CLINICAL PRACTICE GUIDELINES

August 2006 MOH/P/PAK/116.06 (GU)

MANAGEMENT OF POST-OPERATIVE INFECTIOUS ENDOPHTHALMITIS

MINISTRY OF HEALTH MALAYSIA

ACADEMY OF MEDICINE

Statement of Intent

This clinical practice guideline is meant to be a guide for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily ensure the best outcome in every case. Every health care provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

Review of the Guidelines

This guideline was issued in August 2006 and will be reviewed in August 2009 or sooner if new evidence becomes available.

CPG Secretariat
c/o Health Technology Assessment Unit
Medical Development Division
Ministry of Health Malaysia
Level 4, Block E1, Parcel E,
Government Office Complex,
62590, Putrajaya.

Available on the following website : http//www.moh.gov.my
http://www.acadmed.org.my

GUIDELINE DEVELOPMENT AND OBJECTIVE

Guideline Development

Post-operative endophthalmitis, though infrequent, remains a serious and blinding complication following intraocular surgery. However, variations in the management of post-operative infectious endophthalmitis still exist amongst ophthalmologists in Malaysia. This national guideline has been compiled by a committee comprising of ophthalmologists, a pharmacist and a nursing officer from the public and private sector. It aims to present evidence-based recommendations as a guide for the prophylaxis and management of post-operative infectious endophthalmitis.

Relevant key words 'post-operative endophthalmitis', 'endophthalmitis', 'endophthalmitis AND causative organism', 'endophthalmitis AND prophylaxis', 'endophthalmitis AND infection control', 'endophthalmitis AND clinical features', 'endophthalmitis AND management' were used to generate literature from the following databases (PubMed), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews and Cochrane Controlled Trial Register via OVID search engine. Searches were also manually done in non-indexed journals and "grey literature". Existing guideline, mainly the ESCRS Guidelines on prevention, investigation and management of post-operative endophthalmitis was included as reference. The experience and knowledge of the CPG development group was also considered when formulating the guideline.

Assessment of the evidence was conducted independently by individual members and discussed as a group before decisions were made. In each area considered, the best evidence available was given more weightage. Less well designed studies were either merely mentioned or excluded unless they added a different perspective. Related articles were selected and out of these, relevant articles were chosen and graded using the modified version of the Catalonian Agency for Health Technology Assessment and Research (CAHTAR) model. The grading of recommendations was modified from the Scottish Intercollegiate Guideline Network (SIGN).

Objective

To provide guidelines to ophthalmic surgeons in the prophylaxis and treatment of post-operative infectious endophthalmitis based on best available evidence.

Clinical Questions

The clinical questions of these guidelines are:

i) What are the risk factors of post-operative infectious endophthalmitis?
ii) What are the prophylactic measures for the condition?
iii) What are the clinical features and investigations required for patients with post-operative infectious endophthalmitis?
iv) What is the management of post-operative infectious endophthalmitis?

Target Population

Patients undergoing intraocular surgery and patients who develop post-operative infectious endophthalmitis.

Target Group

This guideline is applicable to doctors and eye care providers who perform ocular surgery and are involved in the management of patients with post-operative infectious endophthalmitis.

Clinical Indicators for Quality Management

Treatment setting	:	Secondary care/ tertiary care
Name of indicator	:	Rate of post-operative infectious endophthalmitis
Numerator	:	Number of cases with post-operative infectious endophthalmitis in a year
Denominator	:	Total number of intraocular surgery performed in the corresponding year, excluding surgery for penetrating eye injury

Rate of post-operative infectious endophthalmitis
= (Numerator/ Denominator) x 100%

GUIDELINE DEVELOPMENT GROUP

CHAIRPERSON

Dr. Mariam Ismail
Consultant Ophthalmologist
Selayang Hospital
Selangor

MEMBERS

Dr. Bethel Indira Livingstone
Consultant Ophthalmologist
Seremban Hospital
Negeri Sembilan

Dr. Elias Hussein
Consultant Ophthalmologist
Selayang Hospital
Selangor

Dr. Goh Pik Pin
Consultant Ophthalmologist
Selayang Hospital
Selangor

Dr. Lim Kian Seng
Consultant Ophthalmologist
Selayang Hospital
Selangor

Dr. Loh Swee Seng
Consultant Ophthalmologist
Sultanah Aminah Hospital
Johor Baru

Prof. Dr. Hajjah Muhaya Muhammad
Consultant Ophthalmologist
UKM Hospital
Cheras

Dr Nor Fariza Ngah
Consultant Ophthalmologist
Selayang Hospital
Selangor

Mr. T. Subramaniam
Pharmacist
Putrajaya Hospital

Ms Zurina Mohamad Saleh
Infection Control Unit
UKM Hospital
Cheras

COORDINATORS

Dr S Sivalal
Deputy Director
Health Technology
Assessment Unit
Medical Development Division
Ministry of Health Malaysia

Dr Sheamini Sivasampu
Principal Assistant Director
Health Technology
Assessment Unit
Medical Development Division
Ministry of Health Malaysia

Mr. Ganesan a/l Thankaveloo
Senior Medical Assistant
Health Technology
Assessment Unit
Medical Development Division
Ministry of Health Malaysia

Ms Jeya Devi Cooramasamy
Senior Nursing Officer
Health Technology
Assessment Unit
Medical Development Division
Ministry of Health Malaysia

SPECIALIST REVIEWERS

The draft guideline was reviewed by a panel of independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence supporting the recommendations in the guideline.

Dr Lai Yoon Kee	Consultant Ophthalmologist Gleneagles Medical Centre Penang 1 Jalan Pangkor 10500 Penang
Professor Susan Lightman	Consultant Ophthalmologist Moorfields Eye Hospital City Road EV12 2PD London United Kingdom

The draft guideline was also available on the websites of Ministry of Health Malaysia and Academy of Medicine to allow interested parties to submit opinions and comments of the guideline.

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1. INTRODUCTION

Post-operative infectious endophthalmitis is an infrequent but devastating complication of ophthalmic surgery. Its occurrence can lead to poor visual prognosis, and increase in health care cost. The rate of post-operative infectious endophthalmitis therefore is frequently used as an indicator for quality assurance of ophthalmology services. It is currently used as one of the national indicator approaches (NIA) in the Ministry of Health Malaysia (MOH).

1.1 Definition

For practical purposes, post-operative infectious endophthalmitis is defined as intraocular inflammation caused by an infective process following intraocular surgery. Intra-ocular surgery is defined as any ocular surgery where the full thickness of the cornea and / or sclera has been breached. This definition excludes patients with penetrating eye injury.

Acute infectious endophthalmitis usually presents within two weeks of surgery, whereas chronic infectious endophthalmitis usually present a few weeks or months following surgery.

1.2 Magnitude of Problem

Over the past decades, the incidence of post-operative infectious endophthalmitis has shown a decline due to improvements in surgical techniques and instrumentation. Emphasis on sterility and prophylactic measures may also have a role in this decline. The incidence of post-operative endophthalmitis ranges from 0.07% [1, Level 8; 2, Level 8] to 1.8% [3, Level 8]. Incidence rates differ with the type of surgery. Cataract surgery, being the most commonly performed ocular surgery, is the most common type of surgery preceding endophthalmitis, with incidences ranging from 0.07% to 0.13% [4, Level 8]. The incidence following specific type of surgery was : secondary intraocular lens (IOL) 0.30% to 0.40 %, extra-capsular cataract extraction (ECCE) with or without IOL implantation 0.072% to 0.18%, phacoemulsification 0.015% to 0.5%, penetrating keratoplasty 0.11 % to 0.18%, glaucoma filtering surgery 0.06% to 1.8%, pars plana vitrectomy 0.046% to 0.07%, combined trabeculectomy and cataract surgery 0.11%, combined penetrating keratoplasty and cataract surgery 0.19% [4, Level 9, 5 Level 8].

In Malaysia, the rates of post-operative infectious endophthalmitis following all intraocular surgery in MOH hospitals ranged from 0% to 1.13%, with a mean of 0.26 % for 2 consecutive years (2003 and 2004) and a mean of 0.18% for the year 2005 (Unpublished data, Annual MOH census).

The rate following cataract surgery based on the National Cataract Surgery Registry of MOH hospitals was 0.19% in 2002, 0.24% in 2003 and 0.16% in 2004 [6, Level 9 ; 7, Level 9; 8, Level 9].

1.3 Causative Organism

The microbial spectrum seen in post-operative endophthalmitis depends on various factors including environmental, geographic climatic conditions as well as types of surgery.

Table 1 : Causative Organism- Microbial Spectrum Based on Type of Surgery

Type of surgery	Micro organism	Percentage
Cataract surgery (acute)	Coagulase negative staphylococcus i.e. *Staphylococcus epidermidis*	33-77%
	Staphylococcus aureus	10-21%
	Beta haemolytic streptococcus, *Streptococcus pneumoniae,* alpha-haemolytic streptococci including *S.mitis* and *S. salivarius*	9-19%
	Gram negative bacteria including *Pseudomonas aeruginosa*, *Bacteroids* species	6-22 %
	Fungi including *Candida* species, *Aspergillus* species, *Fusarium* species	Up to 8%
Cataract surgery (chronic)	*Propionibacterium acnes, Corynebacterium* including *C.macginleyi*, and fungi	-
Glaucoma surgery (acute)	Coagulase negative *staphylococcus*	Up to 67%
Glaucoma surgery (chronic)	*Streptococcus*, gram negative bacteria especially *Haemophilus influenza*	-

(Adapted from ESCRS Guidelines 2005 with permission)

1.4 Risk Factors

The source of infection following intraocular surgery include lids, adnexa, ocular tear film, respiratory and skin flora of the surgeons and assistants, surgical instruments including IOL, irrigating solutions and operating room air [9, Level 1]. As sterile surgical technique addresses many of these factors, the common sources of pathogens are thus from ocular surface and adnexa [10, Level 2; 11, Level 8].

Table 2 : General Risk Factors

General Factors	Evidence / Level of Evidence
Ocular Factors	Preoperative risk factors include presence of blepharitis, conjunctivitis, dacryocystitis, lacrimal duct obstruction, contact lens wear, and ocular prosthesis in the fellow orbit [12, Level 9] Intra-operative risk factors include inadequate eyelid and conjunctival disinfection [13, Level 7], inadequate draping of lid and lashes [14, Level 9], prolonged surgery [13, Level 7] and presence of intra-operative complications [15, Level 7] Post-operative risk factors include wound leak and wound dehiscence, inadequately buried sutures, suture removal, vitreous incarceration in the surgical wound and occurrence of filtering bleb [4, Level 9]
Systemic Factors	Host immunosuppression, diabetes mellitus [16, Level 7; 1 Level 8, 17, Level 2] Presence of atopic dermatitis and keratoconjunctivitis sicca [18, Level 9] Patient on topical or systemic immunosuppressive drugs such as corticosteroid and antimetabolites [19, Level 7]
Other Factors	Respiratory and skin flora of the surgeons and assistants [9 , Level 1] Surgical instruments including intraocular lens [9, Level 1] Irrigating solutions and medications [9, Level 1] Operating room air [9, Level 1]

Table 3 : Specific Risk Factors In Relation to the Type of Intraocular Surgery

General Factors	Evidence / Level of Evidence
Cataract Surgery	
Type of Cataract Surgery	Intracapsular cataract extraction (ICCE) has higher risk when compared to extracapsular cataract extraction (ECCE) (5, Level 8) ECCE has higher risk when compared to phacoemulsification (20, Level 8) Secondary IOL implantation has higher risk due to associated factors such as transcleral suture fixation of posterior chamber IOL, polypropylene haptics, re-entering the eye through a previous wound and post-operative wound defects (21, Level 8)
Site of incision	The risk is higher with clear cornea incision when compared to scleral tunnel incision (22, Level 8; 23, Level 2)
Duration of surgery	The risk is higher with longer duration of surgery (13, Level7)
Intra-operative complications and anterior vitrectomy	Occurrence of posterior capsular rupture and vitreous loss, as well as performance of anterior vitrectomy is associated with higher risk (5, Level 8; 15, Level 6; 20, Level 8; 24, Level 8; 25, Level 8)
IOL material	Polypropylene haptic IOL is associated with higher risk (13, Level 7) Silicon IOL has higher risk as compared to polymethylmethalcrylate (PMMA) and acrylic IOL (15, Level 7) Foldable lenses have higher risk when compared to injectable lenses (20, Level 8)
Glaucoma Filtering Surgery	Inferiorly located bleb is associated with higher risk. (26, Level 9; 27, Level 8; 3, Level 8; 28, Level 7) The use of mitomycin C is associated with higher risk (26, Level 9; 29, Level 7) Performance of full thickness rather than a guarded filtration procedure (29, Level 7) Highly elevated or leaking bleb is associated with higher risk (29, Level 7)
Penetrating Keratoplasty	Contaminated donor button is associated with higher risk (30, Level 8)

Patients who are exposed to any of the above risk factors should be monitored closely for symptoms and signs of infection.

2. PROPHYLACTIC MEASURES

The low incidence of post-operative infectious endophthalmitis makes it difficult to assess accurately the efficacy of preventive measures. Many studies either have low statistical power in assessing the influence of a change in procedure on the incidence of post-operative endophthalmitis, or measure surrogate outcomes such as change in conjunctival flora or aqueous bacterial counts. In addition, most of the studies on prophylaxis were related to cataract surgery and thus its application to other forms of ocular surgeries may not apply.

As the ocular surface is a common source of pathogens (10, Level 2; 11, Level 8) various measures have been used to prepare the ocular surface before surgery to reduce normal ocular surface flora.

2.1 Antiseptic Measures

a. Preoperative povidone iodine on skin and conjunctival sac

Povidone iodine 5% solution has been shown to decrease the number of colonies isolated from the conjunctiva by 91% and decrease the number of species by 50%. (9, Level I; 31, Level 3; 32, Level 7; 33, Level 7; 34, Level 7; 35, Level 4; 36, Level 8; 37, Level 8). Instillation of topical 5% povidone iodine solution into the conjunctival sac just before surgery significantly reduced the incidence of culture positive endophthalmitis as compared to silver nitrate solution (38, Level 4; 9, Level I). Even when used at 1.25% preoperatively, topical povidone iodine has shown a significant reduction in the conjunctival bacterial counts (39, Level 4).

Its application to the eye at the end of surgery has also been shown to be effective in reducing conjunctival bacterial flora and was in fact more effective when compared to topical broad spectrum antibiotics (40, Level 7).

However, on the basis of available clinical studies, only povidone iodine in a concentration of 5% in balanced salt solution (BSS) or isotonic saline can be recommended as the preoperative antiseptic of choice (26, Level 9). Chlorhexidine 0.05% should be used as the alternative in patients who are allergic to povidone iodine (26, Level 9).

The use of povidone iodine was not associated with significant adverse reactions (38, Level 4).

b. Draping of periorbital area

Inadequate draping of the periorbital areas with exposed lids and lashes to the surgical site might be a possible risk factor [14, Level 9].

c. Trimming of eyelash

Preoperative trimming of eyelashes is not associated with a reduction of risk of post-operative endophthalmitis [22, Level 8; 9, Level 1].

d. Preoperative irrigation of lacrimal passages

Preoperative irrigation of the lacrimal passages has no significant effect as prophylactic measure [9, Level 1].

e. Preoperative saline irrigation of conjunctival sac

Saline irrigation of conjunctival sac did not reduce the bacterial flora [9, Level 1; 34, Level 4].

2.2 Antibiotics Prophylaxis

a. Intracameral antibiotic

i. Intracameral injection of cefuroxime at the end of surgery

Intracameral injection of 1mg cefuroxime in 0.1 ml at the end of phacoemulsification surgery has been shown to significantly reduce the risk of post-operative endophthalmitis up to five folds in a multicenter European study [41, Level 2]. This prophylactic measure has been adopted by all Swedish cataract surgeons [42, Level 7]. Refer Appendix 4 for the dilution of intracameral cefuroxime. Careful dilution should be undertaken to ensure its safe use and to prevent potential toxicity.

ii. Intracameral irrigation of antibiotic through addition of vancomycin into irrigating solution

Anterior chamber contamination at the end of cataract surgery varies from 0.18% to 13.7% [26, Level 9; 43, Level 8]. Although some studies evaluating intraocular fluid contamination have shown that irrigating solution with vancomycin have reduced positive aqueous cultures [44, Level 9; 45, Level 8; 46, Level 2], whether the reduction is meaningful remains doubtful [26, Level 9]. Furthermore, it has been shown that exposure to an antibiotic for a short duration during

intraocular surgery has little effect on organisms commonly responsible for endophthalmitis [47, Level 9]. As its use can cause retinal toxicity from inadvertent dilution error including irreversible macular infarct, as well as resulting in antibiotic resistance, it is generally not recommended [48, Level 9; 49, Level 9; 50, Level 9].

b. Preoperative topical antibiotic

There is insufficient evidence to show that the use of preoperative topical antibiotic significantly reduces the risk of post-operative infectious endophthalmitis [9, Level 1; 41, Level 2].

c. Preoperative systemic antibiotic

Intravenous antibiotic prophylaxis is not proven to be of benefit in preventing post-operative endophthalmitis [26, Level 9].

d. Post-operative subconjunctival antibiotic injection

Sub-conjunctival antibiotic injection at the conclusion of surgery does not appear to prevent post-operative endophthalmitis [22, Level 9].

2.3 Heparinized Intraocular Infusion Solution and Heparin Coated IOL

Heparin coats the lens and intraocular surface and thus prevent bacterial adherence [51, Level 9]. However there is no sufficient evidence to indicate benefits of both heparinized irrigating solution and heparin coated IOL in preventing post-operative infectious endophthalmitis [52, Level 3].

2.4 Operating Theatre

a. Air flow design

There are no current guidelines for the type of airflow best required to prevent post-operative infectious endophthalmitis for intraocular surgery. The ideal type of airflow system is being investigated by the ESCRS multi-centre study on endophthalmitis after phacoemulsification surgery [26, Level 9].

b. Equipment sterilization

All equipment for surgery should be sterile. Care is required with both washing and autoclaving the instruments. It is preferable that tubing that becomes wet within the operative procedure

should not be reused. Bottles of balanced salt solution (BSS) should never be kept overnight or used for more than one operating session. Operating theatre trolleys must be kept dry as wet areas are easily contaminated with Pseudomonas aeruginosa [26, Level 9].

Further details of prophylactic measures are given in Appendix 1.

Recommendations for prophylaxis
Use of povidone iodine 5% as an antiseptic agent for preparation of skin and conjunctival sac preoperatively is recommended. (Grade A)
Proper draping of the eyelid margin using an adhesive non porous drape and the use of speculum to cover all the eyelashes is recommended. (Grade C)
Intracameral injection of 1 mg cefuroxime in 0.1ml at the end of surgery is recommended. Careful dilution should be undertaken to prevent potential toxicity. (Grade A)

3. DIAGNOSIS AND INVESTIGATIONS

Patients who have undergone intraocular surgery and who develop the following clinical features should be assessed and monitored closely. Prompt management with intravitreal tap and intravitreal antibiotic injection should be performed in clinically suspected cases of post-operative infectious endophthalmitis.

3.1 Clinical Features

a. Acute post-operative endophthalmitis

The symptoms and signs may include the following:

- Ocular pain (74-85%) [53, Level 2; 16, Level 7; 26, Level 9; 50, Level 9]
- Reduced vision (>90%) [53, Level 2; 16, Level 7 ; 50, Level 9; 26, Level 9]
- Swollen lids (35%) [54, Level 8; 50, Level 9]
- Inflamed or oedematous conjunctiva (>80%) [54, Level 8; 50, Level 9; 26, Level 9]
- Discharge into conjunctiva [26, Level 9; 50, Level 9]

- Corneal oedema (26, Level 9, 50, Level 9)
- Cloudy anterior chamber with cells, hypopyon or fibrin (75-85%) (54, Level 8; 26 , Level 9; 50, Level 9)
- Vitreous clouding (vitritis) (26, Level 9; 50, Level 9)
- Involvement of posterior segment with retinitis, and/or retinal periphlebitis, retinal oedema and papillary oedema (26, Level 9; 50, Level 9)

Involvement of posterior segment is virtually always accompanied by severe anterior segment inflammation.

b. Chronic post-operative infectious endophthalmitis

Patients may present with any of the symptoms and signs of acute post-operative endophthalmitis. Features include:

- Corneal oedema (55, Level 8)
- Mutton fat keratic precipitates on IOL or corneal endothelium (4, Level 9)
- Persistent low grade uveitis that may respond to corticosteroids initially (typical) (4, Level 9)
- Hypopyon – sometimes so small that it can only be visible with gonioscopy, or recurrent hypopyon that fails to respond to corticosteroid (4, Level 9; 26,level 9)
- White 'string-of-pearl' infiltrate in the anterior chamber and vitreous are sometimes seen in fungal infections (4, Level 9)
- Plaque located on the posterior capsule, IOL or retained lens particles (40-89%) (56, Level 9; 57, Level 9; 4, Level 9)
- Vitreous clouding (vitritis) from chronic inflammation (4, Level 9; 26, Level 9)

3.2 Investigations

When a clinical diagnosis of acute or chronic post-operative infectious endophthalmitis is made, a vitreous tap should be performed **within ONE hour** after clinical diagnosis, together with administration of an intravitreal antibiotic injection (26, Level 9). Anterior chamber tap is helpful in the identification of the causative organism as some organisms grow from the aqueous but not from the vitreous sample.

Aqueous and vitreous specimens should be sent for gram stain, culture and sensitivity. Polymerase chain reaction (PCR) methods offer much improved pathogen detection especially in the case of chronic endophthalmitis with low pathogen counts (58, Level 8).

However, due to its high sensitivity, problems with availability and the risk of contamination, its use as routine diagnostic test is limited [26, Level 9].

Vitreous biopsy has not been shown to have better microbial yield as compared to vitreous tap [59, Level 2].

Conjunctival and corneal swabs are usually not helpful in isolating the causative microorganisms [38, Level 4].

Refer Appendix 2 for the performance of anterior chamber tap, vitreous tap and intravitreal antibiotic injection.

4. TREATMENT

There is variation in the treatment of post-operative infectious endophthalmitis and the treatment approach is usually based on institutional protocol.

4.1 Treatment of Acute Post-operative Infectious Endophthalmitis

a. Antimicrobial therapy

i. Intravitreal antibiotics

Intravitreal antibiotics should be given as soon as possible after clinical diagnosis has been made [4, Level 9; 26, Level 9; 50, Level 9]. This should be preceded by intravitreal tap. Intravitreal antibiotic may be repeated as necessary judging by the clinical response, usually at an interval of 48-72 hours [50, Level 9]. The time interval for repeat intravitreal antibiotic depends on the half-life of the antibiotic used.

A combination of broad-spectrum antibiotics covering both gram positive and negative organism is used. The choice of antibiotics should be reviewed following the culture and sensitivity results.

The commonly used antibiotic combinations are:

- Vancomycin (2mg in 0.1ml) AND Ceftazidime (2mg in 0.1ml) [60, Level 2; 4, Level 8; 61, Level 9] OR
- Vancomycin (2mg in 0.1ml) AND Amikacin (0.4mg in 0.1ml) [4, Level 8; 53, Level 2]

Ceftazidime is preferred over amikacin in view of amikacin related retinal toxicity [53, level 2; 62, level 9; 48, Level 9; 4, Level 9].

Patient's clinical progress should be observed and monitored closely. Early referral for a vitreoretinal opinion after intravitreal antibiotic injection is recommended.

Refer Appendix 3 for the preparation of intravitreal drugs using aseptic technique.

ii. Topical and subconjunctival injection of antibiotic

The aim of topical and subconjunctival injection of broad spectrum antibiotics use is to treate possible ocular surface and anterior segment infection. Topical ceftazidime (5% or 50mg/ml), topical vancomycin (5% or 50mg/ml) or other broad spectrum antibiotics eye drops are used, either as monotherapy or combined therapy, hourly round the clock initially with subsequent tapering according to clinical response [50, Level 9]. Subconjunctival injection of antibiotic can be used together with intravitreal antibiotics in the treatment of post-operative endophthalmitis. This is done in the hope of achieving higher concentration of antibiotics around the eye and in the anterior chamber, especially when the frequent round the clock instillation of topical antibiotics at the initial period is not possible [4, Level 9]. When giving subconjunctival antibiotic, subconjunctival mydricane can be given to get pupillary dilatation which helps the movement of antibiotic around the eye.

iii. Systemic antimicrobial therapy

The Endophthalmitis Vitrectomy Study concluded that systemic ceftazidime and amikacin did not have any effect on the course and outcome of endophthalmitis after cataract surgery [53, Level 2].

In cases of severe, virulent endophthalmitis, systemic intravenous antibiotics of the same choice as intravitreal antibiotics should be given [4, Level 9]. Alternatively, oral moxifloxacin (400mg daily for 10 days) or oral ciprofloxacin (750mg bd for 14 days) can be given. However, systemic fluoroquinolones are to be used with caution in children [50, Level 9].

Oral clarithromycin (500mg bd for 2 weeks) is recommended for patients with acute post-operative endophthalmitis with a culture

negative eye (66, Level 8; 67, Level 8). It acts as a biofilm reducing agent to enhance the efficacy of cefuroxime, ceftazidime and amikacin.

In view of a high incidence of resistance to ciprofloxacin, fourth generation fluoroquinolones, oral moxifloxacin (400mg daily for 10 days) has been used (65, Level 9). In addition, moxifloxacin has an anti-biofilm effect on coagulase- negative staphylococci, which are one of the commonest infecting organisms following cataract surgery. Besides, moxifloxacin has also been shown to have better penetration to inflamed ocular tissue (68, Level 9; 69, 2006, Level 8). This may therefore improve the ocular prognosis. When oral moxifloxacin is used, the use of oral clarithromycin is not indicated (65, Level 9).

b. Anti-inflammatory therapy

There is limited evidence on the efficacy of intravitreal and periocular corticosteroids in the treatment of post-operative infectious endophthalmitis. While intravitreal dexamethasone reduces early inflammation in bacterial endophthalmitis, it has no independent influence on the visual outcome (63, Level 8; 64, Level 8).

Intensive topical prednisolone acetate 1% or dexamethasone 1% every 1 to 2 hours is recommended to control anterior chamber inflammation. Its use should begin soon after intravitreal injection of antibiotics (65, Level 9).

Oral prednisolone one day after intra-vitreal antibiotic therapy has not been shown to have any negative effect on the course of infection in bacterial endophthalmitis (53, Level 2). It may be used in those who have no contraindications for corticosteroid (50, Level 9; 65, Level 9). The dosage of oral prednisolone is 1 mg/kg/day, to be tapered by 10mg each week for a total duration of up to 3 weeks (65, Level 9). Tablet ranitidine is prescribed simultaneously for gastric protection. Patients with fungal endophthalmitis should not be given prednisolone.

c. Tissue Plasminogen Activator (TPA)

TPA has only been reported to be useful as adjunctive therapy in animal studies and in a small case series of endophthalmitis with severe fibrinous anterior chamber reaction (70, Level 9; 71, Level 9; 72, Level 9).

There is insufficient evidence for its routine use for both acute and chronic post-operative endophthalmitis. However, intracameral injection of 25 mg in 0.1 ml is recommended in patients with severe fibrinous anterior chamber reactions particularly in eyes with pupils that do not dilate with mydriatics.

d. Vitrectomy

According to Endopthalmitis Vitrectomy Study (EVS), routine immediate vitrectomy is not necessary in patients with better than light perception vision at presentation but is of substantial benefit for those who have light perception- only vision [53, level 2; 73, Level 9]. However, limitations of EVS leave this conclusion open to future modification [26, Level 9; 74, Level 9].

Recommendation for treatment of acute post-operative endophthalmitis
Intravitreal antibiotic should be given within 1 hour of diagnosis and repeated when necessary. (Grade C)
Intensive topical antibiotic and steroid should be given round the clock initially. (Grade C)
Subconjunctival antibiotic is given when indicated. (Grade C)
The use of oral or intravenous antibiotics is recommended for endophthalmitis patients with virulent infection. (Grade C)
Systemic corticosteroid may be given. (Grade C)
Oral clarithromycin (500mg bd for 2 weeks) is recommended in culture negative cases with poor clinical response. (Grade C)
Intracameral tissue plasminogen activator (25mg in 0.1ml) is recommended in patients with severe anterior chamber reaction. (Grade C)
Vitrectomy may have a role in improving prognosis. Therefore, early referral for a vitreoretinal opinion is recommended. (Grade C)

Refer algorithm for the management of acute post-operative endophthalmitis

Vitrectomy with or without silicone oil tamponade has been shown in recent case series, to increase the chance of surgical success and decrease the number of additional procedures in eyes with post-operative infectious endophthalmitis [75, Level 7].

4.2 Treatment of Chronic Post-operative Infectious Endophthalmitis

a. Antimicrobial therapy

Intravitreal antibiotic is given to all patients with chronic post-operative endophthalmitis. The choice of intravitreal antibiotic is similar to that in acute post-operative endophthalmitis [76, Level 6; 4, Level 9].

The decision to use topical and systemic antimicrobials in chronic post-operative infectious endophthalmitis is the same as that for acute post-operative infectious endophthalmitis [26, Level 9].

For suspected fungal endophthalmitis, intravitreal amphotericin B (5ug or 10ug in 0.1ml) has been proven to be effective. Intravitreal miconazole (0.01mg in 0.1ml) should be considered for fungi resistant to amphotericin B [76, level 9; 4, Level 9].

Combined systemic therapy with amphotericin B and imidazole is effective in infection with Fusarium sp. whereas voriconazole or fluconazole is effective for Candida albicans. Itraconazole can be used for other Candida species, Aspergillus or Cryptococcus [77, Level 9].

The indication for he use of systemic clarithromycin is as per acute post-operative endophthalmitis [66, Level 8; 67, Level 8; 26, level 9].

b. Vitrectomy

There is insufficient evidence for or against vitrectomy in the treatment of chronic post-operative endophthalmitis. However, in cases of suspected or confirmed Propionebacterium acnes or fungal endophthalmitis following cataract surgery, removal of IOL and posterior lens capsule with vitrectomy should be considered [4, Level 9; 18, Level 9].

Recommendation for treatment of chronic post-operative endophthalmitis	
Intravitreal antibiotic should be given promptly.	(Grade C)
Intravitreal amphotericin B (5ug or 10ug in 0.1ml) is to be given if fungal endophthalmitis is suspected.	(Grade C)
Topical antibiotics and steroid should be given.	(Grade C)
Systemic anti-fungals to be given when indicated.	(Grade C)
The use of oral or intravenous antibiotics is indicated in patients with severe endophthalmitis.	(Grade C)
Oral clarithromycin (500mg bd for 2 weeks) is recommended in culture negative cases with poor clinical response.	(Grade C)
Intracameral tissue plasminogen activator (25mg in 0.1ml) is recommended in patients with severe anterior chamber reaction.	(Grade C)
Early referral for vitreoretinal consultation is recommended.	(Grade C)

Refer algorithm for the management of chronic post-operative endophthalmitis

5. CLINICAL AUDIT INDICATOR

The incidence rate of post-operative infectious endophthalmitis should be monitored as a performance indicator by all ophthalmic facilities. Currently data from MOH hospitals are being collected by the ophthalmology service, MOH.

ALGORITHM FOR THE MANAGEMENT OF ACUTE POST-OPERATIVE INFECTIOUS ENDOPHTHALMITIS

CLINICAL DIAGNOSIS

History:
Patient who presents within 2 weeks of intraocular surgery with signs and symptoms suspicious of endophthalmitis (refer to text)

Examination
1. Perform anterior and posterior segment examinations
2. Perform B-scan ultrasonography if necessary

↓

INVESTIGATIONS

1. Perform vitreous tap +/- anterior chamber tap. Preferably to be done within **ONE** hour of clinical diagnosis
2. Send specimen for gram stain, culture and sensitivity, and PCR test where indicated

↓

TREATMENT

1. Intravitreal antibiotic injections to be given within 1 hour of diagnosis
   vancomycin and ceftazidime
   OR
   vancomycin and amikacin

2. Begin intensive topical antibiotics and topical steroid soon after intravitreal antibiotic injection, round the clock initially
3. Systemic antibiotics for severe, virulent endophthalmitis
4. Oral prednisolone to be considered and may be given 24 hours following intravitreal antibiotics injection
5. Review antibiotic regimen after microbiology results
6. Repeat intravitreal antibiotics after 48 to 72 hours if indicated
7. Consider oral clarithromycin in culture negative cases with poor clinical response
8. Early referral for a vitreoretinal opinion

ALGORITHM FOR THE MANAGEMENT OF CHRONIC POST-OPERATIVE INFECTIOUS ENDOPHTHALMITIS

CLINICAL DIAGNOSIS

History:
Patient who presents after 2 weeks of intraocular surgery with signs and symptoms suspicious of endophthalmitis (refer to text)

Examination
1. Perform anterior and posterior segment examinations
2. Perform B-scan ultrasonography if necessary

↓

INVESTIGATIONS

1. Perform vitreous tap +/- anterior chamber tap
2. Send specimen for gram stain, culture and sensitivity, and PCR test if indicated
3. If decision is made to remove the IOL, then send the lens capsule fragments for gram stain, culture and sensitivity, and PCR test if indicated

↓

TREATMENT

1. Intravitreal antibiotic injections
   vancomycin and ceftazidime
   OR
   vancomycin and amikacin
   AND/OR
   intravitreal amphotericin B if suspicious of fungal endophthalmitis

2. Begin topical steroid and topical antibiotics soon after intravitreal antibiotic injection
3. Review antibiotic regimen after microbiology results
4. Systemic anti-fungals if indicated
5. Consider oral clarithromycin in culture negative cases with poor clinical response
6. Consider intracameral tissue plasminogen activator in patients with severe anterior chamber reaction
7. Early referral for a vitreoretinal opinion

Appendix 1

PROPHYLACTIC MEASURES

1. Careful preoperative assessment of patients
   1.1. Treat patients who have predisposing risk factors such as eyelid infection, conjunctivitis, dacryocystitis and nasolacrimal duct obstruction.
   1.2. Optimize patients' medical conditions, which may affect wound healing such as diabetes mellitus and anemia.
2. Proper scrubbing of eyebrow, upper and lower eyelids, eyelashes, adjacent forehead, nose, cheek and temporal orbital areas with 5% povidone iodine*. Use chlorhexidine 0.05% as an alternative in patients who are allergic to povidone iodine.
3. Apply 5% povidone iodine to the conjunctival sac before surgery begins.
4. Proper draping of eyelid margins, and with proper use of speculum to tuck in all eyelashes under the non porous adhesive drape.
5. Ensure sterility of surgical instrument especially the microsurgical instruments that enter the eyes. Only use properly sterilized micro instruments.
6. Avoid soaking of instruments.
7. For cataract surgery
   7.1. Avoid unnecessary contact of IOL on possible areas of contamination including ocular surface.
   7.2. Use of injector for foldable lens is preferred.
   7.3. Do not share viscoelastic material between patients.
   7.4. Ensure incision is water tight at the end of surgery.
   7.5. Consider intracameral injection of 1mg cefuroxime in 0.1 ml at the end of surgery. Careful dilution must be undertaken to prevent potential toxicity.
8. Replenishment of analgesic, steroid and antibiotic eye drops used in the OT at regular intervals to prevent contamination. Label date of opening on new bottles.
9. Careful post-operative monitoring for high risk patients.

*Preparation of 5% povidone iodine is done with 1:1 dilution of the 10% solution with sterile balanced salt solution (BSS) or isotonic saline. It should be prepared on the day of surgery. The use of a large bottle of readily diluted povidone iodine or chlorhexidine should be avoided as both antiseptics can become contaminated with Pseudomonas aeruginosa. Povidone iodine solution containing detergent must NOT be used as it coagulates the cornea irreversibly [26, level 9].

Appendix 2

PROCEDURE FOR ANTERIOR CHAMBER TAP, VITREOUS TAP AND INTRAVITREAL ANTIBIOTIC INJECTION

Anterior Chamber Tap

1. Obtain consent from patient.
2. Instill topical anaesthetic drops.
3. Perform limbal paracentesis at the slit lamp, using a 1 ml syringe (not an insulin syringe) with a half inch 25 gauge needle. A larger bore needle, e.g. 23 gauge needle, may be used if there is hypopyon. Loosen the plunger first before entering the eye to ease the aspiration of aqueous.
4. Aspirate 0.1 to 0.2 ml of aqueous.
5. Inoculate aqueous specimen onto culture plates and smear it on glass slide.
6. Label the syringe, culture plates, glass slide or culture bottle before sending them to the laboratory.

Vitreous Tap

1. Obtain consent from patient.
2. Prepare vitreous tap set consisting of eyelid retractor, caliper, conjunctival forceps, 5ml syringes, 23G needle, cotton buds, eye pad, and povidone iodine 5% solution.
3. Perform procedure using aseptic technique in a quiet and clean place, either at the outpatient clinic, ward or operating theatre.
4. Clean the periorbital skin and conjunctival sac with povidone iodine 5%.
5. Drape the eye.
6. Instill topical anaesthetic drops and subconjunctival injection of 2% lignocaine.
7. Perform vitreous tap using a 5ml syringe with 23G needle. Enter the eye about 4 mm posterior to the limbus for phakic eyes or 3.5 mm for aphakic or pseudophakic eyes.
8. Aspirate about 0.2ml to 0.4 ml of vitreous.
9. Inoculate vitreous specimen onto culture plates and smear it on a glass slide.
10. Label the syringe, culture plates, glass slide or culture bottle before sending them to the laboratory

Intravitreal Antibiotic Injection

1. Prepare and dilute intravitreal antibiotics using an aseptic technique.
2. Prepare different antibiotics in separate syringes.
3. Use 26G or 30G needle and inject 4 mm (phakic eyes) or 3.5 mm (pseudophakic/ aphakic eyes) posterior to the limbus into the mid vitreous cavity, with the bevel of the needle pointing anteriorly.

PREPARATION OF INTRAVITREAL DRUGS

Intravitreal drug preparation should be freshly diluted and preferably supplied by the hospital pharmacy department. However, in case of emergency, it can be prepared in the ward using an aseptic technique. The drug preparation guide is given below.

Drug (Recommended dosage)	Preparation
Vancomycin hydrochloride (2mg in 0.1ml)	1. The vial contains 500 mg vancomycin powder 2. Reconstitute the vial with 10 ml of 0.9% normal saline (NS). Mix well 3. Withdraw 4ml (200mg) and add 6ml of 0.9% NS 4. Take 0.1 ml (=2 mg)
Ceftazidime sodium (2mg in 0.1ml)	1. The vial contains 1000 mg ceftazidime powder. 2. Reconstitute the vial with 10 ml of 0.9% NS/water for injection. Mix well 3. Withdraw 1 ml (100mg) and add 4ml of 0.9% NS/water for injection 4. Take 0.1 ml (= 2 mg)
Amikacin sulfate (0.4mg in 0.1ml)	1. The vial contains a solution of **500mg** of amikacin sulfate in 2 ml (250mg/ml) 2. Withdraw 0.8 ml (200 mg) and add 9.2ml of 0.9% NS 3. Withdraw 0.2 ml (4 mg) and add 0.8ml of 0.9% NS 4. Take 0.1 ml (= 0.4mg) 1. The vial contains a solution of **250mg** of amikacin sulfate in 2 ml (125mg/ml) 2. Withdraw 1ml (125 mg) and add 11.5 ml of 0.9% NS 3. Withdraw 0.4ml (4mg) and add 0.6ml of 0.9% NS 4. Take 0.1 ml (= 0.4mg)
Amphotericin B (0.005mg in 0.1ml)	1. The vial contains 50-mg of amphotericin B powder 2. Reconstitute the vial with 10ml sterile water for injection 3. Withdraw 1ml (5mg) and add 9ml of sterile water for injection. Mix well 4. Withdraw 1ml (0.5mg) and add 9ml of sterile water for injection. Mix well 5. Take 0.1 ml (= 0.005mg)
Miconazole (0.01mg in 0.1ml)	1. The ampoule contains 10mg/ml of miconazole 2. Withdraw 1ml (10mg) and add 9ml of 0.9% normal saline. Mix well 3. Withdraw 1ml (1mg) and add 9ml of 0.9% normal saline 4. Take 0.1ml (=0.01mg)
Dexamethasone (0.4mg in 0.1ml)	1. The vial contains a solution of 4mg of dexamethasone in 1ml 2. Take 0.1ml (= 0.4mg)

PREPARATION OF INTRACAMERAL CEFUROXIME

Drug (Recommended dosage)	Preparation	
Cefuroxime (1mg in 0.1ml)	1. The vial contain 1500mg of cefuroxime powder 2. Reconstitute the vial with 15 ml of 0.9% NS 3. Withdraw 1ml (100mg) of this solution and add 9ml of 0.9% NS 4. Take 0.1 ml (=1mg)	1. The vial contain 750mg of cefuroxime powder 2. Reconstitute the vial with 7.5 ml of 0.9% NS 3. Withdraw 1ml (100mg) of this solution and add 9ml of 0.9% NS 4. Take 0.1 ml (=1mg)

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ACKNOWLEDGEMENTS

The committee of this guideline would like to express their gratitude and appreciation to the following for their contribution:

- Panel of external reviewers who reviewed the draft.
- Technical Advisory Committee for Clinical Practice Guidelines for their valuable input and feedback.
- CPG Secretariat, particularly Datin Dr Rugayah Bakri, Head of Health Technology Assessment Unit, and Ms Hanita Muhsin, Nursing Manager, Medical Development Division, Ministry of Health Malaysia.

DISCLOSURE STATEMENT

The panel members have no potential conflict of interest to disclose.

SOURCES OF FUNDING

The development of the CPG on Management of Post-operative Infectious Endophthalmitis was supported financially in its entirety by the Ministry of Health Malaysia and was developed without any involvement of the pharmaceutical industry.

LEVELS OF EVIDENCE SCALE

Level	Strength of Evidence	Study Design
1	Good	Meta-analysis of RCT, Systematic review
2	Good	Large sample RCT
3	Good to Fair	Small sample RCT
4	Good to Fair	Non-randomised controlled prospective trial
5	Fair	Non-randomised controlled prospective trial with historical control
6	Fair	Cohort studies
7	Poor	Case-control studies
8	Poor	Non-controlled clinical series, descriptive studies multi-centre
9	Poor	Expert committees, consensus, case reports anecdotes

Adapted from Catalonian Agency for Health Technology Assessment & Research, (CAHTAR) Spain

GRADES OF RECOMMENDATIONS

A	At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and /or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality

Source : Modified from Scottish Intercollegiate Guidelines Network (SIGN)