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Original Article – Clinical Science

Fungal endophthalmitis: A 20-year experience at a tertiary referral centre

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Short running title: Fungal endophthalmitis

Received 7 February 2020; accepted 28 June 2020

Funding sources / Financial disclosure: Dr Rosie Dawkins holds a RVEEH Early Research Career Support Grant.

Conflict of interest: None

Early findings of this research were presented at the APVRS Congress in Shanghai in November 2019 – awarded “First Prize – Poster Category”.

ABSTRACT

Importance: Fungal endophthalmitis is an uncommon and serious intraocular infection, often with poor outcomes. This study examines the trend in this disease over twenty years, to inform clinician decision-making and optimise patient outcomes.

Background: Due to infrequent presentation of fungal endophthalmitis, there is limited understanding to formulate a standardised approach to management.

Design: A prospective case series over the period January 1, 1999 to December 31, 2018.

Participants: Patients with clinically diagnosed fungal endophthalmitis managed at the Royal Victorian Eye and Ear Hospital, Melbourne, Australia.

Methods: Review of the Victorian Endophthalmitis Registry for endophthalmitis episode of each patient.

Main outcome measures: Patient demographics, co-morbidities, visual acuity at presentation, aetiology, treatment, microbiology results and final visual acuity outcome.

Results: Eighty-four cases of fungal endophthalmitis were identified over the study period with a median age of 43.5 years [IQR 30.8 – 63.0]. 65.5% (n=55) of patients were male. 81.0% (n=68) of these cases were secondary to endogenous causes, of which 55.9% were associated with intravenous drug use (IVDU). Among the exogenous causes, penetrating eye injury (56.3%) was the most common aetiological factor. 39 patients (46.4%) grew Candida species from ocular fluid specimens, all of which were sensitive to fluconazole.

Conclusion and relevance: Our case series provides important insights into fungal endophthalmitis – a high degree of suspicion for fungal endophthalmitis in patients with history of IVDU, and relatively good outlook for vision when Candida is the causative organism. This should allow institutions to implement a standardised management strategy based on evidence.

Keywords: Endophthalmitis, Fungal, Endogenous endophthalmitis

1. INTRODUCTION

Fungal endophthalmitis persists as a devastating and uncommon form of endophthalmitis with poor clinical outcomes, both visual and structural. The aetiology of this intraocular infection can be divided into exogenous and endogenous sources. While endogenous endophthalmitis is secondary to haematogenous spread of the fungal pathogen to the eye via the blood-ocular barrier from distant sites of the body, exogenous tends to be direct invasion of the microorganism secondary to keratitis, trauma, or intraocular surgery. Both types of endophthalmitis can cause devastating structural effects to the eye leading to visual loss.[1,2,3]

Risk factors for endogenous fungal endophthalmitis include recent hospitalisation, diabetes mellitus, immunosuppression, urinary tract infection, intravenous drug use (IVDU), and use of indwelling urinary catheters.[4] It may however occur in immunocompetent and healthy individuals.[5,6,7] Due to Australia's ageing population, advances in medicine and recreational drug abuse, there has been a steady increase in the incidence of fungal endophthalmitis.[8] This disease burden adds to an existing high prevalence of cases of fungal endophthalmitis in developing countries.[8,9,10]

Yeasts have been identified as the most common causative organism of endogenous fungal endophthalmitis in the literature,[11,12,13] whilst the organisms are variable and dependent on the causative mechanism in an exogenous source.[14] The offending pathogens vary geographically with high prevalence of both *Candida* spp. *and Aspergillus* spp. Both of these cause a progressive infection and are associated with a poorer visual prognosis if not managed appropriately.[13,15,16]

Better visual outcomes have been seen in cases with fungal disease when compared to bacterial endophthalmitis.[11] Prompt clinical diagnosis and timely empirical treatment is strongly advised to preserve structural integrity and visual outcomes in all cases of fungal endophthalmitis. An intravitreal antifungal agent and/or systemic fungal therapy can be utilised. The role of vitrectomy in fungal endophthalmitis is controversial and not fully understood but may play a role at least for diagnostic purposes.[2,11]

Currently published data is limited in its spectrum of fungal disease and its management, particularly in the Australian context. The challenge persists due to the difficulty in diagnosis and limited curative options in some situations. The purpose of this study is to capture the trend of fungal endophthalmitis at a tertiary referral centre over twenty years to aid clinicians with the changes seen in presentation and management of these fungal endophthalmitis cases. The incidence, presentation, visual outcomes, microbiological profile and management have been outlined for all cases with suspected fungal endophthalmitis.

2. METHODS

The Victorian Endophthalmitis Registry is prospectively maintained at the Royal Victorian Eye and Ear Hospital (RVEEH), Melbourne, Australia by one of the authors

(PJA). This prospective database was initiated in 1998 and includes all cases of endophthalmitis presenting to the RVEEH.

All fungal endophthalmitis cases during the period of January 1, 1999 to December 31, 2018 were included in this study. This was defined as all cases with proven fungal growth on microbiology analysis or those with features of fungal infection seen on clinical ophthalmic examination, that is, anterior/posterior segment inflammation, vitritis or characteristic fundal lesions. Suspected cases treated for fungal infection without an organism growth also had a supporting history of endogenous source (e.g. history of IVDU), penetrating eye injury (PEI) or delayed presentation of postoperative endophthalmitis.

Supporting data collected within the registry includes demographic information, affected eye (including the side of more severe disease if there was bilateral involvement), possible aetiology and risk factors, visual acuity (VA) on presentation and at 3-month (or most recent) follow – up appointment. The research was conducted in accordance with the principles of Declaration of Helsinki and local hospital ethics committee guidelines.

All microbiological analysis of intraocular fluid (aqueous and/or vitreous) samples was carried out at St. Vincent's Hospital, Melbourne, Australia. The treating clinician acquired these samples in accordance to hospital protocol using an aseptic technique. Pathology results were reviewed for intraocular samples tested, organism growth and sensitivities.

The details of the treatment were also recorded – intravitreal and/or systemic antifungal therapy, early (<24 hours) or delayed (>24 hours) vitrectomy, and further surgical procedures. Presenting Snellen visual acuity (VA) was grouped into

six categories – no vision impairment (better than 6/12), mild vision impairment (6/12 to 6/18), moderate vision impairment (worse than 6/18 to 6/60), severe vision impairment (worse than 6/60 to 3/60), blind (worse than 3/60 including no light perception) as per ICD-11 diagnosis coding.[17] Visual outcomes were defined as improved if the Snellen VA gained by two or more rows and in cases with 'beyond Snellen' acuity of hand movements (HM), count fingers (CF), perception to light (PL) or no perception to light (NPL); it improved by one or more steps.

Descriptive statistics were processed in RStudio and Microsoft Excel. Statistical analysis was performed using RStudio statistics program. Chi-square test of independence was performed on variables to determine if an association exists, with p-value ≤0.05 were considered statistically significant.

3. RESULTS

A total of eighty-four consecutive cases of fungal endophthalmitis, that is eighty-four eyes, were included in this single centre case series over the 20-year period. The registry captured an average of 4.8 fungal cases per year. The median age of patients was 43.5 years [IQR 30.8 – 63.0], and 65.5% (n= 55) of patients were male. Clinical characteristics of patients are listed in Table 1 and Appendix 1. 11 (13.1%) patients had history of type II diabetes; with further 15 (17.9%) patients had immunosuppression in form of chemotherapy or systemic steroids. 24 (28.6%) patients had a history of Hepatitis C.

43 (51.2%) patients showed left eye laterality on presentation. 82 patients had a documented presenting VA. Presenting VA ranged from 6/5 to PL with median VA of 6/120. 9 out of 82 cases (11.0%) presented with no vision impairment, 8 cases (9.8%) presented with mild vision impairment, 23 cases (28.0%) presented with

moderate vision impairment, 6 cases (7.3%) presented with severe vision impairment and 39 cases (47.6%) were blind on presentation (Table 1).

Table 1: Basic demographics (n=84)

	n	*%*
Sex – Male	55	65.5
Median age (years)	43.5 [IQR 30.8 – 63.0]	
Type II diabetes	11	13.1
Immunosuppression	15	17.9
Hepatitis C	24	28.6
Presenting Snellen VA		
No vision impairment (≥6/12)	9	11.0
Mild vision impairment (>6/12 to ≤6/18)	8	9.8
Moderate vision impairment (>6/18 to ≤6/60)	23	28.0
Severe vision impairment (>6/60 to ≤3/60)	6	7.3
Blind (<3/60 to no light perception)	39	47.6
Final Snellen VA		
No vision impairment (≥6/12)	31	36.9
Mild vision impairment (>6/12 to ≤6/18)	8	9.5
Moderate vision impairment (>6/18 to ≤6/60)	13	15.5
Severe vision impairment (>6/60 to ≤3/60)	1	1.2
Blind (<3/60 to no light perception)	14	16.7
Enucleation	4	4.8
LFU	13	15.5
LOS (median)	4.0 [IQR 2.0 – 6.0]	

VA, visual acuity; LOS, length of stay; LFU, lost to follow-up

An endogenous source was suspected in 68 (81.0%) cases, followed by penetrating eye injury (n=9, 10.7%) and cataract surgery (n=3, 3.6%) (Table 2). The source of

endogenous seeding was mainly attributable to IVDU (n= 38, 55.9%), followed by other haematogenous source (n=13, 19.1%), grafts/intravenous lines (n=7, 10.3%), urinary source (n=4, 5.9%), bowel (n=4, 5.9%) and transplants (n=2, 2.9%). The time to presentation with fungal endophthalmitis was variable for patients with history of IVDU and other endogenous sources due to incomplete history. All cases presenting with PEI were reviewed in the emergency department within 3 to 48 hours. One case presented 370 days post-glaucoma surgery while the mean time to presentation was 78.5 days (range 67 to 90 days) for 2 post-cataract surgery cases and unknown for 1 case. One fungal endophthalmitis case secondary to penetrating keratoplasty presented 4 days post procedure.

Table 2: Causes of fungal endophthalmitis cases over 20 years (n=84)

Causes	*Total (n)*	*%*
Endogenous	68	81.0
PEI	9	10.7
Cataract	3	3.6
Corneal ulceration	1	1.2
Glaucoma related	1	1.2
IVI	1	1.2
Other surgery (penetrating keratoplasty)	1	1.2

PEI, penetrating eye injury; IVI, intravitreal injections

79 out of 84 (94.0%) cases underwent intravitreal acquisition of ocular fluids and administration of intravitreal therapy (tap-and-inject procedure). Repeat injection was performed in 44 (52.4%) cases due to poor clinical response to the initial injection. For initial intravitreal therapy, Amphotericin B and Vancomycin were the most commonly used agents in combination or single agent regimes, followed by Ceftazidime and Voriconazole (Table 3). The median number of tap-and-inject procedures per patient was 2 (Range 0 to 4). The average number of intravitreal anti-fungal agents given during the tap-and-inject procedure was 1.3 (Range 0 to 3). 72 out of 84 (85.7%) patients received systemic antifungal therapy (single agent or

combined), where 35 (48.6%) patients received Fluconazole and 15 (20.8%) patients received Voriconazole. The duration of systemic antifungal therapy was given for a minimum of 4 to 6 weeks in cases with Candida positive endophthalmitis. The duration of therapy in other cases was variable and was determined by the aetiology, microbiology growth, extent and response to systemic antifungal therapy. The exact duration of treatment was difficult to ascertain in certain cases being lost to follow-up.

Table 3: First intravitreal injection (n=79)

Medication	*Total (n)*	*%*
Amphotericin B	*42*	*53.2*
Vancomycin	*42*	*53.2*
Ceftazidime	*36*	*45.6*
Voriconazole	*19*	*24.1*
Dexamethasone†	*11*	*13.9*
Fluconazole	*1*	*1.3*
Foscarnet	*1*	*1.3*
Teicoplanin	*1*	*1.3*

† Intravitreal dexamethasone was used in cases initially suspected to be secondary to bacterial aetiology. These cases were included in the study as they subsequently grew fungal species in the ocular fluid specimens.

37 (44.0%) patients underwent pars plana vitrectomy (PPV). 20 (54.1%) of these procedures were performed during the first 24 hours of their presentation (classified as early) due to severe inflammation on presentation. The remainder of cases 17 (45.9%) cases underwent vitrectomy after 24 hours (classified as delayed) due to worsening disease. There was no statistically significant correlation between presenting VA (less or severe vision impairment vs. worse or blind) and PPV (χ^2 = 0.001, p=0.97). There was also no statistically significant correlation between patient immunosuppression and PPV (χ^2 = 0.015, p=0.90).

Microbiology analysis showed 55 (65.6%) cases were culture positive for fungal species (Table 4). 17 out 20 cases with early PPV were culture positive. Remainder of cases (n=41) showed fungal growth with vitreous biopsy (tap) alone. All pathology results positive for *Candida* spp. were sensitive to treatment with Fluconazole. 3 cases, initially managed as fungal endophthalmitis based on examination findings or clinical suspicion, grew bacterial pathogens. One patient cultured *Streptococcus salivarius* in blood, another cultured *Streptococcus oralis* from aqueous humour and another patient with history of *Human Immunodeficiency Virus* infection was positive for *Treponema pallidum*. There was no growth documented in 26 cases, including some cases with repeat tap-and-inject procedure. In patients with a history of IVDU, 13 out of 38 patients had no growth, 23 cases grew *Candida* spp., 1 patient isolated *Aspergillus* spp. and 1 patient isolated *Streptococcus salivarius.*

Table 4: Fungal isolates from intraocular fluid samples (n=55)

Genus	*Species*	*Total*
Candida		39
	albicans	23
	dubliniensis	6
	parapsilosis	3
	tropicalis	5
	sake	1
	Undifferentiated	1
Aspergillus		5
	Undifferentiated	4
	terrein	1
Cryptococcus	*neoformans*	1
Curvularia		2
	lunata	1
	Undifferentiated	1
Gongronella	*butleri*	1

Paecilomyces	*lilacinus*	1
Scedosporium		3
	prolificans	2
	apiospermum	1
Undifferentiated fungi/yeast		3

In terms of visual outcomes, 43 (51.2%) of the cases showed improvement in their Snellen VA, while 12 cases (14.3%) showed no change, 11 cases (13.1%) deteriorated, and 14 cases (16.7%) were lost to follow up (Figure 1).

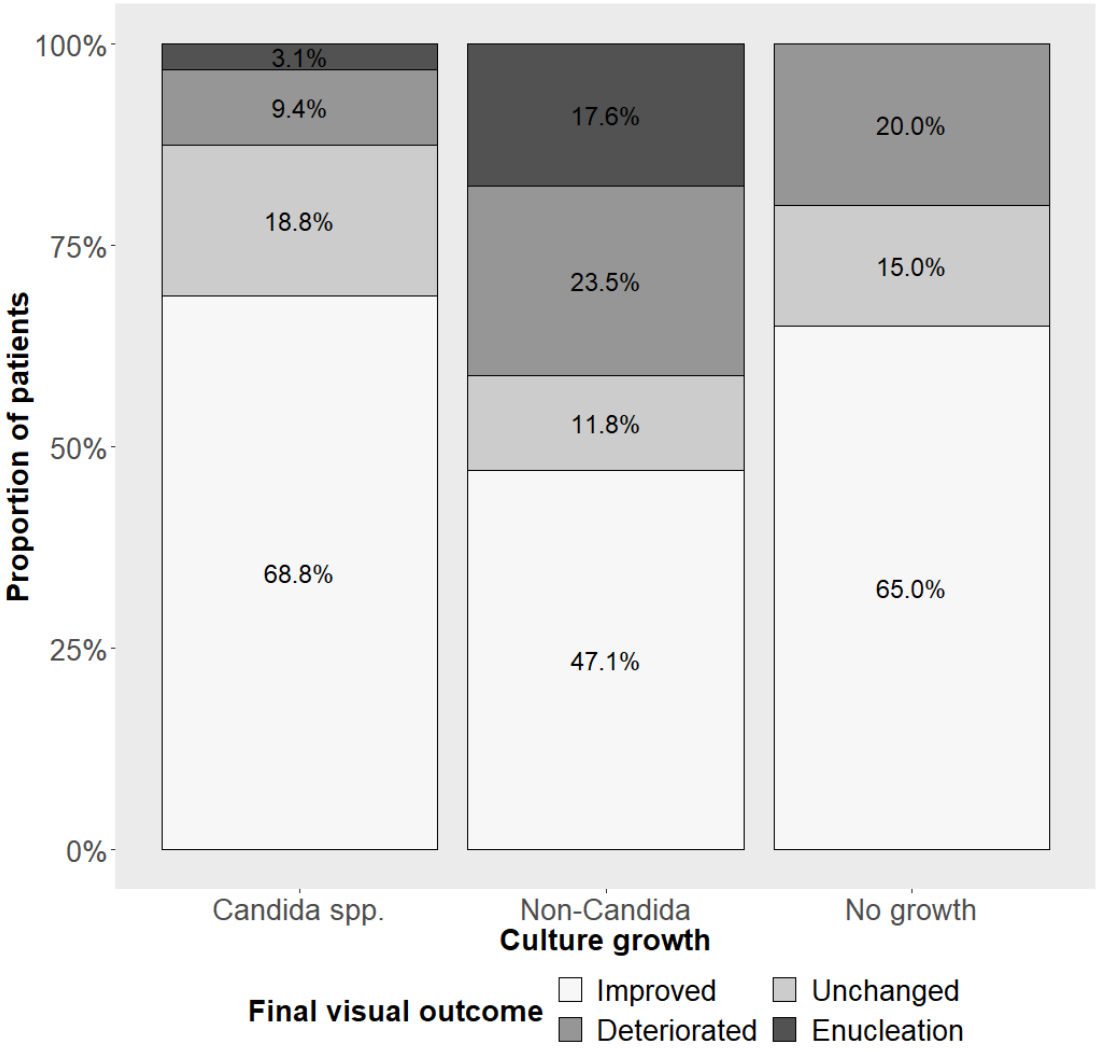

Figure 1: Final visual outcomes and culture growth

Further breakdown of presenting visual acuity and final visual outcomes according to fungal genus growth is demonstrated in Table 5.

Table 5: Fungal isolates from intraocular fluid samples vs. presenting and final visual acuity (n=81)

Genus (n)	*Presenting VA*	*n*	*Final VA*	*n*
Candida (39)	No	2	No	15
	Mild	2	Mild	7
	Moderate	14	Moderate	4
	Severe	4	Severe	1
	Blind	16	Blind	5
	NA	1	Enucleation	1
			LFU	6
Aspergillus (5)	Moderate	1	Moderate	2
	Blind	4	Blind	1
			Enucleation	2
Cryptococcus (1)	Blind	1	Moderate	1
Curvularia (2)	No	1	No	1
	Blind	1	Blind	1
Gongronella (1)	Moderate	1	No	1
Paecilomyces (1)	Blind	1	Moderate	1
Scedosporium (3)	Moderate	1	Blind	1
	Blind	2	Enucleation	1
			LFU	1
Undifferentiated	No	1	No	2
fungi/yeast (3)	Moderate	1	Blind	1
	Blind	1		
No growth (26)	No	4	No	10
	Mild	4	Mild	1
	Moderate	3	Moderate	4
	Severe	2	Blind	5
	Blind	12	LFU	6
	NA	1		

VA, visual acuity; No vision impairment (≥6/12); Mild vision impairment (>6/12 to ≤6/18); Moderate vision impairment (>6/18 to ≤6/60); Severe vision impairment

(>6/60 to ≤3/60); Blind (<3/60 to no light perception); LFU, lost to follow-up; NA, not available.

There was no statistically significant correlation between patients undergoing PPV and improved visual outcomes (χ^2 = 0.278, p=0.60). The 4 cases that underwent enucleation were culture positive for *Aspergillus* spp. (n=2), *Candida albicans* (n=1) and *Scedosporium prolificans* (n=1). There was no significant difference between Candida or non-Candida growth or no growth and presence of improvement in visual outcome (χ^2 = 2.311, df = 2, p=0.32).

4. DISCUSSION

Our study outlines the presentation of clinically diagnosed and/or microbiologically proven fungal endophthalmitis cases over twenty years at a tertiary referral centre for ocular emergencies. Our data shows that the majority of patients with fungal endophthalmitis were secondary to an endogenous source, with IVDU being the most common cause, comprising 55.9% (n=38) of these cases. Similarly, case series from centres in South Australia and Florida have reported a high proportion of fungal endophthalmitis cases secondary to IVDU.[19,20] There has been a steady increase of IVDU related cases observed in developed countries when compared to the data from the developing world.[8,18] Fewer cases of fungal endogenous endophthalmitis have been reported in population studies from China, India and Korea.[21,22,23] Conversely, a low number of fungal endophthalmitis secondary to PEI (n=9, 10.7%) was seen in our study group. In a 14-year review of patients from a centre in India, Chakrabarti et al demonstrated a high incidence of fungal endophthalmitis attributed to post-trauma cases.[10]

As a result, the causative organisms in our population were dissimilar to those seen in India and China.[8,27] *Aspergillus* spp. has been commonly reported in those fungal endophthalmitis cohorts while our series shows higher number of *Candida* spp. growth. This is likely secondary to the causative mechanisms attributable to fungal endophthalmitis. Yeasts have been commonly associated with endogenous fungal endophthalmitis (especially in cases with IVDU), while pathogens related to exogenous fungal endophthalmitis are variable. Higher rates of evisceration and poor visual outcomes have been reported in cases with *Aspergillus* spp. growth.[20,29] Some of the risk factors associated with enucleation/evisceration include endophthalmitis secondary to corneal ulceration or endogenous endophthalmitis and initial poor visual acuity.[30] This is reflected in our case series but the number of cases (n=4, 4.5%) undergoing enucleation was low. Two out of the four cases grew *Aspergillus* spp. The range of presenting Snellen VAs for these patients ranged from 6/24 to HM. Additionally, two patients were immunosuppressed and one patient had a penetrating eye injury.

In an Indian population, a high proportion of fungal endophthalmitis was reported in post-cataract surgery patients, [24] while a review by Smith et al demonstrated a lower proportion of fungal endophthalmitis attributable to cataract surgery in a Western population.[25] Patient factors associated with this include immunocompromised status, pre-operative fungal keratitis, or operative factors like contamination of intraocular fluid with irrigation solutions used during surgery or environmental factors.[25] This lower proportion of post-cataract surgery fungal endophthalmitis is reflected in our dataset; only 3 out of 84 (3.6%) cases were attributable to cataract surgery. One patient had a history of diabetes mellitus but remainder of the cases had no identifiable immunocompromise.

69.0% culture positivity rate in our study is higher when compared to global standards. Two large endophthalmitis cohort studies over 14 and 25 years demonstrated a lower culture positivity rate in Indian populations when compared to our results.[10,27] Similarly, a lower culture positivity rate of 51% in blood samples and 48% from vitreous samples has been described in Danish population with endogenous endophthalmitis.[39] These differences seen may be secondary to microbiology analysis techniques used at each of these centres.

A large proportion of our study population received systemic therapy with Fluconazole and Voriconazole. Fluconazole and Voriconazole – intravitreally or systemically - remain a safe choice for treatment of fungal endophthalmitis due to excellent intraocular concentrations and safety.[28] Intravenous Amphotericin B carries risk of nephrotoxicity and infusion related toxicity, along with poor intraocular penetration.[2,28] Amphotericin B was the treatment of choice for first intravitreal injection up until 2010, where the standard treatment changed to intravitreal Voriconazole in our study population.

The role of pars plana vitrectomy (PPV) in fungal endophthalmitis remains controversial. PPV may aid diagnosis by providing a better sample quality; reduce the fungal load from the intraocular structures, improve retinal oxygenation; reduce the incidence and severity of retinal complications, especially macular complications. Early PPV has prophylactic benefits in reduction of the duration of disease processes.[40] A small number of case series have reported improvement in visual outcomes following PPV. [1,2,12] We did not find an association between patients undergoing PPV and final visual outcome. Furthermore, it is uncertain if the time from presentation to PPV has an impact on visual outcomes. Studies examining the difference between early (<24 hours from presentation) and delayed (>24 hours) PPV are limited in fungal endophthalmitis populations due to small sample sizes.

Only 20/37 of our cases underwent early PPV. The sample size was too small to comment on any difference between the groups. Although vitrectomy has not been proven to directly improve visual outcomes, PPV remains a useful diagnostic tool. Our case series showed initial pathogen isolation rate with vitreous biopsy was 48.8% compared to 85% with early PPV. PPV is also useful in the management of post-infection sequelae such as retinal detachment, epiretinal membrane, choroidal neovascular membrane, and macular hole formation. [2]

There is an important limitation to this study. Whilst an endophthalmitis management guideline is in place, given the nature of fungal endophthalmitis clinician discretion plays a major role in management of these cases, resulting in variation in treatment.

In conclusion, whilst fungal endophthalmitis is a diagnostic and management challenge with potential for significant long-term visual impairment, there is scope for improvement in patient outcomes. Due to a large of proportion of cases attributable to IVDU in our group, a thorough drug history and a higher index of suspicion of fungal endophthalmitis amongst these patients is recommended. Secondly, there is a wide range of causative organisms, most frequently involving *Candida* spp., which were all sensitive to Fluconazole from our population. Hence, empirical treatment with Fluconazole might be beneficial in suspected cases to reduce pathogen load promptly (Figure 2). Lastly, vitrectomy is a useful diagnostic tool with high pathogen isolation rate, however its role in improvement of visual outcomes needs to be further examined.

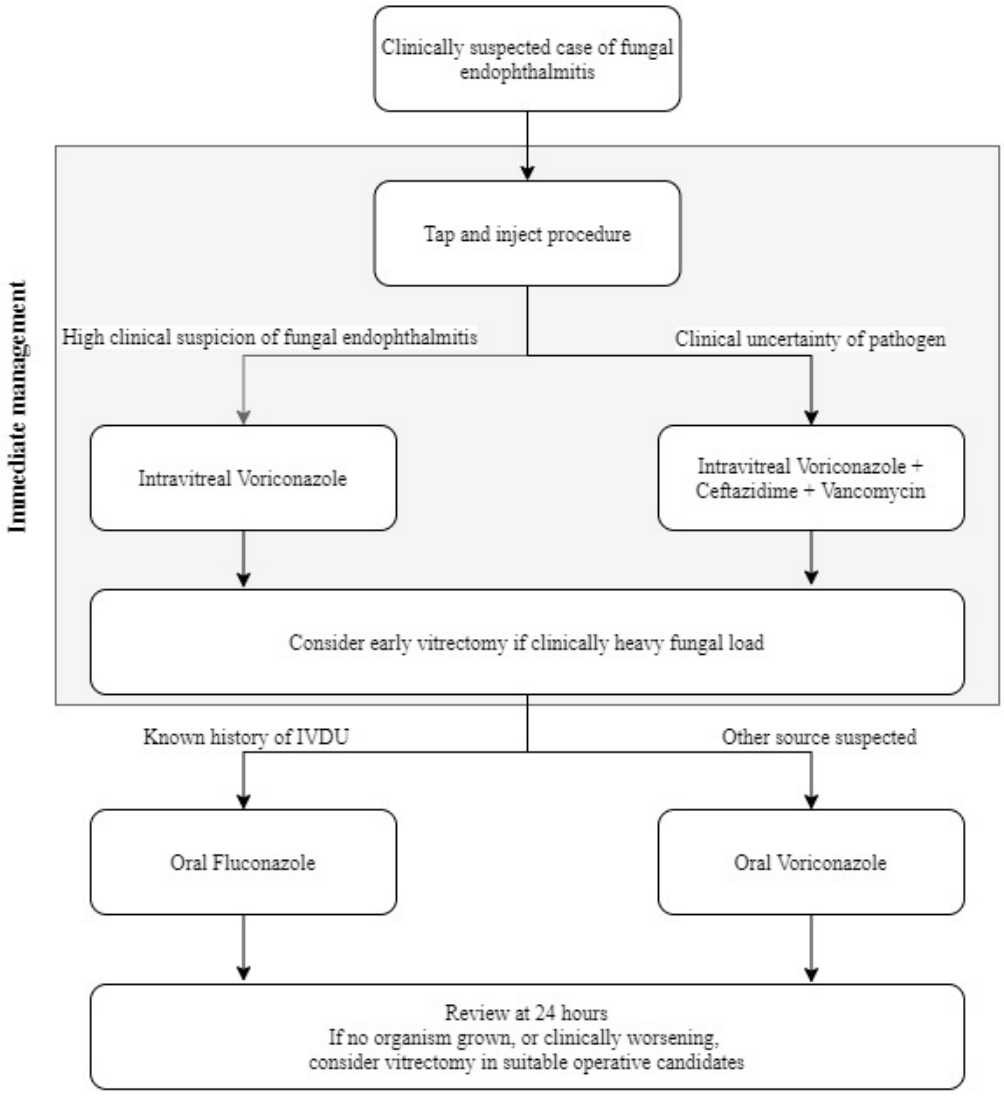

Figure 2: Protocol for management of patient with suspected fungal endophthalmitis

ACKNOWLEDGEMENTS

Study data was collected and managed using REDCap electronic data capture tools hosted at the Centre for Eye Research Australia. The Centre of Eye Research Australia receives operational infrastructure support from the Victorian Government.

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