
21	limit 20 to english language	504
22	**limit 21 to yr="2010 -Current"**	**280**

Embase:

Line	Search Term	Result number
1	*cataract extraction/	20593
2	(cataract$ adj4 (surg$ or operat$ or extract$ or aspirat$ or excis$ or remov$ or emulsif$ or implant$)).ti,ab,kf.	39488
3	post?cataract.ti,ab,kf.	261
4	phacoemulsification/	17987
5	(pha?oemulsif$ or phaco or phako).ti,ab,kf.	14329
6	1 or 2 or 3 or 4 or 5	53244
7	*endophthalmitis/	6953

8	*fungal endophthalmitis/ **Note:** Embase has a separate subject heading for fungal endophthalmitis, so this has been included in order to ensure that this form of the infection is captured	308
9	endophthalmiti$.ti,ab,kf.	11615
10	ophthalmia.ti,ab,kf.	1432
11	7 or 8 or 9 or 10	13697
12	exp *infection control/	38258
13	exp *cross infection/	12282
14	exp *disease transmission/	40521
15	exp *medical device contamination/	401
16	exp *"prevention and control"/	741670
17	postoperative complication/pc [Prevention]	19072
18	((infect$ or endophthalmiti$) adj3 (prevent$ or control$ or manag$)).ti,ab,kf.	168932
19	(cross infect$ or contamina$ or decontamina$ or sterili$ or disinfect$).ti,ab,kf.	444514
20	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	1338291
21	6 and 11 and 20	725
22	limit 21 to english language	620

23	22 not conference*.so,pt.	543
24	limit 23 to yr="2010 -Current"	329

Results after deduplication: 390