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Facteurs de pronostic visuel des endophtalmies aiguës bactériennes post-chirurgie de cataracte

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Aurélie Combey-De-Lambert. Facteurs de pronostic visuel des endophtalmies aiguës bactériennes post-chirurgie de cataracte. Human health and pathology. 2012. dumas-00704867

HAL Id: dumas-00704867

<https://dumas.ccsd.cnrs.fr/dumas-00704867>

Submitted on 6 Jun 2012

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UNIVERSITE JOSEPH FOURIER
FACULTE DE MEDECINE DE GRENOBLE

Année : 2012

N°

**FACTEURS DE PRONOSTIC VISUEL DES
ENDOPHTALMIES AIGUES BACTERIENNES POST-
CHIRURGIE DE CATARACTE**

THESE PRESENTEE POUR L'OBTENTION DU DOCTORAT EN MEDECINE
DIPLOME D'ETAT

Aurélie COMBEY-de LAMBERT

Née le 09.02.1982 à Chambéry

THESE SOUTENUE PUBLIQUEMENT A LA FACULTE DE MEDECINE DE
GRENOBLE

Le 24 mai 2012

DEVANT LE JURY COMPOSE DE

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Monsieur le Professeur Max MAURIN

Monsieur le Professeur Gilles THURET

A Albé,
Mon âme sœur.

A Ninon et Gaspard,
Mes merveilles. Vous êtes ma plus belle réussite.

Aux membres du jury

A Monsieur le Pr Jean-Paul Romanet,

Votre dévouement pour vos patients, votre investissement pour la pédagogie sont exceptionnels. Mais combien d'heures comptent donc vos journées ? Soyez assurés de ma plus grande reconnaissance.

A Monsieur le Professeur Christophe Chiquet,

Votre passion pour la recherche est exceptionnelle. Merci de nous pousser à donner le meilleur de nous même.

A Monsieur le Professeur Max Maurin

Votre aide pour mes premiers pas en bactériologie a été très précieuse. Merci de juger ce travail.

A Monsieur le Professeur Gilles Thuret

Merci pour votre accueil chaleureux ; je garderai un excellent souvenir de ma parenthèse stéphanoise.

A mes maîtres

A Olivier

Mon modèle professionnel. Je suis fier de notre amitié.
C'est un immense privilège de te rejoindre à Chambéry.

A Karine,

En souvenir de toutes nos discussions au bloc très « féminines »...Et vive Barry White !

A Rux,

Pour ta disponibilité et tous tes avis en rétinologie medical...

A Adel,

Merci pour tous les très bons conseils chirurgicaux et ton excellent accueil.

A Viviane,

Notre meilleure fournisseuse de chocolat !

A Sabine,

Pour nos 6 mois très sympas sur Chambéry.

A Florent

Bonne route à Grenoble.

A Monsieur le Professeur Gain,

Un très grand merci pour ces six mois à Saint Etienne. Et félicitations pour votre équipe parfaite !

A Nelly,

Ta gentillesse et ta générosité n'ont d'égales que tes compétences professionnelles. Je suis très heureuse d'avoir fait ta connaissance et te souhaite tout le bonheur que tu mérites.

A Damien

Ton sens de la pédagogie est exceptionnel. Les internes ont beaucoup de chance de t'avoir.

A Pierre

La star de l'ophtalmo-ped !

A Patricia

La championne du glaucome !

A Catherine

La reine du diabète !

A Manu Bozonnet

En souvenir des apéros et ton accompagnement en chirurgie plastique.

Aux Dr Xavier Piquot et Patrice Moyenin

Pour mes premiers pas en ophtalmo

A mes co-internes

Qui pour beaucoup maintenant sont devenus chefs !

A Elisabeth

La plus grenobloise d'entre nous! Le meilleur est à venir...

A Matthieu

Nous n'aurons malheureusement que très peu travaillé ensemble. Un jour peut-être ?

A Cindy

La joie de vivre. Dommage qu'on ne se voit pas plus souvent.

A Hafide

Le speedy-gonzales de la cataracte!

A Pierre-Marie

L'expert du barbecue ! Pour les grillades à venir avec tous nos loulous...

A Youssef

Mon youyou à moi ! Je suis heureuse que tu t'épanouisses dans Ton service. Bonne route chef !

A Tiffany

Quel bonheur de partager mon assistanat avec toi.

A Diane

Miss 100 000 Volts. Comment fais-tu ?

A Ahmed

Pour ton courage exemplaire.

A Mag

Merci pour ces 6 derniers mois vraiment supers sympas à Grenoble. Tu es une fille en or ! Une petite pensée pour nos révisions acharnées de l'EBO... et bon mariage !

A Eva

Aussi belle que brillante. Bonne continuation à Bourgoin.

A Ralitsa

Un caractère bien trempé!! J'adorerais n'avoir que 10% de ton franc parler... Mais je suis surtout ravie d'avoir découvert ta grande générosité. Christian est un homme chanceux...

A Benj

Le meilleur d'entre nous. Je te souhaite tout le bonheur que tu mérites avec ton Auré.

A Thierry

La gentillesse à l'état pur.

A Joséphine

Bon séjour à Marseille. Reviens-nous quand même !

A Antoine

La zenitude...

A Mathilde

Je t'aurai bien envoyée passer l'EBO à ma place mais il paraît que ce n'est pas possible... A défaut je t'ai emmenée avec moi pour mes 6 derniers mois à Chambé ! Tu es une fille extra : ne change rien.

A Nischal, Caro, Fred, Georges, Marc-Antoine, Perrine, Cécile, Adriane, Olivier, Julie et Rachel : courage pour la suite !

A Aurélie, Mathieu, Marie-Caroline, Mansour, Marine, Maher, Rémi et Claire : mes supers co-internes stéphanois.

A ma famille

A ma Maman,

Tu as fais ce que je suis. Il m'est impossible d'exprimer toute ma gratitude. Merci pour tout l'amour que tu donnes maintenant à mes enfants.

A mon Papa,
Qui m'a toujours regardée avec tant de fierté : tu as fait ma force.

A Cécilia,
Ma petite sœur adorée. Je donnerais beaucoup pour t'avoir plus près de nous. Un jour peut-être ?

A Pierre,
Beau-père modèle.

A Laurence,
Une super mamie supplémentaire pour Ninon et Gaspard.

A Yannick,
Mon super beau-frère. Entre deux randos, continue de rendre ma petite sœur heureuse...

A Monique et Thierry,
Des beaux-parents en or. Je suis heureuse d'être rentrée dans votre famille.

A Elo, Gaetan, Boris, Marie, Coline et Andréa,
Je compte sur vous pour la faire grandir cette famille !

A Julia
Une adorable première cousine pour Ninon et Gaspard.

A mamie Pounette et mon Grand-Père,
Pour toutes les heures que vous m'avez consacrées. Et parce que la vocation est certainement héréditaire...

A mamie Boisserette et Papi,
Les vendanges, la récolte des pommes de terre et des framboises à vos côtés font partis de mes très beaux souvenirs de petite fille.

A Jean-christophe, Jean-Louis, Claudine, Marie, Georges, Jean-Paul, Claudine, Charles, Adrien, Hugo, Gaston, Florence : une jolie tribu !

A Lise
Qui me fait l'honneur d'être présente ce jour, comme à tous les moments importants de ma vie.

A mes amis

A Marie
Ma meilleure amie. Merci pour toutes ces belles années. On aura quand même réussi à les finir ces études !

A Hugo, Julie, Colin et Maud

Des amis très chers. Votre famille est pour moi un exemple. Je regrette encore votre départ mais c'est toujours une immense joie de vous revoir (avec une petite pensée spéciale pour les moules marinières...)

A Mylène,

Que je ne vois malheureusement pas assez souvent.

A Auré, Rom et Léa

Mes « exilés » lyonnais préférés. Grenoble se languit de vous...

A ma tío

Reine de la bonne humeur mais aussi de la déco. Quel we je réserve pour tes chambres d'hôte ?

A Fio

Devenue une vraie Parisienne ! Mais je sais que tu ne nous oublies pas.

A Delphine

Une fille en or.

A Guillaume et Muriel,

Des amis très chers. Merci d'avoir toujours été là pour nous...

A Antoine, Romain, Lolo, Jérôme et Julien,

Des sacrés carabins.

A Sylvain,

Bravo pour ton parcours et plein de bonheur avec Alice.

A Auré, Patrick, Manon et Thibault,

Nos supers voisins.

A Fanny, Julien, Mathis et Ilian,

Bis. Fanny, je ne pourrais jamais assez te remercier de veiller aussi bien sur mes enfants ; vivement l'été prochain que l'on puisse vous honorer à votre juste valeur...

A Arnaud, Domi et Anouk,

On se suit depuis le lycée, je suis ravie de vous retrouver sur Chambé.

A Bernadette,

Ma petite maman de l'ophtalmologie ! Ton dévouement au service est remarquable ; ta générosité extraordinaire. Quelle chance de travailler à tes côtés et de t'avoir comme amie.

Aux équipes

Du service, du bloc et de la consultation de Grenoble,
Merci pour votre gentillesse et votre compétence durant toutes ces années... Une pensée bien sûr particulière pour notre chère Catherine.

Du service, du bloc et de la consultation de Chambéry,
Vous faites de l'hôpital mon petit paradis... Merci pour votre si bel accueil à mon retour.

Du service, du bloc et de la consultation de Saint Etienne

De bactériologie du CHU de Grenoble,
Pour mon année de master.

A Géraldine, Sylvain, Marie, Carole, Fabrice, Yann, Monique, Delphine : pour votre soutien tout au long de l'internat.

Baseline predictive factors of visual prognosis in acute bacterial postcataract endophthalmitis

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Keywords: endophthalmitis, cataract surgery, prognosis, microbiology

Abstract

Objective: To identify baseline clinical factors of visual prognosis in patients with acute endophthalmitis following cataract surgery.

Design: prospective cohort study

Participants: 99 patients hospitalized for acute postcataract endophthalmitis in four academic hospitals (Dijon, Grenoble, Lyon, Saint-Etienne; FRIENDS group).

Methods: Factors related to the cataract surgery (complications), the initial clinical presentation, and the microbiological diagnosis were analyzed based on the final visual outcome, defined as poor ($<20/100$) or good ($\geq 20/40$) using univariate and multivariate analysis (backward-stepping procedure).

Main outcome measures: visual acuity (LogMAR), microbiological identification using culture and panbacterial PCR.

Results: The significant baseline factors for good visual outcome (45% of the series) were the winter season, absence of complications during cataract surgery, initial visual acuity (VA), microbiological investigations revealing no microorganism or a coagulase-negative *Staphylococcus* sp. (CNS), and fundus visibility. Quantitative factors associated with a good clinical prognosis were shorter duration of cataract surgery, younger age, and a hypopyon equal to or less than 1.5 mm. Significant factors associated with poor visual outcome were infection of the right eye, initial VA, corneal edema, hypopyon larger than 1.5 mm, detection of bacterial species other than a CNS, and the absence of fundus visibility. Multiple logistic regression analysis showed that high bacterial virulence was the only independent factor (odds ratio [OR]= 14, 95% confidence interval [CI]: 2.7–71, $p=0.001$) for poor visual outcome. On the other hand, low bacterial virulence (OR=0.1 95%CI: 0.03–0.6, $p=0.01$) and the

absence of complications (OR=0.07, 95%CI: 0.01–0.4, $p=0.003$) during cataract surgery were independent factors for good VA.

Conclusion: Visual outcome factors in acute postcataract endophthalmitis identified in this prospective study (2004–2007) were similar to those reported by the EVS 10 years ago. The bacterial virulence level was the main predictive factor of final visual prognosis. This emphasizes the need for rapid bacterial identification and characterization using new biomolecular techniques.

INTRODUCTION

Postcataract endophthalmitis is a rare (approximately 0.08% of cataract surgeries)^{1,2} but serious complication, which can lead to anatomical and/or functional loss of the eye. Significant advances have been achieved in the field of antibiotic prophylaxis (cefuroxime intracameral injection),³⁻⁵ and microbiological diagnosis.⁶⁻⁹ The identification of baseline prognostic factors at the time of modern clear corneal cataract surgery remains an important step to identify patients who need aggressive therapy as early as possible. Polymerase chain reaction (PCR)-based techniques now provide accurate and rapid identification of the microorganisms directly involved in intraocular samples. This will make it possible to rapidly adapt the therapeutic strategy to both clinical and microbiological factors, and to give more objective information to the patient.

The anatomical and functional prognoses have been reported to be associated with baseline factors such as initial vision,¹⁰⁻¹² absence of a red reflex, history of diabetes or glaucoma, and the bacterial species involved.¹⁰⁻¹⁷ These data were mainly obtained 15 years ago on a selected population to be randomized for pars plana vitrectomy (PPV) in the EVS (Endophthalmitis Vitrectomy Study), with inclusion of patients with clear enough cornea to allow vitrectomy and exclusion of patients who did not consent to therapeutic randomization, VA equal to or better than 20/100).¹⁰ Given the changes in cataract surgery techniques and different epidemiological characteristics of the population studied, new prospective data are needed for the identification of prognostic factors.

The French Institutional Endophthalmitis Study (FRIENDS) group included 100 consecutive patients with acute postcataract endophthalmitis, which allowed the prospective study of the largest series after the EVS. Previous microbiological

results, using conventional cultures and panbacterial polymerase chain reaction (PCR) have been previously published.^{6, 18-21}

The aim of this report was to identify baseline clinical and microbiological factors of good (VA \geq 20/40) and poor (VA $<$ 20/100) visual outcome at 6 months in a large series of acute postcataract endophthalmitis.

PATIENTS AND METHODS

This prospective study included 100 patients (100 eyes) with acute ($<$ 6 weeks) postcataract endophthalmitis, between March 2004 and December 2005 in four French academic hospitals (Dijon, Grenoble, Lyon, Saint-Etienne). One patient was excluded from the analysis given his age (2 years) and the inability to obtain reliable postoperative vision measurement. The study followed the Declaration of Helsinki guidelines for research involving human subjects and was approved by the local Institutional Review Board (Comité de Protection des Personnes, CPP Lyon B). The inclusion criteria, data sheet, sampling techniques and microbiological procedures, antibiotics used for intravitreal injections, and follow-up visits were standardized in the four centers.

Clinical data collection:

Patients were eligible if they had clinical signs of endophthalmitis within 6 weeks after cataract surgery. The diagnosis of acute endophthalmitis was made on the basis of clinical features including pain, decreased visual acuity (VA), diffuse bulbar conjunctival hyperemia, chemosis, inflammation of the anterior segment (anterior chamber reaction including one of the following criteria: flare, cells, hypopyon height, fibrin, cyclitic membrane), and posterior segment inflammation (all patients had

vitreous infiltration diagnosed with biomicroscopy or ophthalmic ultrasound). A baseline evaluation form was completed during the initial examination of each patient and included demographic features, past medical history, ocular history, details of cataract surgery (retrospectively collected from the cataract surgeon including capsular rupture and vitreous loss), and data of the initial ocular examination (see factors in Table 1)..

Performing pars plana vitrectomy (PPV) was left to the discretion of the treating physician, generally following the EVS guidelines. During the 6-month follow-up, patients were defined as having a good (final VA ≤ 0.3 LogMAR, $\geq 20/40$) or poor (final VA > 0.7 LogMAR, $< 20/100$) visual prognosis. Incidence of phthisis was also recorded at 6 months.

Microbiological data:

On admission, an immediate tap of aqueous humor and/or vitreous was performed followed by intravitreal injection of vancomycin (1 mg/0.1 mL) and ceftazidime (2 mg/0.1 mL). Conventional cultures were made by direct inoculation of intraocular samples in Brain Heart Infusion (BHI) broth (BioMérieux, Marcy l'Etoile, France). These culture media were incubated for 2 weeks at 37°C, and were subcultured on chocolate agar supplemented with PolyViteX (BioMérieux) and Columbia agar supplemented with 5% sheep blood (Biomérieux) when bacterial growth was detected or systematically after 2 weeks of incubation if no growth was detected. For positive cultures, Gram stains were performed, and bacterial identifications and antibiograms were obtained using phenotypic methods (Vitek II, BioMérieux, or BD Phoenix, Becton Dickinson). Species identification was confirmed by 16SrDNA amplification and sequencing.

Bacterial DNA extraction, 16S rDNA PCR amplification and sequencing were performed as previously described.⁶ Panbacterial PCR was able to detect 500 cfu of *Staphylococcus epidermidis*. Amplification of the human beta globulin gene served as an internal positive extraction and amplification control. The 16S rDNA sequences obtained were compared with those available in GenBank, EMBL, and DDBJ databases with the BIBI (Bio Informatic Bacterial Identification; <http://pbil.univ-lyon1.fr/bibi/query.php>) program. Identification to the species level was defined as 99% or greater 16S rDNA sequence similarity with that of the GenBank prototype strain sequence. Identification to the genus level was defined as a 97% or greater 16S rDNA sequence similarity with that of the GenBank prototype strain sequence. A failure to identify was defined as a 16S rDNA sequence similarity less than 97% with sequences deposited in GenBank at the time of the analysis.

Patients were then further classified into the following groups according to microbiological results: detection of no microorganism, CNS, or detection of a more virulent species, including *Streptococcus* sp., *S. aureus*, *S. lugdunensis*, and Gram-negative bacteria.¹⁸

Statistical analysis:

Quantitative data were expressed as mean \pm standard deviation (SD). Associations between prognosis and clinical data were primarily studied using ANOVA for quantitative data and chi-square analysis (incorporating Yates's correction when appropriate) for qualitative data. To determine which of these variables were combined with clinical factors to predict visual prognosis, logistic regression models were fitted using a backward-stepping procedure. The odds ratio (OR), which provides an estimate of the relative risk of good or poor prognosis, was calculated.

Multivariate logistic regression analysis was performed using clinical factors that were found to be statistically significant in univariate analysis (with $p < 0.1$). The statistical analysis was performed using the Statistical Package for the Social Science program (SPSS 17.0 for Windows, Chicago, IL, USA). The tests were two-tailed and statistical significance was set $p < 0.05$.

RESULTS

Ninety-nine patients, with a mean age of 73 ± 9 years, were included with acute (<6 weeks) postcataract endophthalmitis. Patients were hospitalized with a median delay of 6 days (range, 1–38 days) after cataract surgery (clear corneal phacoemulsification, $n=95$, manual extracapsular extraction, $n=4$) associated with posterior ($n= 89$) or anterior ($n=6$) lens implantation or with no intraocular lens ($n=4$). The median time between surgery and the onset of symptoms was 5 days (range, 0–35 days). No intracameral antibiotics were used at the time of cataract surgery. Complicated cataract surgery (capsular rupture with or without vitreous loss) was reported in 20% of the cases, including 12 eyes that had undergone an anterior vitrectomy during cataract surgery. Other systemic and ocular risk factors of endophthalmitis were immunosuppression ($n=7$), diabetes mellitus ($n=13$), oral steroids ($n=7$), atopic dermatitis ($n=1$), blepharitis ($n=1$), dry-eye syndrome ($n=2$), and contact lens wear ($n=1$).

Thirty-one percent of the population had a final VA greater than 0.7 logMAR (group of poor visual outcome) including 10 patients with light perception only, and 45% of the population had a final VA lower than 0.3 logMAR (good visual outcome group). Finally, 24% of the patients had a final VA between 20/100 and 20/50.

Univariate analysis (Table 1):

The significant initial factors of good visual outcome were the winter season, absence of complications during cataract surgery, initial VA, detection of CNS or absence of microorganism detection, and fundus visibility. Quantitative factors associated with good clinical prognosis were a shorter duration of cataract surgery, younger age, and a smaller hypopyon.

Significant factors associated with poor visual outcome were infection of the right eye, initial VA, corneal edema, hypopyon larger than 1.5 mm, detection of a bacterial species other than a CNS, and the absence of fundus visibility.

Considering treatment, the number of intravitreal injections was not significantly associated with the visual outcome. PPV was more frequently used in cases of poor visual outcome. PPV was also significantly associated with earlier presentation ($p= 0.03$), detection of a virulent species ($p=0.008$), initial VA ($p<0.001$), and loss of red reflex ($p=0.01$). PPV was performed in 91% of the patients with initial VA limited to light perception (LP), 56.5% of patients with “hand motion” VA, 37.5% of patients with “counting fingers” VA, and 28% of patients with VA $\geq 20/400$.

Table 1: Univariate analysis of factors predictive of poor or good visual outcome

Factor		Number of patients	Number of patients with poor visual outcome (VA<20/100)	P-value	Number of patients with good visual outcome (VA≥20/40)	P-value
Gender	Male	48	19 (39.6%)	0.08	18 (37.5%)	0.12
	Female	51	12 (23.5%)		27 (52.9%)	
Laterality	Right eye	42	18 (42.9%)	0.03	17 (40.5%)	0.4
	Left eye	57	13 (22.8%)		28 (49.1%)	
Season	Winter	31	11 (35.5%)	0.5	8 (25.8%)	0.02
	Spring	29	11 (37.9%)		14 (48.3%)	
	Summer	17	4 (23.5%)		8 (47.1%)	
	Autumn	22	5 (22.7%)		15 (68.2%)	
Intraoperative complication	No	79	23 (29.1%)	0.3	43 (54.4%)	<0.001
	Yes	20	8 (40%)		2 (10%)	
Anterior vitrectomy	No	85	26 (30.6%)	0.8	44 (51.8%)	0.005
	Yes	12	4 (33.3%)		1 (8.3%)	
Infectious risk factors	No	20	9 (45%)	0.1	7 (35%)	0.3
	Yes	79	22 (27.8%)		38 (48.1%)	
Diabetes mellitus	No	86	24 (27.9%)	0.06	40 (46.5%)	0.5
	Yes	13	7 (53.8%)		5 (38.5%)	
Pain	No	24	5 (20.8%)	0.2	12 (50%)	0.5
	Yes	74	26 (35.1%)		32 (43.2%)	
Visual acuity loss (symptoms)	No	5	3 (60%)	0.2	1 (20%)	0.2
	Yes	94	28 (29.8%)		44 (46.8%)	
Redness	No	9	1 (11.1%)	0.3	6 (66.7%)	0.3
	Yes	88	39 (44.3%)		39 (44.3%)	
Secretions	No	52	18 (25%)	0.2	23 (44.2%)	0.7
	Yes	38	14 (36.8%)		18 (47.4%)	
Initial acuity	LP+	32	16 (50%)	0.007	8 (25%)	0.004
	VBLM	46	14 (30.4%)		21 (45.7%)	
	CLD	8	0 (0%)		6 (75%)	
	≥ 20/400	13	1 (7.7%)		10 (76.9%)	
Ptosis	No	85	25 (29.4%)	0.2	40 (47.1%)	0.5
	Yes	13	6 (46.2%)		5 (38.5%)	
Swollen lid	No	77	21 (27.3%)	0.1	36 (46.8%)	0.7
	Yes	21	9 (42.9%)		9 (42.9%)	
Chemosis	No	74	20 (27%)	0.06	34 (45.9%)	0.8
	Yes	23	11 (47.8%)		10 (43.5%)	
Conjunctival hyperemia	No	13	4 (30.8%)	0.9	7 (53.8%)	0.5
	Yes	84	27 (32.1%)		38 (45.2%)	
Corneal edema	No	56	12 (21.4%)	0.01	30 (53.6%)	0.06
	Yes	43	19 (44.2%)		15 (34.9%)	

Cyclitic membrane	No	22	4 (18.2%)	0.1	12 (54.5%)	0.4
	Yes	75	25 (33.3%)		33 (44%)	
Hypopyon	No	28	5 (17.9%)	0.07	14 (50%)	0.5
	Yes	71	26 (36.6%)		31 (43.7%)	
Hypopyon >1.5 mm	No	80	20 (25%)	0.01	40 (50%)	0.1
	Yes	16	9 (56.3%)		5 (31.3%)	
Bacterial identification	No	30	3 (10%)	0.003	20 (66.7%)	0.005
	Yes	69	28 (40.6%)		25 (36.2%)	
Pars plana vitrectomy	No	38	7 (18.4%)	0.03	24 (63.2%)	0.005
	Yes	61	24 (39.3%)		21 (34.4%)	
Corneal suture	No	42	13 (31%)	0.7	22 (52.4%)	0.1
	Yes	52	18 (34.6%)		20 (38.5%)	
Fundus visibility	No	89	31 (34.8%)	0.02	37 (41.6%)	0.02
	Yes	10	0 (0%)		8 (80%)	
Red reflex	No	41	11 (26.8%)	0.35	21 (45.7%)	0.6
	Yes	56	20 (35.7%)		25 (44.6%)	
Bacterial identification	sterile	30	3 (10%)	< 0.001	20 (66.7%)	0.003
	CNS	33	3 (9.1%)		16 (48.5%)	
	virulent	36	25 (69.4%)		9 (25%)	

Factor	Number of patients	Mean (\pm SD) in patients with poor visual outcome (VA<20/100) vs patients with VA \geq 20/100	P-value	Mean (\pm SD) in patients with good visual outcome (VA \geq 20/40) vs patients with VA <20/40	P-value
Duration of surgery	62	23.6 \pm 19.9 vs 20.8 \pm 10.9	0.4	17.5 \pm 5.5 vs 25.27 \pm 17.9	0.02
Age	99	75 \pm 8 vs 71.9 \pm 10	0.1	70 \pm 10 vs 75.6 \pm 8	0.004
IOP	92	19.4 \pm 10 vs 19.5 \pm 10.2	0.4	17.7 \pm 10.8 vs 18.4 \pm 9.6	0.7
Hypopyon	99	2.35 \pm 3.3 vs 1.13 \pm 1.9	0.06	0.9 \pm 0.8 vs 2.03 \pm 3.2	0.01
Incision (size)	90	4 \pm 1.46 vs 5.15 \pm 12.4	0.6	3.2 \pm 0.64 vs 6.1 \pm 13.6	0.1
Time to PPV	54	-3.9 \pm 1.9 vs -5 \pm 4.9	0.3	-4.11 \pm 1.8 vs -4.7 \pm 4.8	0.6
Endophthalmitis onset (days)	99	8.5 \pm 10.2 vs 8.2 \pm 8.5	0.8	8.62 \pm 8 vs 8.1 \pm 9.8	0.7
Time between symptoms and hospitalization	99	2.09 \pm 3.6 vs 2.16 \pm 3.8	0.9	2.4 \pm 4.2 vs 1.9 \pm 3.1	0.5
Number of intravitreal injections	99	1.84 \pm 1.1 vs 1.68 \pm 0.6	0.6	1.79 \pm 0.6 vs 1.71 \pm 0.9	0.6

Multivariate analysis (Table 2):

Multiple logistic regression analysis (Table 2) showed that bacterial virulence was the only independent factor (odds ratio [OR]=14, 95% confidence interval [CI]: 2.7–71) for poor visual outcome. On the other hand, bacterial virulence (OR=0.16, 95%CI: 0.03–0.6) and complications (OR=0.07, 95%CI: 0.01–0.4) during cataract surgery were independent factors of good visual acuity. Other factors, significantly identified using univariate analysis, were not independent factors and included diabetes, VA, corneal edema, hypopyon, fundus visibility, and PPV.

Table 2: Significant predictors of poor visual outcome after acute postcataract endophthalmitis (multivariate logistic regression analysis).

<i>Factor (j)</i>	<i>Numerical variable X_i</i>	<i>Logistic coefficient (b_i)</i>	<i>Standard error</i>	<i>P-value</i>	<i>Exp (logistic coefficient) 95%CI</i>
Bacterial identification					
- Sterile					1
- CNS		-0.4	0.9	0.6	1.2 (0.1–4)
- Virulent bacteria		2.6	0.8	0.001	14 (2.7–71)
	Constant term	$b = -1.8$	1.05	0.05	

Estimated multiple logistic model:

$\log p/(1-p) = -1.8 + 2.6 X_1$. The odds ratio (OR or $\text{Exp}(\text{logistic coefficient})$) provides a practical estimate of the relative risk of belonging to the poor visual outcome group.

The logistic coefficient b_i is a measurement of the importance of each X_i in the prediction of the probability of having a poor visual prognosis.

CNS: coagulase-negative staphylococci

Table 3: Significant predictors of good visual outcome after acute postcataract endophthalmitis (multivariate logistic regression analysis).

<i>Factor (j)</i>	<i>Numerical variable X_i</i>	<i>Logistic coefficient (b_i)</i>	<i>Standard error</i>	<i>P-value</i>	<i>Exp (logistic coefficient) 95%CI</i>
Bacterial identification					
- Sterile	0 = absence				1
- CNS	1 = presence	-0.7	0.6	0.2	0.4 (0.1–1.7)
- Virulent bacteria		-1.8	0.7	0.01	0.1 (0.03–0.6)
Complications during cataract surgery					
	0 = absence				1
	1 = presence	-2.5	0.8	0.003	0.07 (0.01–0.4)
	Constant term	b = 0.5	0.8	0.5	

CNS: coagulase-negative staphylococci

Discussion

This prospective study analyzing baseline prognostic clinical and microbiological factors shows that bacterial virulence is the main independent factor of good or poor visual outcome after acute postcataract endophthalmitis. One additional independent factor of good visual outcome is the absence of complications during cataract surgery.

Most studies considering prognostic factors after acute postoperative endophthalmitis¹⁰⁻¹⁶ were retrospective. We should emphasize that only prospective studies are contributive to collecting baseline clinical and microbiological data because initial examination is difficult in the emergency context and the microbiological diagnosis should be performed using standardized methods. Our study was based on previously validated microbiological techniques.^{6, 18, 19} Our prospective study differed from the EVS by less restrictive inclusion criteria since it was not designed to randomize patients for treatment (in the EVS: inclusion of patients with cornea clear enough to allow PPV, exclusion of patients who did not consent to therapeutic randomization, VA equal to or better than 20/100).¹⁰ Other considerations should also be taken into account, such as the number of patients studied (99 patients in FRIENDS vs 420 in EVS), the number of centers (4 vs 24), the duration (1.5 years vs 4 years), and the study period (2004–2005 vs 1990–1994), and the type of surgery (phacoemulsification rate, scleral or corneal incisions, secondary implantation). One additional strength of the present study was that the population was not limited to culture-positive cases¹⁵ and included microbiologically unproven cases ($n=30$) and cases diagnosed by PCR only ($n=25$ in this series). Complications at the time of cataract surgery were also included.

The final visual outcome data reported in this recent series showed that 31% of patients had a poor visual outcome, while 45% had a good visual outcome (VA $\geq 20/40$). These results are similar to those described in the EVS (53% $\geq 20/40$) and other reports (see Table 4). Defining prognostic factors of poor visual outcome at admission may be useful for clinicians since these patients would probably benefit from more aggressive treatment. The initial VA level has previously shown a good correlation with the visual prognosis.^{10, 12, 13, 15, 16, 22} It was identified as one of the most important prognostic factors in the EVS (OR=2), in addition to diabetes (OR 1.6), corneal infiltrate and/or ring ulcer (OR=1.7), posterior capsular rupture (OR=1.9) and rubeosis iridis (OR=1.8). Other previously reported significant factors such as absence of fundus visibility¹⁰ and absence of red reflex¹⁰ were also identified in the present series. Diabetes is a systemic condition that potentially has an effect on the severity of endophthalmitis, especially with a higher Gram-positive and CNS infection identification rate.¹⁰ We previously showed¹⁸ that eyes infected by *Streptococcus* species were more frequently noted in diabetic patients. The frequency of diabetes in the current study was 13%, nearly identical to that in the EVS patients (14%).¹⁰ A Gram-positive microorganism was always identified in this situation, and in more than half of the cases (7/13) it belonged to the *Streptococcus* species. We found a trend toward a higher frequency of diabetic patients in the group with poor VA. One limitation of all reported studies is the absence of information concerning severity and treatment of diabetes.

The season could also play a role in the severity of infection and therefore in the prognosis. Variations in the bacteria spectrum and virulence may explain the seasonal variation in severity of postoperative endophthalmitis. We previously showed that *Streptococcus* sp., uniformly frequent (30–36%) from winter to summer,

were less frequent in autumn. These data should be taken into account when noting the increased rate of *S. pneumoniae* found in conjunctival cultures in the same periods (March, November, and December).²³ A retrospective Australian study¹⁴ showed a trend toward more isolates in the cooler wetter seasons of autumn and winter.

After univariate analysis, the multivariate analysis identified the bacterial virulence as the main independent factor of visual outcome. We classified patients into three groups: virulent, CNS, and sterile. This classification is based on the reported virulence of bacteria in cohort or case series, such as *Pseudomonas*,^{12, 24, 25} *Enterococcus*,²⁶ *Streptococcus*,^{12, 27, 28} *Staphylococcus aureus*,^{28, 29} and *Staphylococcus lugdunensis*²⁰ in acute postoperative endophthalmitis. Virulence is strongly associated with bacterial characteristics, such as production of toxins (cytolysin of *Enterococcus faecalis*, the quorum-sensing *fsr* system regulating gelatinase and serine protease, pneumolysin and autolysin of *S. pneumoniae*, and *S. aureus* alpha-toxin and beta-toxin), production of biofilms (*Enterococcus*, *Staphylococcus* including CNS), and motility in the eye (*B. cereus*).³⁰

Several reports have emphasized the prognostic role of bacterial virulence in postoperative endophthalmitis¹⁰⁻¹⁶ but this is only the second prospective study after EVS that shows the influence of bacterial virulence on final visual prognosis, taking into account baseline clinical factors. Intraocular lesions during infection have been extensively studied in animal models of endophthalmitis, and experimental studies have strongly suggested that ocular lesions during infection are related to bacterial virulence and secondary intraocular inflammation to the host response to bacterial toxins and cell wall constituents (cellular infiltration, production of cytokines, chemokines and adhesion molecules, Fas ligand).³¹ Culture-negative cases are

usually associated with a better final visual outcome (Table 4)^{11, 32} The sterile group of patients with endophthalmitis (i.e., with negative microbiological results) probably has a low inoculum undetected by conventional cultures and PCR techniques despite infection. This situation is close to CNS infections, which are traditionally associated with a less severe disease course.^{11, 28, 32} However, a subpopulation of patients with CNS infection has a severe prognosis, 9% in our series. The more severe CNS infections may be related to specific virulence traits of the involved strains, such as higher adhesion or biofilm formation.³³ Further development in the field of CNS virulence may help better define specific phenotypic and genotypic traits associated with the occurrence of more severe endophthalmitis cases. Also, it has been previously shown that acquired antibiotic resistance is frequent in *S. epidermidis* isolated from eyes with endophthalmitis (e.g., methicillin resistance),³³ The development of diagnostic tests allowing rapid evaluation of the virulence and antibiotic resistance traits of CNSs may help better define the population of CNS endophthalmitis patients with poorer outcome. Previous studies have shown that the turn-around time of panbacterial PCR is 2–3 days,⁶ and this time could be reduced to only a few hours with real-time PCR, as recently described in the literature.^{7, 8, 9}

Our analysis found the virulence factor to be a powerful indicator of visual prognosis, and VA was not an independent prognostic factor, in contrast to the EVS findings. This discrepancy could be due to different inclusion criteria. Finally, case series and cohort studies, including this one, strongly suggest that identification of Gram-positive cocci belonging to *Streptococcus* sp., *S. aureus*, or *S. lugdunensis*, strongly predict a poor visual outcome.¹¹ For instance, only 29% of patients infected with virulent Gram-positive cocci had a final VA of 20/40 or better.¹¹ Another example concerns infections with *S. aureus*, streptococci, or enterococci with 50%,

30%, and 14%, respectively, having a final VA of 20/100 or better in the EVS study.

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Table 4: Comparison of final visual outcomes by bacterium in previous studies and current study

	≥20/400	≥20/100	≥ 20/40
<i>S. aureus</i>		50% ¹¹ 20% ¹⁵ 3% (present study)	36.7% ¹⁰ 20% ¹⁵ 2% (present study)
<i>Streptococcus</i>	0% ¹² 2% ³⁴	30% ¹¹ 0% ¹⁵ 8% (present study)	13% ¹⁰ 0% ¹⁵ 7% (present study)
<i>Enterococcus</i>		14% ¹¹ 4% (present study)	4% (present study)
Gram-negative bacteria	49% ³⁵	56% ¹¹ 71% ¹⁵ 3% (present study)	38.9% ¹⁰ 28.5% ¹⁵ 2% (present study)
CNS	60–88% ^{12, 28, 36-40}	86% ¹⁵ 80.8% ¹¹ 30% (present study)	58.4% ¹⁰ 62% ¹⁵ 16.2% (present study)
Culture-negative cases	94% ³⁸	27% (present study)	35% ³² 20% (present study)
All populations	47.5% ¹² 62% ⁴¹	71.2% ¹⁵ 74% ¹⁰ 69% (present study)	49.3% (<i>n</i> =73) ¹⁵ 53% ¹⁰ 45% (present study)

The need for pars plana vitrectomy was associated with a poor visual outcome but also with other clinical factors correlated with the severity of the disease (poor initial VA, loss of red reflex, corneal edema, infection with a virulent species, and early onset of symptoms). For this reason, after multivariate analysis, the need for PPV was no longer identified as an independent prognostic factor. This relationship is easier to understand with the legacy of the EVS, showing the benefit of PPV in more severe patients, i.e., those having LP at admission.¹⁰ Another nonrandomized study¹⁵ showed that PPV was associated with a worse prognosis due to the indication bias of vitrectomy.

In conclusion, this prospective study shows that bacterial virulence is a major prognostic factor of final visual function in patients with acute endophthalmitis after cataract surgery. Whereas most patients are currently treated binarily, using PPV or intravitreal injections, mostly according to EVS guidelines based on initial VA, perspectives of rapid bacterial identification and characterization (virulence, antibiotic resistance) are of major interest. This new diagnostic strategy could guide clinicians in adapting the therapeutic regimen to each patient.

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THESE SOUTENUE PAR : Aurélie Combey-de Lambert

TITRE: Baseline predictive factors of visual prognosis in acute bacterial post-cataract endophthalmitis

CONCLUSION

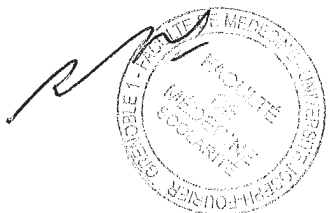
In conclusion, this prospective study showed that bacterial virulence was the main prognostic factor of final visual function in patients with acute endophthalmitis after cataract surgery. Whereas most patients are now treated empirically, with guidelines of EVS based on initial VA, perspectives of rapid bacterial identification and characterization (identity, virulence, resistance) are of major interest. This strategy could guide clinicians to adapt therapeutic regimen for each patient.

VU ET PERMIS D'IMPRIMER

Grenoble, le 12 avril 2012

LE DOYEN

Pr J.P.ROMANET



LE PRESIDENT DE LA THESE

Pr J.P.ROMANET

A handwritten signature in black ink.