META-ANALYSIS OF ENDOPHTHALMITIS AFTER INTRAVITREAL INJECTION OF ANTI–VASCULAR ENDOTHELIAL GROWTH FACTOR AGENTS

Causative Organisms and Possible Prevention Strategies

COLIN A. McCANNEL, MD*†

Purpose: To report the rates of endophthalmitis and the spectrum of causative organisms after intravitreal injection of anti–vascular endothelial growth factor agents and possible prevention strategies.

Methods: Meta-analysis of the U.S. literature from 2005 to 2009 reporting endophthalmitis bacterial isolates after intravitreal injection of anti–vascular endothelial growth factor agents and comparison with reports of endophthalmitis bacterial isolates after intraocular surgery in the United States.

Results: Endophthalmitis after intravitreal injection occurred in 52 of 105,536 injections (0.049%) (95% confidence interval [CI], 0.038–0.065%). Among 50 cases of endophthalmitis with bacterial culture isolates, 24 (48.0% [95% CI, 34.8–61.5%]) were culture negative and 26 (52% [95% CI, 38.5–65.2%]) were culture positive. Among the 26 culture-positive isolates, causative organisms were coagulase-negative Staphylococcus in 17 cases (65.4% [95% CI, 46.0–80.6%]), Streptococcus species in 8 cases (30.8% [95% CI, 16.5–50.2%]), and *Bacillus cereus* in 1 case (3.8% [95% CI, 0.9–19.0%]). Streptococcus species were significantly more frequent after intravitreal injection than after intraocular surgery in the Endophthalmitis Vitrectomy Study (29 of 226 isolates, 9.0% [95% CI, 6.3–12.6%], $P = 0.005$), a report on clear corneal cataract surgery endophthalmitis (6 of 73 isolates, 8.2% [95% CI, 3.9–16.8%], $P = 0.022$), and a report on postvitrectomy endophthalmitis with no cases of Streptococcus species.

Conclusion: Streptococcal isolates are approximately three times more frequent after intravitreal anti–vascular endothelial growth factor injection than after intraocular surgery. Strategies to consider minimizing oropharyngeal droplet transmission may include avoiding talking, coughing, and sneezing or wearing surgical masks.

RETINA 31:654–661, 2011

Endophthalmitis after penetrating ocular procedures is a rare but devastating complication. The range of acute postoperative endophthalmitis in the United States has been reported to be 0.04% to 0.076%.[1–4] The most common causative organisms are coagulase-negative Staphylococcus species.

Endophthalmitis after intravitreal injection of anti–vascular endothelial growth factor (VEGF) agents (pegaptanib, bevacizumab, and ranibizumab) is similarly rare. Reported endophthalmitis rates vary from 0.019%[5] to 0.54%.[6] These rates are low despite the injections being performed in the office setting. To date, there have been no reports on the spectrum of causative organisms observed after endophthalmitis after anti-VEGF agent injection compared with those observed in acute postoperative endophthalmitis. This study describes a meta-analysis performed to determine the spectrum of causative organisms in endophthalmitis after intravitreal injection of anti-VEGF agents compared with those in the setting of acute postoperative endophthalmitis.

Materials and Methods

Using the National Library of Medicine PubMed interface (www.pubmed.gov), a literature search was

performed. All articles containing the keywords ''endophthalmitis'' and ''injection'' during the years 2005 to March 22, 2010, inclusive (Medline search date: March 22, 2010) were identified. Additionally, the articles were reviewed for references that might identify additional relevant studies, and these were also reviewed. Those articles in which the title suggested that the publication might contain information on anti-VEGF agent injection endophthalmitis were reviewed to assess whether the article met inclusion criteria. The inclusion criteria were threefold. First, articles were required to report on endophthalmitis after intravitreal injection of an anti-VEGF agent. Second, articles were required to provide the endophthalmitis culture results, including bacterial species that were isolated (''isolates''). Third, articles were required to report on patient populations in the United States, given the possible variation in procedures, settings, and bacterial colonization patterns elsewhere. Articles that fulfilled all inclusion criteria were included in the meta-analysis. Additionally, references in the selected articles and those of review articles on endophthalmitis were used to identify additional publications that might be eligible for inclusion. Any additional publications that met the inclusion criteria were also included in the meta-analysis. Articles that reported on endophthalmitis rates but did not include the causative organism information or those that had no cases of endophthalmitis were excluded. A large series of endophthalmitis after surgery performed in the operating room that provided information on causative organisms, or isolates, from the United States were selected for comparison.

Statistical analyses between the meta-analysis and the comparative postoperative studies were made using the chi-square test. A funnel plot was performed to assess systematic publication bias of the meta-analysis.

From the *Jules Stein Eye Institute; and †Department of Ophthalmology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California.

Funded in part by an unrestricted grant from the Research to Prevent Blindness and the Jules Stein Eye Institute, Los Angeles, CA.

Parts of this work were presented at the 2010 Annual Meetings of the American Association of Retina Specialists, Vancouver, Canada, and the American Academy of Ophthalmology, Chicago, IL.

The author has no proprietary interest in the subjects or technology discussed in this article.

Reprint requests: Colin A. McCannel, MD, Jules Stein Eye Institute, University of California, Los Angeles, 100 Stein Plaza, Los Angeles, CA 90095; e mail: cmccannel@jsei.ucla.edu

Results

The initial PubMed search returned a total of 432 articles. After additional inclusion of referenced articles, there were 24 articles that provided information on endophthalmitis and causative organisms after anti-VEGF agent injection. After all inclusion criteria were applied, there were 16 remaining articles that fulfilled all inclusion criteria. The relevant information from these articles is summarized in Table 1.[5–20]

Studies reporting endophthalmitis and causative organisms after intravitreal injection outside the United States were reports by Aggio et al,[21] Alkuraya et al,[22] Artunay et al,[23] and Yenerel et al,[24] and Wu et al.[25] A report by Lee et al[26] was excluded because the authors convincingly tracked the occurrence of two cases of *Serratia marcescens* endophthalmitis to pharmacy contamination. In the VEGF Inhibition Study in Ocular Neovascularization (VISION) trial[27,28] publications, causative organisms of the 12 cases of endophthalmitis were not reported, and thus, these cases were not considered in the meta-analysis.

A total of 54 cases of endophthalmitis were considered in the meta-analysis. The cumulative rate of endophthalmitis was determined to be 52 cases after 105,536 injections (0.049%) (95% confidence interval [CI], 0.038–0.065%). Two case reports were not included in the rate calculation because no denominator was provided in the publications for these cases. A culture was obtained for 50 cases, 24 (48.0% [95% CI, 34.8–61.5%]) of which were negative. Among the 26 cultured endophthalmitis cases for which the isolates were reported, the most common causative organisms were coagulase-negative Staphylococcus species, which accounted for 17 of the 26 cases (65.4% [95% CI, 46.0–80.6%]). The second most common causative organisms were Streptococcus species (8 of 26 or 30.8% [95% CI, 16.5–50.2%]). One case was caused by *Bacillus cereus* (30.8% [95% CI, 16.5–50.2%]).

In comparison, the causative organisms and their relative rates among the 3 largest studies of postoperative endophthalmitis with causative organisms after surgery in the operating room are summarized in Table 2.[29–31] For comparison, isolates of normal conjunctival flora from patients about to undergo intravitreal injection for the first time are summarized in Table 3.[32] Comparing the distribution of organisms in the meta-analysis with these postoperative reference studies, Streptococcus species were significantly more frequent after intravitreal injection than after intraocular surgery in the Endophthalmitis Vitrectomy Study[29,33] (29 of 323 isolates, 9.0%, $P = 0.005$), a recent report on post–clear corneal cataract surgery

Table 1. Studies of Endophthalmitis After Anti-VEGF Agent Injection Included in the Meta-analysis

Study	Anti-VEGF Agent	Injections	Endophthalmitis	
			Cases	Rate (%)
Rosenfeld[7] (MARINA)	Ranibizumab	10,443	5	0.048
Heier[8] (FOCUS)	Ranibizumab	1,544‡	5	0.324
Heier[9] (Phase I/II)	Ranibizumab	407	1	0.246
Scott[6] (DRCRnet)	Bevacizumab	185	1	0.541
Kopel[10]	Bevacizumab	*	1*	NA
Mason[5]	Bevacizumab	5,223	1	0.019
Pili et al[11]	Pegaptanib	406	0	0.029
	Bevacizumab	3,501	1	
	Ranibizumab	6,347	2	
Fintak et al[12]	Bevacizumab	12,585	3	0.024
	Ranibizumab	14,320	3	0.021
Brown et al[13] (ANCHOR)†	Ranibizumab	3,125‡	3	0.096
Diago et al[14]		3,875	3	0.077
Bhavsar et al[15] (DRCRnet)	Ranibizumab	3,226	3	0.093
Lima et al[16]	Bevacizumab	6,527	1	0.034
	Ranibizumab	2,416	2	
Klein et al[17]	Pegaptanib	128	0	0.049
	Bevacizumab	8,039	5	
	Ranibizumab	22,579	10	
Bakri et al[18]	Bevacizumab	208	1	0.481
Chen et al[19]	Pegaptanib	*	1*	NA
Fong et al[20]	Bevacizumab	324	1	0.442
	Ranibizumab	128	1	
Total	All	105,536	52 (+2*)	0.049*
Total by category				

	Categories of Organism Identified						
	Non-Streptococcus Species		Streptococcus Species			No Isolate	
Study	Coagulase-Negative Staphylococcus	*Bacillus cereus*	*Streptococcus viridans*	*Streptococcus salivarius*	*Streptococcus mitis*	No Growth/ ''Sterile''	Not Cultured
Rosenfeld[7] (MARINA)	—	—	—	—	—	4	1
Heier[8] (FOCUS)	1	—	—	—	—	4	—
Heier[9] (Phase I/II)	1	—	—	—	—	—	—
Scott[6] (DRCRnet)	1	—	—	—	—	—	—
Kopel[10]	—	1	—	—	—	—	—
Mason[5]	1	—	—	—	—	—	—
Pili et al[11]	—	—	—	—	—	—	—
	—	—	—	—	—	1	—
	—	—	—	—	—	2	—
Fintak et al[12]	1	—	2	—	—	—	—
	—	—	—	—	1	2	—
Brown et al[13] (ANCHOR)†	1	—	—	—	—	1	1
Diago et al[14]	2	—	—	—	—	1	—
Bhavsar et al[15] (DRCRnet)	2	—	1	—	—	—	—
Lima et al[16]		—	—	—	—	1	—
	1	—	1	—	—	—	—
Klein et al[17]	—	—	—	—	—	—	—
	1	—	1	1	—	2	—
	3	—	—	—	—	5	2
Bakri et al[18]	—	—	—	—	—	1	—
Chen et al[19]	—	—	—	—	1	—	—

Table 1. *(continued)*

	Categories of Organism Identified						
	Non-Streptococcus Species		Streptococcus Species			No Isolate	
Study	Coagulase-Negative Staphylococcus	*Bacillus cereus*	*Streptococcus viridans*	*Streptococcus salivarius*	*Streptococcus mitis*	No Growth/ ''Sterile''	Not Cultured
Fong et al[20]	1	—	—	—	—	—	—
	1	—	—	—	—	—	—
Total	17	1	5	1	2	24	4
Total by category	18	8	28				

*Case reports that did not indicate among how many injections the infection occurred; these cases were excluded in the endophthalmitis rate calculation.

†A small number of study centers were located outside the United States.

‡The number of injections is not reported and estimated from the publication's methods and number of enrollees.

The table summarizes the studies' endophthalmitis rate stratified by anti-VEGF agent, and overall, and indicates the specific isolates when available. Three larger groups are summarized: that is, non-Streptococcus species organisms, Streptococcus species organisms, and no isolate. MARINA, Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; FOCUS, RhuFab V2 Ocular Treatment Combining the Use of Visudyne to Evaluate Safety; DRCRnet, Diabetic Retinopathy Clinical Research Network; ANCHOR, Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; NA, not applicable.

endophthalmitis[30] (6 of 73 isolates, 8.2%, $P = 0.022$), and a report on postvitrectomy endophthalmitis[31] with no cases of Streptococcus species. The report on normal conjunctival flora preinjection also indicated fewer Streptococcus species (9 of 129 isolates, 7%, $P = 0.0016$).

A funnel plot estimating endophthalmitis rates against the number of injections reported in each study is shown in Figure 1.[34] Among 4 small studies with the number of injections <2,000, there was a wide spread of overestimates of endophthalmitis rates, ranging from 0.24% to 0.55%. Among large studies with the number of injections ranging from 3,125 to 30,746, the estimated rate of endophthalmitis ranged from 0.02% to 0.1%. Therefore, there may be ''small study effects'' overestimating the endophthalmitis rate, and it is unlikely that a systematic publication bias exists for reported rates of endophthalmitis after intravitreal anti-VEGF injections.

Discussion

This meta-analysis of endophthalmitis after intravitreal anti-VEGF injections found a significantly greater rate of endophthalmitis cases caused by Streptococcus species than has been reported for postoperative endophthalmitis. Streptococcus species, which comprise at least 41% culturable adult salivary flora,[35,36] are thought to contaminate operative fields by aerosolization or droplet spread[37–41] and may be related to the difference in causative organisms in these 2 settings.

Staphylococcal organisms (coagulase-negative Staphylococcus, *Staphylococcus aureus*, and methicillin-resistant *S. aureus*) occur rather uniformly at rates of approximately 70% to 80% across all studies (Tables 1–3), including the current meta-analysis of anti-VEGF injections (Table 1). However, the rate of Streptococcus species as a causative organism of postoperative endophthalmitis or preexisting colonization of the conjunctiva is in the range of 0% to 9% (Tables 2 and 3), which contrasts dramatically with the 30.2% rate of streptococcal endophthalmitis after intravitreal injection (Table 1) found in the meta-analysis. This three to four times higher rate of endophthalmitis from Streptococcus species suggests that the spectrum of organisms is different than in the operating room setting and that Streptococcus species are more common causatives of endophthalmitis after intravitreal injection.

A review of the ophthalmic literature indicates no explanation for the different streptococcal endophthalmitis rates after intravitreal anti-VEGF agents compared with the postoperative setting. However, there is compelling evidence that aerosol contamination of the surgical field by respiratory flora may be contributory. Dural puncture (i.e., lumbar puncture for spinal anesthesia) is a procedure similar to intravitreal injection in that it involves needle penetration into a nutrient-rich body cavity in a nonoperating room setting. The rate of postdural puncture meningitis is low (0.2–1.8/10,000)[42–44] compared with that of postintravitreal injection endophthalmitis (4.9/10,000 in this meta-analysis).

A closer look at the factors that have been determined to increase the risk of postdural puncture

Tab e 2. Representat ve Stud es of Postoperat ve Endophtha m t s and the Reported Iso ates

	Iso ates	Coagu ase-Negat ve Staphy ococcus	*Staphylococcus aureus*	Streptococcus Spec es	M sce aneous Gram-Pos t ve Organ sms	Gram-Negat ve Spec es
Acute postoperat ve endophtha m t s (Endophtha m t s V trectomy Study)[29]	323	226 (70% [95% CI, 64.8–74.7%])	32 (9.9% [95% CI, 7.1–13.7%])	29 (9.0% [95% CI, 6.3–12.6%])	17 (5.3% [95% CI, 3.3–8.3%])	19 (5.9% [95% CI, 3.8–9.0%])
Acute postoperat ve endophtha m t s after c ear cornea cataract surgery[30]	73	50 (68.5% [95% CI, 57.1–78.0%])	5 (6.8% [95% CI, 3.0–15.1%])	6 (8.2% [95% CI, 3.9–16.8%])	5 (6.8% [95% CI, 3.0–15.1%])	7 (9.6% [95% CI, 4.8–18.5%])
Acute postoperat ve endophtha m t s after 25- or 20-gauge v trectomy[31]	7	6 (85.7% [95% CI, 47.4–96.8%])	—	—	—	1 (14.3% [95% CI, 3.2–52.6%])
Acute endophtha m t s after ntrav trea nject on n the office sett ng meta-ana ys s (current study)	26	17 (65.4% [95% CI, 46.0–80.6%])	—	8 (30.8% [95% CI, 16.5–50.2%])	1 (3.8% [95% CI, 0.9–19.0%])	—

The tab e summar zes three representat ve stud es of postoperat ve endophtha m t s. The ast co umn summar zes the so ates from the current meta-ana ys s for compar son.

meningitis may help ophthalmologists further reduce the risk of endophthalmitis after intravitreal injections. McLure et al[40] and Phillips et al[45] in similar studies investigated whether wearing soft pleated face masks affects agar dish contamination. These reports determined that the absence of a surgical mask was associated with a statistically significant increase in colonies per exposed plate. They recovered α-hemolytic Streptococci, nonhemolytic Streptococci, and coagulase-negative Staphylococci.[40]

O'Kelly and Marsh[39] and Phillips et al[45] in similar studies investigated the effect of talking and wearing a face mask on agar plate contamination to assess procedure infection risk. In these studies, there was a significant increase in colony counts when not wearing a mask and talking compared with not talking or wearing a mask. Furthermore, O'Kelly and Marsh[39] suggest that not talking is nearly as effective as wearing a face mask in preventing agar plate contamination and thus reducing procedure infection risk from respiratory tract flora.

Another procedure that is similar to an intravitreal injection is intraarticular injection. A recent report by Reeves and Hovart[46] implicates the absence of a face mask as the likely cause of infection with α-hemolytic Streptococcus after an intraarticular knee injection. In this report, infection risk in a retrospective series of injections is associated with talking when no mask was worn.[46]

There is also direct evidence that respiratory droplet transmission from the health care provider may be the source of procedure-related infection. Using molecular techniques, causative organism of meningitis cases after dural puncture procedures was indistinguishable from those recovered from the procedurist's mouth.[37,41,47] Sheretz et al[38] describe an outbreak of 5 cases of methicillin-resistant *S. aureus* infections, 5 cases of pneumonia, 1 case of bacteremia, and an additional 3 cases of colonization with methicillin-resistant *S. aureus* over a 3-week period. Investigation traced the probable source of the outbreak to a physician colonized with the same organism, and that during the outbreak, he had a viral upper respiratory infection (URI). Further investigation also showed that while this individual had very little "bacterial shedding" when not experiencing a viral URI, he did shed a large amount of bacteria when purposely reinfected with a rhinovirus (Type 39). This observation suggests that viral URI increases bacterial shedding. A surgical mask was able to minimize dispersal of bacteria during the study of the URI episode.[38]

These publications lend critical evidence that supports droplet or aerosol transmission of infections

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.