Chapter 6
Epidemiology and Treatment Trends in North America

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Pathogenesis of Endophthalmitis

The intraocular contents are normally sterile and protected from microorganisms by the blood-ocular barrier. However, the vitreous gel can act as a culture medium for microorganisms. Pathogens from the environment as well as normal ocular flora from the patient's biome can lead to infectious endophthalmitis should they gain access to the intraocular space. This may occur from a breakdown of the blood-ocular barrier in endogenous endophthalmitis. Alternatively, the microorganisms may obtain access via wounds breaching the eye wall at the time of surgery, trauma, scleritis, or keratitis, leading to exogenous endophthalmitis.

In North America, bacteria and less commonly fungi or parasites are responsible for exogenous endophthalmitis. They may originate from the rich conjunctival and eyelid flora, from airborne particles or contaminated surgical devices. While not much has been published on the North American patient population recently, the continued understanding is that lid and conjunctival flora remain the main source of pathogens for endophthalmitis caused by access to the intraocular space through an open or incompletely sealed wound. In a prospective study at the New York Eye and Ear Infirmary, 82% of 17 cases of postoperative endophthalmitis showed bacteriological and genetic similarities between microorganisms isolated from the infected vitreous and those isolated from the conjunctiva and lid margin of the patient, in an era before PCR [1].

The normal conjunctival flora in 42 healthy post-WWII San Franciscans mostly consisted of coagulase-negative staphylococci (76% of patients) often coexisting with nonpathogenic *Corynebacterium* (50% of patients). Coagulase-positive staphylococci were present in 10% of patients. *Streptococcus* species were not isolated [2]. Sixty years later, the most common bacteria on conjunctival cultures of

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24 patients at Vanderbilt University, Tennessee, were coagulase-negative staphylococci in 65% of isolates, *Micrococcus* species in 14%, *Staphylococcus aureus* in 9%, gram-negative bacteria in 7%, and *Streptococcus agalactiae* in 2% [3].

This breakdown of conjunctival flora is consistent with pathogens isolated in endophthalmitis series [4–6].

Microbiologic Spectrum of Exogenous Endophthalmitis in North America

Three large retrospective studies have looked at the microbiological spectrum and antibiotic susceptibilities of endophthalmitis-causing pathogens in North American centers over the past decades.

The first study, at Yale in Connecticut, analyzed 143 positive vitreous cultures taken for endophthalmitis between 1988 and 2008. Gram-positive bacteria were identified in 80.6% of isolates, gram-negative bacteria in 12.5% of isolates, and fungi in 6.9% of isolates. The most prevalent organisms in the Yale study were coagulase-negative *Staphylococcus* (37.5%), viridans streptococci (11.3%), *Streptococcus pneumoniae* (6.9%), and *Propionibacterium acnes* (5.6%). While no change in the prevalence of common bacteria was noted over the 20-year study period, rates of staphylococcal resistance to at least one antibiotic tested increased over time. Despite this, no methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant cocci were isolated. All gram-positive bacteria remained sensitive to vancomycin, and all gram-negative bacteria remained sensitive to ceftazidime throughout the study period. Resistance of coagulase-negative staphylococci to gentamicin decreased from 33.3% in the early years of the study to 0% in the later years [4].

The second study, in Florida, looked at all 448 bacterial isolates cultured from vitreous of patients with endophthalmitis at Bascom Palmer from 2002 to 2011. The most common organisms identified were *Staphylococcus epidermidis* in 30.1%, viridans streptococci in 10.9%, *Staphylococcus aureus* in 7.8%, *Candida albicans* in 5.8%, other coagulase-negative staphylococci in 6.0%, *Propionibacterium acnes* in 4.7%, and *Pseudomonas aeruginosa* in 3.1%. Overall, 72.9% of isolates were gram-positive organisms, 10.7% were gram-negative organisms, and 15.8% were fungi. All gram-positive organisms were susceptible to vancomycin, and all gram-negative organisms were susceptible to ceftazidime and levofloxacin. When comparing to vitreous culture results from the same center in the previous decade, susceptibility of both gram-positive and -negative organisms to gentamicin increased, while that of coagulase-negative staphylococci to fluoroquinolones was halved [5].

The third study at the New York Eye and Ear Infirmary looked at the 988 bacterial isolates grown from aqueous or vitreous samples of patients with endophthalmitis, between 1987 and 2011. Overall, 85.1% of isolates were gram positive, 10.3% were gram negative, and 4.6% were fungal. The most common pathogens were *Staphylococcus epidermidis* (30.3%), followed by viridans streptococci species

(12.1%), *Staphylococcus aureus* (11.1%), and other coagulase-negative staphylococci (9.1%). Among the gram-negative organisms isolated, *Enterobacteriaceae* (3.4%) and *Pseudomonas aeruginosa* (2.5%) were isolated most frequently. *Candida* was the most frequently isolated fungus (2.8%). A trend toward the increased prevalence of gram-negative bacteria (p = 0.08) and decrease in *Streptococcus pneumoniae* (p = 0.03) was observed over the study period. The latter could be attributed to the availability of vaccination against *Streptococcus pneumoniae* and the decline in the use of trabeculectomies in the United States during the study period. Two (out of 727) gram-positive isolates displayed resistance to vancomycin over the 25-year study period, *Enterococcus* in 2005 and *Nocardia* in 2009 [6].

These three studies from Yale, Bascom Palmer, and New York Eye and Ear Infirmary retrospectively analyzed all cases of endophthalmitis submitted to their microbiology laboratories, including postoperative, traumatic, and endogenous etiologies, with little clinical data available on the history of the patients or their visual outcomes. Data on the number of surgical procedures or the antibiotic perioperative regimens was unavailable, as was whether postoperative endophthalmitis cases received povidone-iodine as part of the surgical regimen. Overall, intravitreal vancomycin and ceftazidime administration proved to offer excellent coverage of the microbiological spectrum isolated in those studies. Only at the New York Eye and Ear Infirmary were bacteria resistant to this standard antibiotic treatment isolated. The 0.28% (2 of 727) incidence of vancomycin-resistant bacteria in New York appeared, however, lower than that reported by a similar retrospective study of endophthalmitis bacterial isolates in India where the incidence of vancomycin-resistant bacteria was 1.56% (7 of 448) [7]. Microbiological profile of exogenous endophthalmitis is shown in Table 6.1.

Table 6.1 Microbiological spectrum of exogenous endophthalmitis

	Yale 1998–2008	Bascom Palmer 1996–2001	Bascom Palmer 2002–2012	New York 1987–2001
Authors	Chen 2012 [4]	Schimel 2013 [5]		Gentile 2014 [6]
Coagulase-negative staph	37.5%	37.1%	36.1%	39.4%
S. aureus	4.4%	7.7%	8.0%	11.1%
Viridans streptococci	11.3%	12.8%	10.9%	12.1%
S. pneumoniae	6.9%	–	–	5.2%
P. acnes	5.6%	7.0%	4.7%	8.8%
P. aeruginosa	–	2.2%	3.1%	2.5%
E. faecalis	3.8%	–	–	2.2%
Klebsiella sp.	3.1%	–	–	–
Moraxella sp.	3.1%	–	–	–
H. influenzae	2.5%	–	–	–
Enterobacteriaceae	–	–	–	3.4%
C. albicans	–	2.9%	6.3%	2.8%

Endophthalmitis Following Cataract Surgery

Cataract surgery is the most commonly performed surgical procedure in the United States. The American Academy of Ophthalmology estimates that two million cataract surgeries are performed each year in the United States. In 2010, 1.82 million cataract surgeries were performed on Medicare beneficiaries not enrolled in health maintenance organizations. By comparison, only approximately 250,000 vitrectomies are performed annually in the United States according to the American Society of Retina Specialists (ASRS). Given the large number of cataract surgeries performed, it is easier to study the rare complication of endophthalmitis in cataract surgery than in other less frequently performed eye surgeries.

Incidence

Incidence of post-cataract surgery endophthalmitis in the United States has been investigated with smaller institution-based studies and larger Medicare-based studies. Medicare is a federal health insurance program in the United States. It provides coverage for approximately 50 million Americans, including virtually all people aged 65 years and older and some younger adults with permanent disabilities or end-stage renal disease. A retrospective study was based on a 5% sampling of the 1994–2001 Medicare claims identifying cataract surgeries and subsequent cases of presumed endophthalmitis occurring within the same or next calendar quarter of surgery. The incidence of endophthalmitis in the United States rose from 1.79 cases per 1000 in 1994 to 2.47 cases per 1000 in 2001, an overall increase of 37%. This increase paralleled the adoption of clear corneal wounds from scleral tunnel incisions for phacoemulsification [8]. In another retrospective study based on the Medicare database from 2006 to 2011, out of 2,261,779 cataract surgery cases, 4416 (0.195%) patients were diagnosed with endophthalmitis within 6 months of the surgery. The 0.195% rate from 2006 to 2011 was comparable to the 0.179% rate observed in 1994 in the previous study, prior to the increase to 0.274% in 2001 associated with the adoption of clear corneal wounds. This suggests that with increased experience of creating clear corneal wounds, the rate of endophthalmitis decreased from 2001 to 2006 returning to that observed with scleral tunnels. This study also reports the incidence of fungal endophthalmitis at 0.0005% (121 cases) [9]. A more recent review of 5% of Medicare claims between 2010 and 2013 revealed that 300 patients were diagnosed with endophthalmitis during the year following 216,703 cataract surgeries, which yielded an endophthalmitis rate of 0.14%, also supporting the return of the incidence of this complication at or below the levels seen at the era of scleral tunnels [10]. A smaller retrospective study based in Utah found that endophthalmitis was diagnosed in 26 of 9079 cataract surgeries (0.286%) performed between 1997 and 2001 at the Moran Eye Center [11]. When looking at a longer period in the same center, from 1997 to 2007,

Table 6.2 Incidence of post-cataract endophthalmitis

Author	Years	Number of surgeries	Incidence (%)	Incidence
West 2005 [8]	1998–2001	477,627	0.215	1/466
Du 2014 [9]	2006–2011	2,261,779	0.195	1/512
Jensen 2005 [11]	1997–2001	9079	0.286	1/349
Jensen 2008 [12]	1997–2007	29276	0.157	1/636
Coleman 2015 [10]	2010–2013	216,703	0.14	1/722
Coleman 2015 [10]	2013–2014	511,182	0.06	1/1278

the rate of endophthalmitis decreased to 0.157%, with 46 cases of endophthalmitis out of 29,276 cataract surgeries performed during a 10-year period, once again suggesting that with increased experience with clear corneal wound construction, the incidence of endophthalmitis decreases to a baseline number [12]. The incidence of post-cataract surgery endophthalmitis is shown in Table 6.2.

Microbiologic Spectrum

The majority of cases of postoperative endophthalmitis were caused by gram-positive organisms that are normal flora of the eyelid and conjunctiva. These bacteria may gain access to the intraocular space either through direct inoculation during surgery or due to migration of local flora into an incomplete wound closure postoperatively. In a prospective study consisting of 700 consecutive patients undergoing planned extracapsular cataract extraction, anterior chamber aspirates were culture positive in 14.1% at the beginning and in 13.7% at the end of surgery, despite the use of povidone-iodine 10% antisepsis; coagulase-negative staphylococci and *Corynebacterium* were the most common isolates [13]. In a smaller study on 113 patients undergoing cataract surgery, two patients (1.8%) showed growth in culture of the aqueous humor sampled at the end of the surgery, despite the use of povidone-iodine antisepsis. Fortunately, no patient developed endophthalmitis [14]. These studies suggest that host factors can clear a low inoculum of bacteria in the anterior chamber after cataract surgery without developing endophthalmitis. The increased endophthalmitis rate with posterior capsular defects suggests that the body cannot clear a bacterial inoculum in the vitreous cavity as effectively as in the anterior chamber.

In 1995, the Endophthalmitis Vitrectomy Study addressed the management of endophthalmitis following cataract surgery, which was performed by extracapsular extraction. It remains today the prospective study with the largest number of endophthalmitis patients. Among the 422 patients, vitreous cultures were positive in 69.3% of cases and 9.3% presented with polymicrobial growth. The most common bacteria were *Staphylococcus epidermidis* in 70% of bacterial isolates, *Streptococcus* species in 9.0%, *Staphylococcus aureus* in 9.9%, and enterococci in 2.2%. Gram-positive bacteria represented 94% of isolates, with 5.9% gram-negative species.

Table 6.3 Microbiological spectrum of post-cataract endophthalmitis

	EVS Han 1996 [15] Yield 69.3%	Medicare 2003–2004 Gower 2015 [16] Yield 58%	Bascom Palmer 1996–2005 Lalwani 2008 [17]
Coagulase-negative staphylococci	70.0%	45.0%	68.4%
Staphylococcus aureus	9.9%	–	6.8%
Streptococcus sp.	9.0%	12.0%	8.2%
Enterococcus sp.	2.2%	–	–
Gram negative	5.9%	7.0%	9.6%

All gram-positive species were sensitive to vancomycin [15]. Later studies, during the clear cornea wound phacoemulsification era, reported similar microbiological spectra for endophthalmitis following cataract surgery. A retrospective study of 502 endophthalmitis patients, selected using the 2003–2004 Medicare database, found culture yield to be 58% (lower than 69.3% in EVS), with coagulase-negative *Staphylococcus* in 45% of isolates and *Streptococcus* species in 12% of isolates. Gram-positive bacteria represented 93% of isolates. This study also reported that patients with *Streptococcus* were ten times more likely to have poor visual outcomes than those with coagulase-negative *Staphylococcus*. Worse visual outcomes were similarly noted when comparing patients with gram-negative bacteria to those with gram-positive ones. Finally, a smaller difference in poor visual outcomes was also noted between patients with culture-positive and culture-negative vitreous [16]. Another retrospective study reviewed 73 patients presenting with endophthalmitis at Bascom Palmer, within 6 weeks of cataract surgery from 1996 to 2005. Coagulase-negative staphylococci were isolated in 68.4% of eyes, *Streptococcus* species in 8.2%, and *Staphylococcus aureus* in 6.8%. Worse visual acuity outcomes were noted for infections caused by *Staphylococcus aureus* or *Streptococcus* species compared to those caused by coagulase-negative staphylococci [17]. The uniform microbiologic spectrum in these North American studies may sometimes contrast with the spectra reported on other continents. For instance, an institution-based retrospective study in Taiwan from 2004 to 2015 found that among 32 patients that developed endophthalmitis following cataract surgery, the most common isolates were *Enterococcus* species at 38.1%, *Staphylococcus epidermidis* at 28.6%, and *Staphylococcus aureus* at 9.5% of isolates [18]. Microbiological spectrum of post-cataract surgery endophthalmitis is shown in Table 6.3.

Treatment

Treatment of this sight-threatening disease has historically consisted of administration of intravitreal, subconjunctival, and intravenous antibiotics, with or without intravitreal or oral corticosteroids to minimize inflammatory damage, and drainage of the vitreous abscess by pars plana vitrectomy. The Endophthalmitis Vitrectomy

Study (EVS) is the major landmark evidence-based trial, which established treatment criteria for this condition. This prospective multicenter randomized clinical trial studied the treatment of endophthalmitis developed within 6 weeks of cataract surgery in patients who presented with vision between 20/50 and light perception (LP), without a history of comorbidities which could reduce their visual potential. All 420 patients received intravitreal vancomycin to cover gram-positive organisms and amikacin to cover the gram-negative ones, as well as subconjunctival dexamethasone, vancomycin, and ceftazidime. Patients were randomized to receive additional immediate pars plana vitrectomy or administration of intravenous antibiotics. The results determined that immediate vitrectomy would only benefit patients with LP, while in those with hand motions (HM) or better vision, using intravitreal antibiotics without vitrectomy would provide a similar long-term visual outcome. Moreover, the use of intravenous antibiotics provided no additional benefits to the intravitreal treatment. In the subgroup of diabetic patients, however, those who had HM or better vision also appeared to benefit from immediate vitrectomy as 57% of them achieved 20/40 vision, whereas only 40% did so without vitrectomy [19].

The mainstay of post-cataract endophthalmitis treatment in North America remains close to the one recommended two decades ago by the EVS study. Patients presenting with LP vision or worse undergo emergent pars plana vitrectomy, while those presenting with HM vision or better undergo the less invasive vitreous tap instead. All patients receive empiric intravitreal antibiotic injections, which most often include 1 mg vancomycin to cover gram-positive organisms and 2.25 mg ceftazidime for gram-negative organisms. The latter can be substituted with 0.4 mg amikacin in patients allergic to beta-lactams, although there have been reports of retinal infarction with aminoglycosides at therapeutic dosages. While all patients received subconjunctival antibiotics in the Endophthalmitis Vitrectomy Study, these have been dropped from standard treatment in North America over the past 20 years. In one retrospective study between 1991 and 2002, the final visual outcome of 43 patients presenting with HM vision and acute post-cataract endophthalmitis was similar whether subconjunctival antibiotics were added to the intravitreal ones or not. Moreover, the visual outcomes were comparable to those of the EVS patients [20]. Similar findings regarding the use of subconjunctival antibiotics were reported for treatment of endophthalmitis secondary to trauma, cataract, or glaucoma surgery in a retrospective study of 54 patients treated at Bascom Palmer from 1995 to 2002. This lack of additional effect occurred despite the nonrandomized nature of these trials where the subconjunctival antibiotics may presumably have been used in eyes with more severe disease, as the eyes who did not receive them had a lower rate of enucleation or absent LP outcomes [21]. With the improvement of vitrectomy technology over the past 20 years, allowing safer cutting close to the retina and better intraoperative viewing, more complete vitrectomies are performed, contrasting with the limited vitreous removal suggested in the EVS protocol prohibiting posterior vitreous detachment induction and advising "to remove at least 50% of vitreous gel in eyes with no vitreous separation." In a consecutive series of 47 eyes, which underwent complete vitrectomy for endophthalmitis with similar inclusion/exclusion criteria to the EVS, 91% achieved ≥20/40 final visual acuity, as opposed to a 53% rate in the EVS ($p < 0.0001$, Fisher's exact test). No serious adverse effects developed such as retinal detachment and phthisis bulbi or indications for enucleation. There was no case of anatomical failure, as opposed to the EVS with an 11% rate in the nonsurgical group and a 5% rate in the vitrectomy group [22]. Whether early vitrectomy in eyes with hand motions or better vision provides a better outcome by removing harmful agents and inflammatory mediators from the vitreous cavity could benefit from a randomized clinical trial. An indication of expected results could be found in a Medicare-based retrospective study. Across the five states in the study, the use of vitrectomy varied significantly in patients with better than light perception vision. Rates of vitrectomy in such patients ranged from 19% in Michigan to 56% in California, although no evidence was found that this was associated with better visual outcomes [16]. The good bioavailability of oral moxifloxacin following two or five orally administered 400 mg tablets, with obtained intravitreal drug concentrations exceeding the MIC90 (minimal inhibitory concentration in which 90% of isolates were inhibited) of most bacteria responsible for endophthalmitis, would also merit revisiting in future studies addressing the use of systemic antibiotics in the treatment of endophthalmitis [23–25].

Prophylactic Treatment

In order to reduce the risk of endophthalmitis following cataract surgeries, varied treatments have been attempted pre-, peri-, and postoperatively. Given the low incidence of endophthalmitis, an exceedingly large number of patients would be required for a treatment study to be powered to demonstrate a statistically significant effect. A comprehensive review of studies published between 1966 and 2000 found only perioperative povidone-iodine antisepsis to be effective at reducing endophthalmitis rates. Subconjunctival antibiotics, topical antibiotics, antibiotics inside irrigating solution, and lash trimming did not present conclusive evidence of further reducing this risk [26]. Despite this, many American surgeons prescribe antibiotic drops in the pre- and postoperative period in order to reduce the bacterial load and potential inoculum through the surgical wound. A retrospective study at the Moran Eye Center in Utah found topical ofloxacin postoperative use between 1997 and 2001 was more beneficial than ciprofloxacin. While the use of both antibiotics was equal during that period, 85% of endophthalmitis cases developed in patients under topical ciprofloxacin and 15% of them in patients under ofloxacin. The difference between antibiotics was significant ($p < 0.00026$) and may have been due to better penetration of topical ofloxacin into the anterior chamber and a lower kill time for this medication [11]. The replacement of these third-generation agents by newer fourth-generation fluoroquinolone antibiotics prompted a second retrospective study at the Moran Eye Center, from 1997 to 2007. The use of moxifloxacin and gatifloxacin eye drops from 2003 to 2007 was associated to a lower rate of endophthalmitis of 0.056% when compared with the 0.197% rate under ciprofloxacin and ofloxacin eye drop use from 1997 to 2003 ($p = 0.0011$). When looking at individual agents, the 0.015% rate with gatifloxacin was lower than the 0.1% rate with moxifloxacin ($p = 0.04$) [12]. With the increase in endophthalmitis isolate resistance to fluoroquinolones identified in New York and Florida over the past decades, the benefits of these topical antibiotics as prophylactic treatment may prove to be short-lived however [5, 6]. The use of intracameral cefuroxime at the end of cataract surgery reduced the occurrence of postoperative endophthalmitis by an odds ratio of 4.92 ($p = 0.001$) in a European prospective randomized study of 16,603 patients undergoing cataract surgery from 2003 to 2006. The study reported rates of culture-proven infectious endophthalmitis at 0.07% in the groups receiving intracameral cefuroxime prophylaxis compared with rates of 0.34% in the control groups not receiving intracameral cefuroxime and was stopped ahead of targeted enrolment once this benefit became apparent [27]. Concerns were raised however with the limited coverage against gram-negative bacteria and poor coverage against methicillin-resistant *Staphylococcus epidermidis* and *Staphylococcus aureus*. One consideration to keep in mind is the routine use of intracameral cefuroxime, moxifloxacin, or vancomycin as a prophylactic treatment could lead to increased resistance and sacrifice the benefits of these agents as first-line treatment.

Endophthalmitis Following Pars Plana Vitrectomy

Endophthalmitis is a rare complication of pars plana vitrectomy. Approximately 250,000 vitrectomies are performed yearly in the United States. During the first decade of this procedure (1970–1981) at the Massachusetts Eye and Ear Infirmary, 4 patients (0.137%) with endophthalmitis were reported among the 2917 closed vitrectomies performed. These vitrectomies were performed with 20 gauge or larger instrumentation. All four eyes were lost to this complication [28]. One decade later, from 1985 to 1993, the incidence of endophthalmitis remained low and was reported in 9 patients (0.074%) out of the 12,216 that underwent 20 G vitrectomy in 4 centers across the United States [29]. At Bascom Palmer, 6 cases of endophthalmitis (0.039%) presented following 15,326 pars plana vitrectomies performed between 1984 and 2003. Of these, five cases (83%) had positive vitreous culture growth. All patients resulted in a visual acuity worse than 20/200 and presented virulent bacteria such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Proteus mirabilis* [30].

20 G vitrectomy continued to predominate until 2004 when smaller gauge instrumentation became widely available. In the early stages of its adoption, 25 G vitrectomy presented with a higher rate of endophthalmitis than 20 G vitrectomy. In the retrospective analysis of 8601 consecutive vitrectomies performed at the Wills Eye Retina Service, from 2004 to 2006, the incidence of endophthalmitis

was 12 times higher with 25 G procedures (7 of 3103 cases, or 0.23%) than with 20 G procedures (1 of 5498 cases, or 0.018%). The same surgeons performed both procedure types. Indications for surgery in patients who developed endophthalmitis included vitreous hemorrhage and epiretinal membrane, and 50% of patients were diabetic. Incisions with 25 G instruments in this study were not beveled, and all the eyes that developed endophthalmitis were fluid filled at the end of surgery. 25 G vitrectomy was in its earlier phases of adoption at the Wills Eye retina service where approximately 100 cases were performed in 2004, increasing to nearly 2000 surgeries in 2006 [31]. The authors concluded that wound construction and adoption of a new technology likely contributed to the spike in endophthalmitis incidence in 25 G vitrectomy, a conclusion which has borne out with the publication of many subsequent series with lower endophthalmitis rates in 25 G vitrectomy. Another study, published soon after the aforementioned one, provided confirmatory data when it compared 25 G vitrectomy in its early years to the established 20 G procedure. This multicenter, international, retrospective study from 2005 to 2006 reported two cases of endophthalmitis (0.035%) out of 6375 that underwent 20 G surgery, whereas 11 cases (0.84%) out of 1307 25 G vitrectomies did the same. The difference in incidence of endophthalmitis between the different gauge procedures, performed by the same surgeons, in the same settings, was statistically significant ($p < 0.0001$). In the 25 G endophthalmitis eyes, 8 of 11 did not have beveled sclerotomies, and all eyes were fluid filled at the end of the case. Culture yield was 70% in the 25 G cases, and 85% of cultures were positive for coagulase-negative staphylococci. One of the two 20 G endophthalmitis cases grew both staphylococci and *Propionibacterium acnes* in culture. Visual outcomes were variable [32].

With time, however, 25 G vitrectomy displayed lower rates of endophthalmitis comparable to those of the established 20 G procedure. The same international multicenter group retrospectively compared rates of post-vitrectomy endophthalmitis in 2007–2008 among 20 G, 23 G, and 25 G instrumentations. The instrument gauge no longer had an effect on the incidence of postoperative endophthalmitis, which was 1 of 4403 (0.02%) for 20 G vitrectomy, 1 of 3362 (0.03%) for 23 G, and 1 of 789 (0.13%) for 25 G. Comparing these results to those of the same group of surgeons from 2005 to 2006, the incidence of endophthalmitis following 25 G vitrectomies has fallen from 0.84% to 0.13% ($p < 0.056$). The decreased rate of endophthalmitis following 25 gauge vitrectomy in the later series compared to the prior one may be related to increased experience with small-gauge vitrectomy, more complete vitrectomies, adopted use of angled sclerotomy incisions, and more careful closure of the wounds [33]. A similar evolution occurred with the adoption of clear corneal wounds for phacoemulsification. As both the 20 G and 25 G endophthalmitis patients from 2007 to 2008 were left with gas in the eye following vitrectomy surgery, it was unclear if vitreous tamponade had an effect on the rate of endophthalmitis. Table 6.4 lists the endophthalmitis incidence after 20 G and 25 G vitrectomy at different time periods. The incidence of post-vitrectomy endophthalmitis is shown in Table 6.4.

Table 6.4 Incidence of post-vitrectomy endophthalmitis

Author	Years	Gauge	Number of surgeries	Incidence (%)	Incidence
Ho 1984 [28]	1970–1981	20	2917	0.137	1/729
Cohen 1995 [29]	1985–1993	20	12216	0.074	1/1357
Eifrig 2004 [30]	1984–2003	20	15326	0.039	1/2554
Kunimoto 2007 [31]	2004–2006	20	5498	0.018	1/5498
		25	3103	0.230	1/443
Scott 2008 [32]	2005–2006	20	6375	0.031	1/3188
		25	1307	0.841	1/119
Scott 2011 [33]	2007–2008	20	4403	0.023	1/4403
		25	789	0.127	1/709
Garg 2016 [35]	2009–2012	25	14163	0.134	1/745

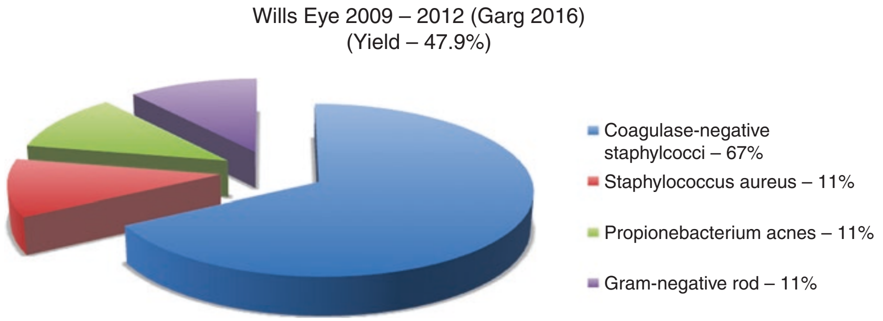

Fig. 6.1 Microbiological spectrum of post-vitrectomy endophthalmitis

In order to help decrease the rate of endophthalmitis following smaller-gauge vitrectomy, a Microsurgical Safety Task Force was formed in 2010 to provide guidelines based on surgical experience if not on scientific evidence. The following steps were believed to be crucial to prevent endophthalmitis [34]:

1. Povidone-iodine preparation
2. Eyelashes completely out of surgical field
3. Conjunctival displacement during entrance into the eye
4. Angled scleral incisions
5. Minimizing vitreous incarceration
6. Wound inspection and suture placement when necessary
7. Perioperative antibiotics

In another, more recent, retrospective study at the Wills Eye Retina Service, from 2009 to 2012, 19 patients (0.134%) presented with endophthalmitis following 14,146 vitrectomy surgeries using 25 G instruments. Culture yield was 47.4% (9 out of 19 patients). Microbial spectrum involved skin flora-associated bacteria, mostly coagulase-negative *Staphylococcus*, followed by *Staphylococcus aureus* and *Propionibacterium acnes* (Fig. 6.1) [35].

Figure 6.1 illustrates the microbiological spectrum of post-vitrectomy endophthalmitis in this study.

Treatment for post-vitrectomy endophthalmitis in the United States does not differ from that of post-cataract endophthalmitis and remains largely based on the findings of the EVS as discussed previously.

Endophthalmitis Following Intravitreal Injections

Intravitreal injections of air were first used in 1911 for the purpose of repairing retinal detachments. Later in the century, they were also adopted for administering intravitreal antibiotics, antivirals, and corticosteroids for endophthalmitis, retinitis, and retinal vascular diseases. The dawn of the twenty-first century saw their use expanded with anti-VEGF agents for the treatment of choroidal neovascularization and macular edema. In 2012, a total of 2.3 million intravitreal injections were performed in the United States. This number was projected to rise to six million in 2016 or twice the annual number of cataract surgeries in the United States.

Microbiologic Spectrum

Commensurate to the number of injections performed, there is a large body of literature on endophthalmitis following intravitreal injection. While most studies addressing endophthalmitis are retrospective in nature, prospective data from clinical trials are also available.

A small meta-analysis of 16 articles published between 2005 and 2009 on endophthalmitis isolates following intravitreal injections in the United States tallied 52 cases following 105,536 injections, resulting in a rate of 0.049%. The most common isolates were coagulase-negative staphylococci at 65.4% and *Streptococcus* species at 30.8%. Streptococci were remarkably more prevalent than following cataract surgery where they represent 8–12% of endophthalmitis isolates. Given that they represent up to 41% of the normal respiratory flora, contamination was presumed to occur not only from the patient's eyelid and conjunctival flora but also from their or the physician's aerosolized upper respiratory biome [36]. A larger meta-analysis of 43 publications between 2005 and 2012 on endophthalmitis after anti-VEGF injections tallied 197 cases following 350,535 injections, or a rate of 0.056%. Positive cultures were obtained in 54% of samples. The most common organisms isolated were coagulase-negative staphylococci in 58%, *Streptococcus* species in 30%, *Staphylococcus aureus* in 5.8%, and *Enterococcus faecalis* in 2.9%. Streptococci were more prevalent and coagulase-negative staphylococci less prevalent than in postsurgical endophthalmitis. This meta-analysis failed to substantiate a significant difference in visual outcomes between streptococci and staphylococci ($p = 0.22$). The endophthalmitis rate was higher in the prospective studies at 0.068% than in the retrospective studies at 0.053%, although this was not statistically significant ($p = 0.52$). The majority of visual outcome data associated with culture-positive endophthalmitis cases were presented in the retrospective series [37].

A retrospective study at Wills Eye Retina Service from 2009 to 2012 addressed the difference in endophthalmitis after intravitreal injections compared to that following vitrectomy surgery. The former group presented a rate of 0.038% (44 of 117,171 injections) and the latter a rate of 0.134% (19 of 14,146 vitrectomies). Culture yield was similar for both groups with 38.6% of injection cases and 47.4% of vitrectomy cases. The majority of culture-positive cases from postinjection eyes grew oral flora-associated organisms such *Streptococcus* species (35.3%), *Enterococcus* (11.8%), and *Lactobacillus* (5.9%). None of the post-vitrectomy positive culture eyes grew oral flora-associated bacteria. The microbial spectrum in the postinjection cases was significantly different from the post-vitrectomy cases where coagulase-negative staphylococci grew the most, followed by other skin flora-associated bacteria. There were significantly worse visual outcomes in patients with oral flora-caused endophthalmitis in a subgroup analysis of the postinjection patients [35].

A large multicenter retrospective study of 503,890 intravitreal injections performed between 2009 and 2013 reported 183 cases of endophthalmitis or a rate of 0.036%. No significant difference was noted between the three available anti-VEGF agents (bevacizumab, ranibizumab, and aflibercept) in the incidence of endophthalmitis, causative organisms, or final visual outcomes. Positive cultures were obtained in 38% of vitreous and anterior chamber samples. The visual outcome was better in patients with negative cultures than with positive cultures. Among those with positive cultures, visual outcomes were worse following *Streptococcus* infections than they were following coagulase-negative *Staphylococcus* infections. Coagulase-negative staphylococci were the most commonly isolated organisms (52.9%), followed by *Streptococcus* species (24.3%), *Staphylococcus aureus* (7.1%), and *Enterococcus faecalis* (7.1%) [38]. The incidence of post-intravitreal injection endophthalmitis is shown in Table 6.5.

Table 6.6 compares the microbiological profile of endophthalmitis following cataract surgery, following vitrectomy, and following intravitreal injections.

Table 6.5 Incidence of post-intravitreal injection endophthalmitis

Author	Years	Number of injections	Incidence (%)	Incidence
Mccannel 2011 [36]	2005–2009	105,536	0.049	1/2030
Fileta 2014 [37]	2005–2012	350,535	0.056	1/1779
Garg 2016 [35]	2009–2012	117,171	0.038	1/2663
Rayess 2016 [38]	2009–2013	503,890	0.036	1/2753

Table 6.6 Comparison of the microbiological profile of endophthalmitis following cataract surgery, vitrectomy, and intravitreal injections

Endophthalmitis	Study	CONS (%)	*S. aureus* (%)	Strep (%)	Entero (%)	*P. acnes* (%)	GNB (%)	Lacto (%)	*Haemophilus* (%)	*B. cereus* (%)
Post-cat	EVS [15]	70	9.9	9	2.2	–	5.9	–	–	–
	Medicare [16]	45	–	12	–	–	7	–	–	–
	BPEI [17]	68.4	6.8	8.2	–	–	9.6	–	–	–
Post-vit	WEI [35]	67	11	–	–	11	11	–	–	–
Post-intravit inj	Meta [36]	65.4	–	30.8	30.8	–	–	–	–	3.9
	Meta [37]	58	5.8	30	30	–	–	–	1.4	1.4
	WEI [35]	29.4	11.8	35.3	35.3	–	–	5.9	–	–
	Multicenter [38]	52.9	7.1	24.3	24.3	1.4	–	1.4	2.9	–

Post-cataract endophthalmitis: EVS, Endophthalmitis Vitrectomy Study [15]; Medicare 2003–2004 [16]; BPEI, Bascom Palmer Eye Institute 1996–2005 [17]
Post-vitrectomy endophthalmitis: Wills Eye Institute 2009–2012 [35]
Post-intravit injection endophthalmitis: meta-analyses 2005–2009 [36] and 2005–2012 [37]; WEI, Wills Eye Institute 2009–2012 [35]; Multicenter 2009–2013 [38]

Prophylactic Treatment

In the past, some surgeons have performed intravitreal injections in the operating room with similar sterile technique and conditions as incisional surgery, including ventilation systems, masks, sterile gloves and gowns, draping, speculum use, and povidone-iodine scrubs. The sheer volume of intravitreal injections in the United States has led other surgeons out of the operating room to a more efficient examination room setting, increasing access to these treatments while reducing burden on both patients and surgeons. In the office-based setting, povidone-iodine antisepsis, plus or minus the use of speculums and gloves, was carried over, leaving behind the surgical ventilation systems, sterile gloves, gowns, masks, and draping.

Povidone-iodine use remains a cornerstone of the eye preparation prior to intravitreal injections. A retrospective review of 28,786 injections performed during the DRCR network studies, between 2006 and 2015, reported 11 cases of endophthalmitis, or a rate of 0.038%. The use of topical antibiotics made no difference in the rate of endophthalmitis, with a rate of 0.05% reported in eyes receiving them and 0.02% in eyes without ($p = 0.17$). Despite study protocols specifying the exposure of the injection site for 30 s to povidone-iodine, 13 injections in 3 eyes of 2 patients were performed without this agent. One eye in each of those patients developed postinjection endophthalmitis, representing a 15% risk per injection or 100% risk per patient [39].

The use of eyelid speculum has been shown in one large retrospective series to be optional, as long as lid margins are safely kept away from the injection site and needle. A multicenter retrospective study of 27,736 injections performed from 2009 to 2010 in 16 practices associated with the Wills Eye Hospital reported 23 cases (0.083%) of endophthalmitis. Neither the use of a speculum or the hemisphere of injection location affected the risk of endophthalmitis [40]. In a retrospective study of 10,208 intravitreal injections performed at the Massachusetts Eye and Ear Infirmary in Boston, between 2007 and 2011, where 3 cases of endophthalmitis were diagnosed (0.029%), omission of a sterile drape, eyelid speculum, or postinjection antibiotics by several of the treating ophthalmologists did not result in an increased rate of endophthalmitis [41]. Another retrospective study of 10,614 intravitreal injections performed in the Wills Eye clinics, using a manual lid retraction technique instead of a metal speculum, reported 4 cases of endophthalmitis or a rate of 0.03%, similar to that reported in studies where speculums were used [42].

The role of topical antibiotic drops as prophylaxis against endophthalmitis has been debated over the past decade. A prospective study on 24 patients using a 5-day course of topical antibiotics following monthly intravitreal injections found that while the bacterial load was reduced by 41% in treated eyes, *Staphylococcus* populations shifted toward *S. epidermidis* with azithromycin use and toward *S. aureus* with fluoroquinolone use. Exposure to antibiotics increased bacterial resistance in the treated eyes, while no such effect was found in the fellow untreated eyes. Following exposure to the respective antibiotics, coagulase-negative staphylococcal resistance to azithromycin increased from 58.6% to 95% ($p < 0.01$), that to ofloxacin increased from 59.4% to 82% ($p = 0.02$), that to gatifloxacin increased from 19.7% to 42% ($p < 0.01$), and that to moxifloxacin increased from 25.6% to 65% ($p = 0.04$). While exposure to azithromycin resulted in an increased resistance to macrolides, it reduced that to fluoroquinolones. Lastly, all strains resistant to fourth-generation fluoroquinolones were also resistant to third-generation agents [43]. Contrary to the previous study, no difference in culture positivity rate or bacterial population was noted when comparing 40 eyes treated with 4-day topical antibiotics following monthly anti-VEGF injections to the fellow untreated eyes. In 11 patients treated with third- or fourth-generation fluoroquinolone drops, resistance to these antibiotics among their coagulase-negative conjunctival flora increased from 25% in the fellow untreated eyes to 87.5% in their treated eyes ($p = 0.04$). However, no change in resistance to trimethoprim was noted in the 29 patients treated with polymyxin-trimethoprim eye drops [44]. A retrospective study of 117,171 intravitreal injections performed at the Will Eye Hospital Retina Service between 2009 and 2012 revealed 44 (0.038%) cases diagnosed with endophthalmitis. Culture-positive results were obtained in 17 (39%) cases. There was no statistically significant difference in endophthalmitis incidence among the various intravitreal medications administered. The endophthalmitis rate was 0.032% (11 of 34,900) in patients who did not receive topical antibiotic prophylaxis and 0.049% (28 of 57,645) in patients who did. There was a concern that the use of topical antibiotics was associated with a trend toward increased incidence of both culture-negative endophthalmitis (odds ratio, 1.54; 95% confidence interval, 0.77–3.10) and culture-positive endophthalmitis (odds ratio, 1.51; 95% confidence interval, 0.47–4.83). However, using a simpler Z-score for two population proportions, there was a lack of significant difference between the two rates ($p = 0.22$). Culture yield was 36% whether patients received antibiotic drops or not. Visual acuity outcomes were significantly worse for culture-positive cases compared with culture-negative cases, regardless of antibiotic use [45]. In a Texas multicenter retrospective study, 30 cases of endophthalmitis (0.033%) were identified following 90,339 injections performed from 2011 to 2014. The use of prophylactic antibiotics once again appeared to increase the risk of endophthalmitis from 0.021% when avoided to 0.035% when used, although this was still not statistically significant ($p = 0.261$). The culture yield was 53% (16 of 30). The most common organisms isolated were coagulase-negative staphylococci in 62.5% of culture-positive patients, followed by *Streptococcus mitis* in 12.5% [46]. Contrary to prophylactic topical antibiotic use, repeated povidone-iodine 5% use did not promote emergence of antibiotic-resistant bacteria in conjunctival swab cultures performed on 13 patients undergoing monthly intravitreal injections [47].

Intravitreal injection guidelines were updated in 2014 to reflect the lack of evidence supporting the use of topical antibiotics to reduce the risk of endophthalmitis. The prophylactic measures recommended by this panel include [48]:

1. Surgical masks should be worn, or both the patient and the providers should minimize speaking during the injection preparation and procedure.
2. Povidone-iodine could be applied to the eyelashes and eyelid margins (optional).
3. Eyelids should be retracted away from the intended injection site for the duration of the procedure.

4. Povidone-iodine should be applied to the conjunctival surface, including the intended injection site, at least 30 s before injection. True povidone-iodine allergy is rare. Anaphylaxis has not been reported after ophthalmic application of povidone-iodine.
5. Postpone injection in presence of active external infection, including active blepharitis.

Interventional treatment for postinjection endophthalmitis is essentially the same as for post-cataract endophthalmitis, with the understanding that the microbial spectrum in postinjection endophthalmitis tends to be more virulent, leading to worse visual outcomes.

Endophthalmitis Following Trabeculectomy

Trabeculectomy has remained a mainstay of glaucoma filtering surgery over the past 30 years. In 2012 a total of 12,279 trabeculectomies was performed on Medicare-covered patients, with aqueous shunts (to an extraocular reservoir) increasing to 12,021 and mini-shunts to 5870 [49].

Trabeculectomy creates an aqueous bypass to the trabecular meshwork into a conjunctival bleb where it is absorbed. Bleb-related infections and inflammation could be divided into blebitis, when it is limited to the bleb with varying degrees of anterior chamber inflammation, and bleb-associated endophthalmitis, when this infection spreads posteriorly involving the vitreous gel.

Whereas most postoperative endophthalmitis arises in the days or weeks following penetrating surgery, bleb-associated endophthalmitis may also occur months or years later, when eye surface bacteria manage to cross the bleb conjunctiva because of its gradual thinning or outright defects. To study this rare complication adequately, a long post-trabeculectomy follow-up period is required, in addition to a large number of patients. An American insurance database review of 1461 patients who underwent trabeculectomies (or revisions) in 2007 and maintained insurance for the following 5 years found an incidence of 0.45% for bleb-associated endophthalmitis and 1.3% if other endophthalmitis diagnostic codes were included. The mean time of diagnosis of bleb-associated endophthalmitis after trabeculectomy was 45 months. This decreased to 33 months if the less specific diagnostic codes were included [50].

Microbiologic Spectrum of Bleb-Associated Endophthalmitis

While streptococci are more common in postinjection endophthalmitis than in post-cataract endophthalmitis, they are the most common organisms isolated in bleb-related endophthalmitis. A retrospective study of Wills Eye Hospital medical records from 1989 to 2001 identified 68 cases of bleb-associated endophthalmitis (excluding cases of blebitis). Delay between glaucoma surgery and endophthalmitis ranged between 3 days and 9 years with a mean of 19 months, and 59% of vitreous samples were culture positive. Among those, 36% grew *Streptococcus*, 22% grew *Staphylococcus*, and 8% *Enterococcus*. No difference in visual outcomes was noted between the two species, but patients who were culture-positive fared worse than culture-negative cases, despite having better initial vision. Eyes treated initially with tap-inject progressed toward worse outcomes than those treated with initial vitrectomy, despite no significant difference in presenting vision between the two groups [51]. Another retrospective medical records study, from Bascom Palmer, identified 86 eyes that presented bleb-related endophthalmitis from 1996 to 2009. Sixty-three percent of cultures were positive. Among them, the most common organisms were 40% *Streptococcus*, 17% coagulase-negative *Staphylococcus*, 15% *Moraxella*, and 11% *Enterococcus*. Gram-positive bacteria accounted for 72% of organisms. Culture-negative eyes had better visual outcomes than culture-positive eyes despite similar presenting vision. Eyes with *Streptococcus* unsurprisingly fared worse than those with other gram-positive bacteria and those with coagulase-negative *Staphylococcus*, despite being treated more aggressively with vitrectomy rather than tap-inject. Among gram-negative bacteria, *Serratia*- and *Pseudomonas*-positive eyes had worse presenting and final vision [52]. Comparing data from Bascom Palmer on bleb-associated endophthalmitis between 1969 and 2008, there were significantly fewer *Streptococcus*-related infections during the 1996–2008 period relative to the 1969–1984 period. Similar to the trend observed in post-cataract endophthalmitis, *Streptococcus* prevalence may have decreased with more prevalent exposure to vaccination against *S. pneumoniae* species [53]. Why are *Streptococcus* the most common pathogen genus in bleb-associated endophthalmitis? Are they more likely to cross a thin conjunctiva? Are patients in the bleb cohorts older than those in the cataract cohorts? The risk of endophthalmitis indeed increases with age. For every 10-year increase in age, individuals were 16% more likely to develop endophthalmitis ($p < 0.001$) [8]. Isolation of bacteria on conjunctival swab cultures also increases with age, with culture-positive rates of 16.4% below age 60 increasing to 51.5% above age 81 ($p < 0.001$) [54]. The long-term use of benzalkonium chloride-containing glaucoma eye drops appears to decrease the culture-positive rate of conjunctival swabs in glaucoma patients compared to healthy controls. Counterintuitively, the share of isolates containing *Streptococcus* or *Staphylococcus aureus* decreases with use of benzalkonium chloride, while that of coagulase-negative *Staphylococcus* and gram-negative bacteria increases [55].

As mentioned previously, the preponderance of *Streptococcus* carries a dismal visual prognosis for bleb-associated endophthalmitis. Additionally, bleb-associated endophthalmitis affects eyes with a visual reserve already diminished by glaucoma. And there may be features related to the nature of bleb-associated endophthalmitis itself, which result in worse visual outcome. One may speculate that these features may include a difference in the inoculum-loading dose of pathogenic bacteria or a muted immune response compared with immediate postoperative incisional surgery endophthalmitis, or other host factors, which are yet to be identified. Treatment of bleb-associated endophthalmitis, while still based on the maxims elaborated by the

Table 6.7 Microbiological spectrum of post-trabeculectomy endophthalmitis

	Wills Eye 1981–2001 Busbee 2004 [51] Yield, 59%	Bascom Palmer 1996–2011 Jacobs 2011 [52] Yield, 63%	Bascom Palmer 1996–2008 Leng 2011 [53] Yield, 83%
Coagulase-neg staph	18.0%	17.0%	18.0%
S. aureus	4.0%	–	12.0%
Streptococcus sp.	36.0%	39.6%	30.0%
Enterococcus sp.	–	–	–
P. acnes	2.0	–	1.5%
P. aeruginosa	6.0%	5.7%	6.0%
Moraxella sp.	5.0%	15.1%	10.0%
Haemophilus sp.	4.0%	–	4.5%
Enterobacteriaceae		11.3%	7.5%
S. marcescens	4.0%	–	4.5%
Corynebacterium sp.	–	–	3.0%
C. albicans	2.0%	–	–

EVS, often involves more aggressive use of vitrectomy and multiple tap-inject procedures given the higher prevalence of virulent microorganisms. The microbiological spectrum of post-trabeculectomy endophthalmitis is shown in Table 6.7.

Conclusion

Endophthalmitis is a rare complication associated with any penetrating intraocular procedure. With an incidence usually remaining below 0.1% or 1 in a 1000, it can become more frequent during the early adoption period of new techniques and technology that involves wound construction, as proved to be the case with clear corneal phacoemulsification (0.247% or 1 in 405) or small-gauge vitrectomy (0.84% or 1 in 119). These spikes prove to be short-lived, however, with endophthalmitis rates returning to their baseline within 5 years.

The study of such a rare complication requires large datasets or number of patients, particularly if differences in rates of endophthalmitis are sought with a new procedure or treatment. Prospective trials, while the most valuable, would require standardization across many centers. Few, if any, have been completed besides the EVS 30 years ago and the ESCRS European multicenter study of postoperative endophthalmitis 10 years ago. Most of the studies on endophthalmitis are retrospective in nature. They are institution based or insurance carrier based. The institution-based studies are limited by incomplete follow-up of patients, who may consult different institutions for their surgery and complications. Most studies on microbiological spectrum could not, for instance, assess the incidence of the disease, as they could not accurately estimate the number of surgeries performed on the population (the denominator) referred for complications. Conversely, when an institution reports a low incidence of endophthalmitis, one can question whether some patients have not sought care for endophthalmitis outside the care network where the initial surgery was performed. This fallible follow-up may partially explain why for postinjection endophthalmitis, rates reported by prospective clinical trials tended to be higher than those reported by retrospective studies [37].

Retrospective studies based on payors are limited by the coverage—for instance, Medicare in the United States covers mostly patients older than 65—and also by the lack of diagnostic code precision and clinical data available, such as visual acuity. These shortcomings of payor databases may be overcome by the development of "big data." The rise of electronic medical records has allowed the creation of massive databases and the mining of this expansive information stored in these records across institutions and payors. The American Academy of Ophthalmology initiated the Intelligent Research in Sight (IRIS) Registry in March 2014 as a longitudinal, clinical data registry to track patient outcomes over time and advance knowledge. The enrollment of IRIS has exceeded all expectations. As of November 2015, the registry included information on 61 million patient visits and 17.6 million unique patients. This registry allowed investigators to identify 400 cases of endophthalmitis within a year following cataract surgery performed in 2013 and 2014 on 511,182 patients and calculate an endophthalmitis rate of 0.06% per patient [10]. While the goal of such databases is to inform physicians of their outcomes, compare themselves with others, and improve their practice, the information can also be made available to payors who increasingly link physician reimbursement with performance. While linking financial incentives and disincentives to results collected from such "big data" registries may have a corrupting effect on the quality of the data in the long term, for the time being, they provide an important source of information on low-incidence diseases such as endophthalmitis.

References

1. Speaker MG, Milch FA, Shah MK, et al. Role of external bacterial flora in the pathogenesis of acute postoperative endophthalmitis. Ophthalmology. 1991;98:639–50.
2. Rodin FH. Bacteriologic study of human conjunctival flora*. Am J Ophthalmol. 1945;28:306–14.
3. Kim SJ, Toma HS, Midha NK, et al. Antibiotic resistance of conjunctiva and nasopharynx evaluation study: a prospective study of patients undergoing intravitreal injections. Ophthalmology. 2010;117:2372–8.
4. Chen X, Adelman RA. Microbial spectrum and resistance patterns in endophthalmitis: a 21-year (1988-2008) review in northeast United States. J Ocular Pharmacol Ther. 2012;28:329–34.
5. Schimel AM, Miller D, Flynn HW Jr. Endophthalmitis isolates and antibiotic susceptibilities: a 10-year review of culture-proven cases. Am J Ophthalmol. 2013;156:50–2.
6. Gentile RC, Shukla S, Shah M, et al. Microbiological spectrum and antibiotic sensitivity in endophthalmitis: a 25-year review. Ophthalmology. 2014;121:1634–42.
7. Khera M, Pathengay A, Jindal A, et al. Vancomycin-resistant Gram-positive bacterial endophthalmitis: epidemiology, treatment options, and outcomes. J Ophthalmic Inflam Inf. 2013;3:46. https://doi.org/10.1186/1869-5760-3-46.
8. West ES, Behrens A, McDonnell PJ, et al. The incidence of endophthalmitis after cataract surgery among the U.S. medicare population increased between 1994 and 2001. Ophthalmology. 2005;112:1388–94.

9. Du DT, Wagoner A, Barone SB, et al. Incidence of endophthalmitis after corneal transplant or cataract surgery in a medicare population. Ophthalmology. 2014;121:290–8.
10. Coleman AL. How big data informs Us about cataract surgery: the LXXII Edward Jackson memorial lecture. Am J Ophthalmol. 2015;160:1091–103.
11. Jensen MK, Fiscella RG, Crandall AS, et al. A retrospective study of endophthalmitis rates comparing quinolone antibiotics. Am J Ophthalmol. 2005;139:141–8.
12. Jensen MK, Fiscella RG, Moshirfar M, Mooney B. Third- and fourth-generation fluoroquinolones: retrospective comparison of endophthalmitis after cataract surgery performed over 10 years. J Cataract Refract Surg. 2008;34:1460–7.
13. Mistlberger A, Ruckhofer J, Raithel E, et al. Anterior chamber contamination during cataract surgery with intraocular lens implantation. J Cataract Refract Surg. 1997;23:1064–9.
14. Baillif S, Roure-Sobas C, Le-Duff F, Kodjikian L. Aqueous humor contamination during phacoemulsification in a university teaching hospital. J Fr Ophtalmol. 2012;35:153–6.
15. Han DP, Wisniewski SR, Wilson LA, et al. Spectrum and susceptibilities of microbiologic isolates in the Endophthalmitis Vitrectomy Study. Am J Ophthalmol. 1996;122:1–17.
16. Gower EW, Keay LJ, Stare DE, et al. Characteristics of endophthalmitis after cataract surgery in the United States medicare population. Ophthalmology. 2015;122:1625–32.
17. Lalwani GA, Flynn HW Jr, Scott IU, et al. Acute-onset endophthalmitis after clear corneal cataract surgery (1996–2005). Ophthalmology. 2008;115:473–6.
18. Teng YT, Teng MC, Kuo HK, et al. Isolates and antibiotic susceptibilities of endophthalmitis in post cataract surgery: a 12-year review of culture-proven cases. Int Ophthalmol. 2017;37:513–8. https://doi.org/10.1007/s10792-016-0288-2.
19. Doft BH. Treatment of post cataract extraction endophthalmitis: a summary of the results from the Endophthalmitis Vitrectomy Study. Arch Ophthalmol. 2008;126:554–6.
20. Iyer MN, Han DP, Yun HJ, et al. Subconjunctival antibiotics for acute post cataract extraction endophthalmitis—is it necessary? Am J Ophthalmol. 2004;137:1120–1.
21. Smiddy WE, Smiddy RJ, Ba'Arath B, et al. Subconjunctival antibiotics in the treatment of endophthalmitis managed without vitrectomy. Retina. 2005;25:751–8.
22. Kuhn F, Gini G. Ten years after … are findings of the Endophthalmitis Vitrectomy Study still relevant today? Graefes Arch Clin Exp Ophthalmol. 2005;243:1197–9.
23. Hariprasad SM, Shah GK, Mieler WF, et al. Vitreous and aqueous penetration of orally administered moxifloxacin in humans. Arch Ophthalmol. 2006;124:178–82.
24. Fuller JJ, Lott MN, Henson NM, et al. Vitreal penetration of oral and topical moxifloxacin in humans. Am J Ophthalmol. 2007;143:338–40.
25. Lott MN, Fuller JJ, Hancock HA, et al. Vitreal penetration of oral moxifloxacin in humans. Retina. 2008;28:473–6.
26. Ciulla TA, Starr MB, Masket S. Bacterial endophthalmitis prophylaxis for cataract surgery. Ophthalmology. 2002;109:13–24.
27. ESCRS Endophthalmitis Study Group. Prophylaxis of postoperative endophthalmitis following cataract surgery: results of the ESCRS multicenter study and identification of risk factors. J Cataract Refract Surg. 2007;33:978–88.
28. Ho PC, Tolentino FI. Bacterial endophthalmitis after closed vitrectomy. Arch Ophthalmol. 1984;102:207–10.
29. Cohen SM, Flynn HW, Murray TG, Smiddy WE. Endophthalmitis after pars plana vitrectomy. The Postvitrectomy Endophthalmitis Study Group. Ophthalmology. 1995;102:705–12.
30. Eifrig CWG, Scott IU, Flynn HW Jr, et al. Endophthalmitis after pars plana vitrectomy: incidence, causative organisms, and visual acuity outcomes. Am J Ophthalmol. 2004;138:799–802.
31. Kunimoto DY, Kaiser RS, Wills Eye Retina Service. Incidence of endophthalmitis after 20- and 25-gauge vitrectomy. Ophthalmology. 2007;114:2133–7.
32. Scott IU, Flynn HW, Dev S, et al. Endophthalmitis after 25-gauge and 20-gauge pars plana vitrectomy: incidence and outcomes. Retina. 2008;28:138–42.
33. Scott IU, Flynn HW, Acar N, et al. Incidence of endophthalmitis after 20-gauge vs 23-gauge vs 25-gauge pars plana vitrectomy. Graefes Arch Clin Exp Ophthalmol. 2011;249:377–80.

34. Kaiser RS, Prenner J, Scott IU, et al. The Microsurgical Safety Task Force: evolving guidelines for minimizing the risk of endophthalmitis associated with microincisional vitrectomy surgery. Retina. 2010;30:692–9.
35. Garg SJ, Dollin M, Storey P, et al. Microbial spectrum and outcomes of endophthalmitis after intravitreal injection versus pars plana vitrectomy. Retina. 2016;36:351–9.
36. Mccannel CA. Meta-analysis of endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents. Retina. 2011;31:654–61.
37. Fileta JB, Scott IU, Flynn HW. Meta-analysis of infectious endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents. Ophthalmic Surg Lasers Imaging Retina. 2014;45:143–9.
38. Rayess N, Rahimy E, Storey P, et al. Post injection endophthalmitis rates and characteristics following intravitreal bevacizumab, ranibizumab, and aflibercept. Am J Ophthalmol. 2016;165:88–93.
39. Bhavsar AR, Glassman AR, Stockdale CR, Jampol LM, Diabetic Retinopathy Clinical Research Network. Elimination of topical antibiotics for intravitreous injections and the importance of using povidone-iodine: update from the Diabetic Retinopathy Clinical Research Network. JAMA Ophthalmol. 2016;134:1181. https://doi.org/10.1001/jamaophthalmol.2016.2741.
40. Shah CP, Garg SJ, Vander JF, et al. Outcomes and risk factors associated with endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents. Ophthalmology. 2011;118:2028–34.
41. Englander M, Chen TC, Paschalis EI, et al. Intravitreal injections at the Massachusetts Eye and Ear Infirmary: analysis of treatment indications and post injection endophthalmitis rates. Br J Ophthalmol. 2013;97:460–5.
42. Fineman MS, Hsu J, Spirn MJ, Kaiser RS. Bimanual assisted eye lid retraction techniques for intravitreal injections. Retina. 2013;33:1968–70.
43. Kim SJ, Toma HS. Antimicrobial resistance and ophthalmic antibiotics: 1-year results of a longitudinal controlled study of patients undergoing intravitreal injections. Arch Ophthalmol. 2011;129:1180–8.
44. Milder E, Vander J, Shah C, Garg S. Changes in antibiotic resistance patterns of conjunctival flora due to repeated use of topical antibiotics after intravitreal injection. Ophthalmology. 2012;119:1420–4.
45. Storey P, Dollin M, Pitcher J, et al. The role of topical antibiotic prophylaxis to prevent endophthalmitis after intravitreal injection. Ophthalmology. 2014;121:283–9.
46. Li AL, Wykoff CC, Wang R, et al. Endophthalmitis after intravitreal injection: role of prophylactic topical ophthalmic antibiotics. Retina. 2016;36:1349–56.
47. Hsu J, Gerstenblith AT, Garg SJ, Vander JF. Conjunctival flora antibiotic resistance patterns after serial intravitreal injections without post injection topical antibiotics. Am J Ophthalmol. 2014;157:514–8.
48. Avery RL, Bakri SJ, Blumenkranz MS, et al. Intravitreal injection technique and monitoring. Retina. 2014;34:S1–S18.
49. Arora KS, Robin AL, Corcoran KJ, et al. Use of various glaucoma surgeries and procedures in medicare beneficiaries from 1994 to 2012. Ophthalmology. 2015;122:1615–24.
50. Vaziri K, Kishor K, Schwartz SG, et al. Incidence of bleb-associated endophthalmitis in the United States. Clin Ophthalmol. 2015;9:317–22.
51. Busbee BG, Recchia FM, Kaiser R, et al. Bleb-associated endophthalmitis: clinical characteristics and visual outcomes. Ophthalmology. 2004;111:1495–503. discussion 1503.
52. Jacobs DJ, Leng T, Flynn HW, et al. Delayed-onset bleb-associated endophthalmitis: presentation and outcome by culture result. Clin Ophthalmol. 2011;5:739–44.
53. Leng T, Miller D, Flynn HW, et al. Delayed-onset bleb-associated endophthalmitis (1996-2008): causative organisms and visual acuity outcomes. Retina. 2011;31:344–52.
54. Suto C, et al. Conjunctival sac bacterial flora isolated prior to cataract surgery. Infect Drug Resist. 2012;5:37–41.
55. Honda R, Toshida H, Suto C, et al. Effect of long-term treatment with eye drops for glaucoma on conjunctival bacterial flora. Infect Drug Resist. 2011;4:191–6.