The most dreaded complication following intravitreal injections (IVIs) is endophthalmitis. IVIs have become the most common procedure performed by retina specialists, yet interestingly, there is wide variability in the manner in which these are performed, both nationwide and worldwide. As a group, retina specialists lack uniform recommendations regarding best practices for IVIs.

Stephen J. Kim, MD, from Vanderbilt University in Nashville, Tenn., was the lead author on the landmark prospective study that first demonstrated that short courses of topical antibiotics around the time of intravitreal injections increase the rates of antimicrobial resistance. Since many patients receiving intravitreal injections are elderly and at risk for systemic infections such as pneumonia, antibiotic-resistant bacteria on the conjunctiva and nasopharynx present a major public health problem.

As physicians, we should strive to practice evidence-based medicine. In this edition of Practical Retina, Dr. Kim examines the available evidence regarding the use of sterile gloves, surgical masks, lid speculums, topical povidone-iodine, topical antibiotic drops, and the various methods of anesthesia that will certainly be enlightening to practicing retina specialists.

The expanding use of intravitreal injections (IVIs) represents one of the most dynamic areas of innovation during the past decade. Intravitreal drug delivery directly bypasses the eye’s natural defense barriers, minimizes systemic exposure, and provides intraocular drug levels not achievable via other routes of administration. Hence, the number of injections performed in the United States, as estimated from Medicare procedure codes, has risen from fewer than 3,000 per year in 1999 to more than 1 million in 2008, and that number may reach nearly 6 million in 2016 due to expanding indications.

The advent of novel drug therapies for the treatment of several prevalent retinal diseases has resulted in the exponential growth of IVIs. In 2004, only two agents were specifically approved by the U.S. Food and Drug Administration for IVI delivery: fomivirsen for cytomegalovirus retinitis (in association with acquired immune deficiency syndrome) and pegaptanib (Macugen; Bausch + Lomb, Bridgewater, NJ) for the treatment of neovascular age-related macular degeneration (AMD). At the end of 2014, there were six additional agents approved for IVI delivery for the treatment of one or more of the following diseases: AMD, diabetic macular edema (DME), macular edema following retinal vein occlusion (RVO), vit-
reomacular traction, and uveitis. In addition, bevacizumab (Avastin; Genentech, San Francisco, CA) is commonly used off-label for the treatment of AMD, RVO, and DME.

Although elevated eye pressure, inflammation, cataract formation, and retinal detachment can be serious complications after IVI, endophthalmitis remains its most-feared complication because of its potential for complete vision loss (Figure 1). The reported incidence of endophthalmitis after IVI ranges from 0.02% to 0.2% and may depend, in part, on the specific drug (anti-vascular endothelial growth factor [VEGF] vs. corticosteroid) and/or delivery device (dexamethasone [Ozurdex; Allergan, Irvine, CA] or fluocinolone acetonide [Iluvien; Alimera Sciences, Alpharetta, GA] implants) administered. Specifically, triamcinolone acetonide may be associated with higher rates of endophthalmitis after IVI due to its broad anti-inflammatory properties that may suppress host immune responses. In addition, its larger injection volume compared to anti-VEGF agents (0.1 mL vs. 0.05 mL) may result in greater vitreous reflux, which has been postulated to increase the risk of microbial migration into the vitreous cavity, possibly by means of a vitreous wick. Although earlier studies reported rates of endophthalmitis after IVI of triamcinolone approaching 1%, more contemporary studies reported rates similar to those seen with anti-VEGF agents. Nonetheless, it is prudent to be aware of the potentially higher risk of endophthalmitis after corticosteroid injections.

Recent large series reported endophthalmitis rates of 0.05% (1/2,000) or less after IVI, but the cumulative risk of endophthalmitis per treated patient is far greater since many conditions require long-term serial injections. In the landmark Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA), the cumulative risk of endophthalmitis approached nearly 1% after 2 years of treatment. Furthermore, several outbreaks of endophthalmitis following the use of compounded bevacizumab and triamcinolone have been reported in several cities across the United States, adding further safety concerns regarding this procedure. A search of PubMed in 2014 revealed more than 400 articles related to this topic that have been published during the last decade (and less than half this number in all the cumulative years before) reflecting this growing health concern.

MECHANISMS OF ENDOPHTHALMITIS AFTER INTRAVITREAL INJECTION

Potential mechanisms of infection (other than drug contamination) include direct inoculation of bacteria into the vitreous at the time of injection or subsequent entry through a wound track, potentially mediated by vitreous incarceration. Despite a disproportionate number of recent reports of endophthalmitis due to respiratory organisms (contamination via respiratory droplets), the most common source of bacteria is still believed to be the patient’s own conjunctiva or eyelids. The Endophthalmitis Vitrectomy Study (EVS) demonstrated that bacteria cultured from eyes with endophthalmitis were genetically identical to bacteria cultured from the patient’s own respective conjunctiva and/or eyelid, providing compelling evidence of this association. Under normal conditions, the vitreous cavity is avascular and largely devoid of immune cells. Shockley et al. reported that 51 colony-forming units (CFUs) of Staphylococcus aureus and 98 CFUs of Pseudomonas aeruginosa were required to cause endophthalmitis in aphakic rabbits.

Figure 1. Endophthalmitis 4 days after intravitreal injection due to coagulase-negative Staphylococcus. There is a small hypopyon (left) with dense cellular material in the anterior chamber (right).
This was in contrast with only 19 CFU of *S. aureus* and six CFU of *P. aeruginosa* required to cause endophthalmitis when injected into the vitreous. The vitreous cavity is, therefore, far more vulnerable to infection than the anterior chamber, which emphasizes the importance of preventing introduction of any size inoculum.

**POVIDONE-IODINE**

Povidone-iodine is the most common agent used to reduce ocular flora and is a potent antiseptic that provides rapid and broad-spectrum bactericidal properties. Povidone-iodine, or polyvinyl pyrrolidone-iodine, is an iodophor, meaning it carries iodine in a complexed form so free iodine concentration is low. The antimicrobial action of povidone-iodine can be attributed almost entirely to free molecular iodine, which reacts in electrophilic reactions with enzymes of the respiratory chain, as well as amino acids from the cell membrane proteins located in the cell wall. Because of its nonselective mechanism of action, no cases of resistance have been reported to date. In vitro studies demonstrate rapid bactericidal effects upon contact against common conjunctival bacterial flora, with sterilization times ranging from 30 seconds to 180 seconds. Despite the absence of direct evidence that povidone-iodine prevents or reduces endophthalmitis after IVI, its clinical benefit is extrapolated from a level II prospective trial that demonstrated a reduced rate of endophthalmitis after cataract surgery. Moreover, topical application of 5% povidone-iodine has been shown to significantly reduce positive bacteria cultures in eyes undergoing IVI. Equally as important, povidone-iodine is inexpensive, and adverse reactions are limited to localized allergic reaction or irritation. Consequently, use of povidone-iodine in the setting of IVI is nearly universal.

**OPHTHALMIC ANTIBIOTICS**

In contrast to povidone-iodine, antibiotic use is controversial and declining. Although prospective studies have consistently demonstrated that topically applied antibiotics administered 1 hour before significantly reduces conjunctival bacteria flora, a large observational study by the Diabetic Retinopathy Clinical Research (DRCR) Network did not observe a reduced rate of endophthalmitis in eyes treated with topical antibiotics. In addition, the additive benefit of antibiotics to 5% povidone-iodine is limited since povidone-iodine is extremely effective as a single agent in rapidly sterilizing the conjunctival surface. A prospective, randomized trial involving patients undergoing IVI demonstrated that preoperative use of topical antibiotics conferred no additional benefit compared to povidone-iodine alone with regard to the detection of positive bacterial cultures collected from the conjunctiva and injection needle.

Surveys performed in 2009 indicated that more than 80% of retina specialists in the U.S. used topical antibiotics before and/or after IVI. More recent surveys, however, have suggested a sharp decline in antibiotic use. A survey of members of the American Society of Retina Specialists (ASRS) in 2013 revealed that only around 20% of responding members in the U.S. prescribe topical antibiotics with IVI. This dra-
matic decline in the routine use of antibiotics during the last 4 years can be explained by their lack of perceived effectiveness in preventing endophthalmitis, added cost, and the increasing awareness of antibiotic resistance.

The Antibiotic Resistance of Conjunctiva and Nasopharynx Evaluation (ARCANE) study provided the first direct evidence that short-term and repeated exposure of ocular flora to topical antibiotics selects for antibiotic resistant strains of coagulase-negative Staphylococcus (CNS). More alarming was the fact that these resistant CNS also demonstrated cross-resistance to other commonly used classes of antibiotics. At least one study has shown that resistant S. epidermidis causes greater intraocular inflammation than susceptible ones, and repeated antibiotic use promotes strains of S. epidermidis that have alterations in their biofilm, which facilitate the avoidance of host defense mechanisms. Therefore, antibiotic-resistant strains of S. epidermidis may possess greater virulence.

**RESPIRATORY CONTAMINATION**

A meta-analysis of the U.S. literature from 2005 to 2009 reported an overall rate of endophthalmitis after IVI of approximately 0.05% (52 in 105,536 injections). Among positive culture results, 31% were due to streptococcal species. Streptococcus species, a common component of oral flora, may be dispersed by respiratory droplets by care providers and/or the patient and may subsequently contaminate the conjunctival surface or needle tip. Consequently, wearing a face mask or remaining silent during the critical portions of the procedure may significantly decrease risk of bacterial contamination by Streptococcus. A survey of members of the ASRS in 2012 revealed that approximately 13% of specialists use a mask during IVI; instead, the majority strictly avoid talking during the critical parts of the procedure. Measures to restrict talking by the patient and provider during the procedure can be readily implemented without added cost and are, therefore, reasonable; however, the benefits of wearing a mask remain unproven.

**COMPOUNDED BEVACIZUMAB AND TRIAMCINOLONE**

Several outbreaks of endophthalmitis have occurred in the U.S. presumably due to contaminated drug. In the Nashville VA medical center, four of 18 patients administered bevacizumab developed endophthalmitis due to S. viridans species within 48 to 72 hours after treatment. Bacterial cultures were negative for each of seven bevacizumab vials tested, but were positive in trace amounts for S. viridans in four of 15 unused syringes prepared by the pharmacy. In another outbreak, 14 eyes developed fungal endophthalmitis due to Bipolaris hawaiensis after being injected with compounded preservative-free triamcinolone from a single lot prepared by a single compounding pharmacy. A similar outbreak of fungal endophthalmitis in eight eyes was due to compounded combined bevacizumab and triamcinolone. As a result of these outbreaks and others, the ASRS collects essential quality assurance information from compounding pharmacies regarding their practices and accreditation status to assist members in selecting compounding pharmacies with a strong track record of safety and compliance. If same-day bilateral injections are to be performed, it is recommended that compounded drug from different lots be used.

**ASEPTIC TECHNIQUE**

Although use of a strict aseptic technique has been advocated to reduce infection risk, conclusive data supporting its effectiveness are lacking. Handling of the syringe and needle can be consistently performed in a manner to avoid contamination by the hand or finger-tip, which obviates the need for sterile gloves. Moreover, the lid margin and lashes can be safely avoided without a speculum in the majority of patients who comply with instruction. Excessive manipulation of the lid margin should also be avoided to limit expression of bacteria-laden secretions from the meibomian glands, which may in turn increase contamination of the ocular surface.

**ANESTHESIA**

Although there are many methods employed for anesthesia, there is no consensus on recommendations regarding an optimal method to reduce risk of infection. Lidocaine possesses broad inhibitory effects against gram-positive, gram-negative, mycobacteria, and fungal organisms, and similar to povidone-iodine, its nonselective mechanism of action makes it less susceptible to resistance. An in vitro study performed at the Vanderbilt Eye Institute, Nashville, Tenn., demonstrated that 2% lidocaine possesses rapid bactericidal effects against S. epidermidis, S. aureus, and S. viridans. This inherent antiseptic effect of lidocaine may be advantageous when performing IVIs.

Subconjunctival lidocaine is a commonly used and effective method of anesthesia (Figure 2). Recent surveys by the ASRS demonstrate that approximately 30% of its U.S. members routinely use subconjunctival lidocaine for anesthesia. A retrospective study reported no cases of endophthalmitis of 6,853 IVIs performed with subconjunctival lidocaine and eight cases of endophthalmitis of 8,189 IVIs performed with
other methods of anesthesia (P = .03). In addition to its inherent antiseptic properties, subconjunctival lidocaine may allow for optimal contact of povidone-iodine to the ocular surface in comparison to more viscous formulations of topical lidocaine. Subconjunctival lidocaine may also serve to wash away or dilute pathogens adhering to the injection needle as it passes through the fluid medium of the raised bleb, and by similar mechanisms, retard entry of pathogens from the ocular surface through a wound track.

CONCLUSIONS

IVIs are the fastest-growing procedure in ophthalmology, and if current trends continue, may become the most common cause of endophthalmitis seen in clinical practice. Given the severe consequences of endophthalmitis, its prevention should be a priority. In the face of rising health care costs, emphasis should also be placed on interventions with minimal risk of adverse reactions and low costs. In this regard, there is no evidence to support the additive benefit of topical antibiotics in conjunction with povidone-iodine. In contrast, restricting talking between the provider and patient may reduce the chance of respiratory contamination by Streptococcus species and can be readily implemented at no additional cost. Use of a lid speculum and gloves are unnecessary if the patient can comply with instruction and handling of the needle and syringe can be achieved in a manner as to avoid contact with the skin or lid lashes. Finally, drugs for IVI should be compounded by pharmacies with a strong history of adherence to high quality standards, compliance, and maintenance of accreditation status.

REFERENCES


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