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A Review of the Role of Intravitreal Corticosteroids as an Adjuvant to Antibiotics in Infectious Endophthalmitis

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Abstract

Infectious endophthalmitis is an important cause of vision loss worldwide. This entity most often occurs as a complication of intraocular surgery especially following cataract surgery or intravitreal injection. Endophthalmitis is regarded as a serious complication following ocular surgery and the final visual outcome is fundamentally contingent on timely recognition and intervention. Intravitreal and oral antibiotics in combination with pars plana vitrectomy or vitreous aspiration remain the mainstay in the management of endophthalmitis. However, significant inflammation may persist even after sterilization of the intraocular cavities with appropriate antibiotics resulting in failure of treatment. This forms the basis for the use of intravitreal corticosteroids as an adjuvant to antibiotics in the management of infectious endophthalmitis. In the index manuscript, we review the existing literature to determine the role of intravitreal corticosteroids as an adjuvant to antibiotics in treating infectious endophthalmitis, and discuss their beneficial effects and controversial concerns.

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DECLARATION OF INTEREST

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Keywords

Antibiotics; antifungals; corticosteroids; endophthalmitis; intravitreal steroids; intravitreal therapy; uveitis

Infectious endophthalmitis is a serious and vision-threatening purulent inflammatory condition of the intraocular fluids (i.e., the aqueous and/or vitreous humor). Exogenous endophthalmitis is the most common form of the disease that may occur following penetrating trauma, ocular surgery, or intraocular spread of an external eye infection. It is most often seen as a complication of intraocular surgery, especially after cataract surgery or intravitreal injection, and is among the most serious complications of eye surgery. Endogenous endophthalmitis occasionally occurs after hematogenous spread of organisms from a distant systemic focus of infection. Symptoms and signs of the condition may include pain, redness, and blurred vision, as well as hypopyon and hazy ocular media.

Intravitreal injection of antibiotics in combination with oral antibiotics remains the mainstay in the treatment of endophthalmitis. The use of pars plana vitrectomy as an adjuvant to therapy was proposed for eyes with vision of or less than light perception by the Endophthalmitis Vitrectomy Study (EVS),¹ and remains the standard of care today. All the patients received oral corticosteroids with or without vitrectomy as a standard treatment regimen in the EVS study. While the difference in final visual acuity or media clarity with or without the use of oral corticosteroids was not the objective of the EVS study, oral corticosteroids are variably used to treat endophthalmitis today. Oral corticosteroids are not without side-effects; occasionally, it could be difficult to initiate or continue the therapy. Considering the side-effects of systemic corticosteroids, it is worth exploring the role of intravitreal corticosteroids.

Intravitreal corticosteroids play a crucial role in the management of endophthalmitis, as besides the acute infiltration by bacteria, the ocular inflammatory response caused by bacterial infiltration induces significant damage to retinal tissues. Intravitreal corticosteroids work by blocking the inflammation by acting on various steps of the inflammatory pathway. Steroids interfere with inflammatory cell congregation, passage through vessel walls, prostaglandin synthesis, and release of superoxides. The use of intravitreal corticosteroids is considered in endophthalmitis because of the similar structure and nature of the blood-retinal barrier and the blood-brain barrier.² In the treatment of bacterial meningitis, corticosteroids as an adjunct to antibiotics are already of proven use in reducing morbidity and mortality, presumably by limiting the recruitment of leukocytes, by producing cytoprotectants, and by stabilizing the blood-brain barrier.³

Concerns about the use of intravitreal corticosteroids in endophthalmitis stem from the fact that neutrophil sequestration is the primary tissue response to infection, and is necessary for the elimination of infectious material. There are also concerns about secondary host toxicity and the effect of intravitreal steroids on the pharmacokinetics of intravitreal antibiotics. Finally, immunosuppression leaves the body vulnerable to fungal infections, although the length of therapy would not be enough to deeply immunosuppress the patient. To complicate matters, while approximately 90% of the cases of endophthalmitis are caused by bacteria,⁴ a

significant number of cases may be caused by fungi or mixed infections (Gram-negative bacilli and fungi),⁵ and it is a concern if the use of intravitreal corticosteroids can be extended to fungal or mixed bacterial and fungal endophthalmitis. On the other hand, viral endophthalmitis is less relevant in the review of intravitreal corticosteroids as an adjuvant to antibiotics as the causative organism would not be treated with antibiotics.

By and large, the final visual outcome is contingent on timely recognition and intervention. In light of the potential advantages of intravitreal corticosteroids as a supplementary intervention, the effects of intravitreal corticosteroids, particularly the aforementioned concerns enshrouding their use, deserve discussion. In this article, we analyze the role of intravitreal steroids as an adjuvant to antibiotics in treating infectious endophthalmitis, with specific stress on their controversial concerns.

METHODS

We performed a literature search on the PubMed database for English articles that evaluated the following effects of intravitreal corticosteroids: (1) on antibiotic concentrations; (2) early versus delayed delivery; (3) secondary host toxicity; (4) on bacteria of varying virulence; and (5) in fungal endophthalmitis. The search included randomized studies and observational studies comprised of prospective and retrospective cohort studies, case series and case-control studies. We also included preclinical studies. The search was conducted with the following terminology: (“endophthalmitis”[MeSH Terms] OR “endophthalmitis” [All Fields]) AND (“anti-bacterial agents”[Pharmacological Action] OR “anti-bacterial agents”[MeSH Terms] OR (“anti-bacterial”[All Fields] AND “agents”[All Fields]) OR “anti-bacterial agents”[All Fields] OR “antibiotic”[All Fields]) AND (“steroids”[MeSH Terms] OR “steroids”[All Fields] OR “steroid”[All Fields]) AND intravitreal[All Fields]. This yielded a total of 103 papers on PubMed, last accessed on 23 July 2016. References obtained from these articles were hand-searched to identify relevant literature.

For the purpose of this article, the intravitreal mode of administration of both antibiotics and corticosteroids is considered, due to its primary benefit of targeting the therapeutic agent in the eye while minimizing systemic absorption and complications. Both bacterial and fungal endophthalmitis are considered to cover the spectrum of pathogens and four corticosteroids: hydrocortisone, pre-dnisolone, dexamethasone, and triamcinolone acetonide are considered to encompass the range of corticosteroid management common in practice.

The Effect of Intravitreal Corticosteroids on Antibiotic Concentrations

Both preclinical and clinical trials have been performed to evaluate the effect of intravitreal corticosteroids on the vitreous levels of antibiotics, but the results of published studies are so far mixed, and inconclusive.

In a study of 42 rabbit eyes with pneumococcal endophthalmitis, intravitreal vancomycin concentration 72 h after treatment was significantly higher in eyes treated with intravitreal dexamethasone and vancomycin compared with those treated with vancomycin alone ($p = 0.03$).⁶ Interestingly, in another 42 uninfected rabbit eyes in the same study, intravitreal vancomycin concentration 72 h after injection was significantly lower in uninfected eyes

injected with intravitreal dexamethasone and vancomycin compared with those injected with vancomycin alone ($p < 0.001$). To determine the effect of infection on the elimination of intravitreal vancomycin, intravitreal vancomycin concentrations were compared between infected and uninfected eyes treated with vancomycin alone. Pharmacokinetic analysis showed that infection shortened the vitreous half-life of intravitreal vancomycin from 56 h to 48 h in the absence of intravitreal dexamethasone. In conclusion, in patients with infectious endophthalmitis, the elimination of an intravitreal antibiotic may be reduced when intraocular inflammation is minimized with intravitreal corticosteroid. This may enhance the efficacy of intravitreal antibiotic therapy in treating the infection.

Another preclinical study showed results that paralleled the aforementioned preclinical trial, where the antibiotic concentrations for infected eyes were greater than that for uninfected eyes.⁷ In fact, the infection itself decreased the rate of elimination of vancomycin, regardless of dexamethasone. However, the study acknowledged that it was not possible to establish its relative contribution to differences in vancomycin concentrations with any degree of certainty due to the marginal model fit, namely coefficients of determination and model selection criteria. Further *in vitro* experiments (using disk diffusion assay and *in vitro* effects on methicillin-resistant *Staphylococcus epidermidis* growth) performed in this study showed that dexamethasone did not decrease vancomycin activity *in vitro*. However, it is unclear if the same result can be replicated *in vivo* in rabbits or humans.

Yet another preclinical trial delivered mixed results. The trial appeared to suggest the type of antibiotic as a confounding variable. Vancomycin concentrations in eyes treated with vancomycin and dexamethasone were lower than that of eyes treated with vancomycin alone ($p < 0.05$).⁸ Gatifloxacin concentrations in eyes treated with gatifloxacin and dexamethasone were similar to that of eyes treated with gatifloxacin alone ($p > 0.05$). When both vancomycin and gatifloxacin were combined with dexamethasone, concentrations of vancomycin and gatifloxacin in the vitreous were again well above the minimum inhibitory concentration.

It is worthwhile to note that a checkerboard assay in the same trial showed that the addition of dexamethasone to either antibiotic did not result in reduced killing of *Bacillus cereus in vitro*, regardless of the concentration of the antibiotic tested. This questions the need to discuss the effect of corticosteroids on antibiotic concentrations, but certainly, *in vitro* results may be entirely different *in vivo*, hence these *in vitro* results should be followed up with *in vivo* studies.

One clinical trial on humans is the most promising study performed thus far. A randomized clinical trial showed that intravitreal dexamethasone did not lead to decreased vancomycin concentrations when given simultaneously in the treatment of patients with suspected bacterial endophthalmitis.⁹ In this clinical trial, randomized patients received an initial intravitreal injection of vancomycin and either dexamethasone or saline (placebo group). A second intravitreal injection of vancomycin was given after 3 or 4 days and was preceded by a vitreous biopsy for measurements of intravitreal vancomycin and dexamethasone concentrations. Measurements from the vitreous biopsy found that differences in vancomycin concentrations in patients who were given dexamethasone 3 or 4 days earlier (6.8–16.6 $\mu\text{g/mL}$, mean 11.4, median 12) compared with those in the placebo group (2.6–

10.8 µg/mL, mean 6.7, median 6.3) were not statistically significant ($p = 0.061$). However, it has to be taken into account that a p value of 0.061 is very close to being statistically significant, and statistical insignificance may be attributed to the fact that the study is underpowered ($n = 29$) to detect a difference in the first place.

In conclusion, corticosteroids may prolong the presence of antibiotics at the site of infection. However, the necessity to even consider the effects that corticosteroids have on antibiotics has been questioned in view of revealing clinical experience that an antimicrobial effect is obtained immediately with the current protocol of intravitreal antibiotics, and unlike the inflammatory process, the infectious component does not require a prolonged antimicrobial effect.⁵

The Effect of Early or Delayed Corticosteroids in Endophthalmitis

In 1984, a recommendation was made that anti-inflammatory therapy for endophthalmitis must be postponed for 12 h after antibiotic administration to allow efficient killing of the offending organism.¹⁰

However, in the 1900s, experimental rabbit models of *Enterococcus faecalis* endophthalmitis suggested no additional beneficial effects of early or delayed administration of intravitreal dexamethasone.¹¹ It is worthwhile to note that besides the lack of beneficial effects, the ultimate course of infection caused by cytolytic *Enterococcus faecalis* in rabbits treated with intravitreal antibiotics and dexamethasone did not differ from the course in untreated controls. In contrast, infection caused by specifically attenuated, non-cytolytic strains of *Enterococcus faecalis* responded well to intravitreal antibiotics augmented by dexamethasone. These results underscore the importance of bacterial toxins in infectious diseases of the eye and their contribution to treatment failures. These results further suggest that in cases of endophthalmitis caused by toxin producing bacteria, significant improvement in clinical outcome will require specific therapeutic targeting of the toxins involved with appropriate antibiotics.

In other experimental rabbit models of *Staphylococcus epidermidis* endophthalmitis, increasing inflammation 5–7 days after the initial bacterial inoculum suggested that dying bacterial end-products of infection prolong inflammation even in the absence of active bacterial replication.¹² Hence, control of the inflammatory component in the infectious process, preferably up to and over the period of inflammation, may contribute to a favorable outcome. On a side note, the best results were observed with treatment consisting of vitrectomy, antibiotics, and corticosteroids. More eyes treated with this combination resulted in clear media with visible fundus detail than eyes treated with intravitreal antibiotics alone. This reinforces the ancillary benefits of intravitreal corticosteroids, be they early or delayed.

Perhaps, the greatest limitation of intravitreal dexamethasone therapy is that it is eliminated from the vitreous cavity after 2 days. The half-life of intravitreal dexamethasone is 3.48 h.¹³ This denies prolonged beneficial effect, but also indicates fleeting exposure to the harmful effect of corticosteroids, if any. Since the maximum inflammatory damage to the eye in endophthalmitis occurs in the first few days, intravitreal dexamethasone is ideally most useful during this period.

Meanwhile, the roles of both early and delayed intravitreal corticosteroids seem robust in endophthalmitis as it seems that early corticosteroids with intravitreal antibiotics would reduce concurrent inflammation while delayed corticosteroids after initial cover with intravitreal antibiotics would prevent flare.

The Effect of Intravitreal Corticosteroids on Secondary Host Toxicity

The main concern of intravitreal corticosteroids is retinal toxicity. Corticosteroids induce a non-apoptotic, caspase-independent cell death related to paraptosis, mostly in the retinal pigmented epithelium cells and the Müller cells.¹³ A primary interference in the cell function, possibly through corticosteroid-induced alterations in retinal glutamate or glucose metabolism, is suggested.¹³ Other complications of intravitreal corticosteroids include rebound infective endophthalmitis¹⁴ and increase in intraocular pressure.¹⁵ Systemic toxicity has been rarely reported following intravitreal corticosteroid administration.

However, despite the aforementioned evidence of *in vitro* retinal toxicity in cell cultures, there is dissociation between laboratory and clinical data. There is a lack of preclinical or clinical evidence for *in vivo* retinal toxicity after intravitreal administration of corticosteroids. The discrepancy between *in vitro* and *in vivo* experiments may be explained by protective factors, such as the vitreous gel or the internal limiting membrane, that would prevent the direct contact of steroid crystals and retinal cells.¹⁶

There are no reports of retinal toxicity when acceptable doses of intravitreal corticosteroids are used. In rabbits, Kwak and D'Amico found that an intravitreal dose of 400 µg dexamethasone is non-toxic to the retina.¹³ However, doses >800 µg showed a dose-related retinal toxicity with increasing spectrum of disorganization in Müller and other retinal cells. The homogeneity of rabbits and humans is somewhat indeterminate but while the two species are not altogether homogenous, many preclinical studies in ophthalmology, including the aforementioned studies, continuously use rabbit models as their benchmark, and numerous studies have shown that rabbits and humans share similar inflammatory receptors.¹⁷ In cats, Oppelt et al. found similar results of non-toxicity with intravitreal injection of hydrocortisone.¹⁸ We propose that a targeted study on the Müller cells of humans could be done to follow up on these animal studies.

Moving on from retinal toxicity, another compelling finding is a clinical study that found two out of four patients with *Aspergillus flavus* endophthalmitis undergoing evisceration after use of intravitreal triamcinolone.¹¹ However, in the same study, between two other patients with *Aspergillus flavus* endophthalmitis that did not use intravitreal triamcinolone, one had favorable outcome while the other had phthisis bulbi. The small sample size, coupled with rather indistinct results of the group without triamcinolone being clearly superior to the group with triamcinolone, make this study rather inconclusive but the plausibility of evisceration definitely presses for greater research in this area.

However, since corticosteroids have a short half-life and are quickly eliminated, this may leave little space, and time, for toxicity. Furthermore, systemic toxicity is hardly a concern as the primary benefit of intravitreal injection is the targeting of the therapeutic agent in the eye while minimizing systemic absorption. Oppelt et al.'s cat models recapitulated that

while topical and intravenous hydrocortisone showed a decrease in outflow facility, intravitreal hydrocortisone showed no difference in aqueous humor formation rate or outflow facility compared with buffer-injected eyes.¹⁹

While secondary host toxicity of intravitreal corticosteroids is a scope for further research, we can cautiously assume at present that the intravitreal mode of administration of corticosteroids compared with its topical and intravenous counterparts is¹⁹ the safest, if not the best. There does not seem to be any major contraindications to the use of intravitreal corticosteroids as incidence of endophthalmitis after intravitreal corticosteroid remains <1%,²⁰ and the increase in intraocular pressure can be controlled with topical glaucoma medication (that can be successfully discontinued in patients without pre-existing glaucoma).²¹ However, we propose that patients be monitored carefully and appropriately, and although intravitreal corticosteroids are not without complications, the majority of these complications can be reasonably managed.

The Effect of Intravitreal Corticosteroids on Bacteria of Varying Virulence

Both preclinical and clinical findings are fairly congruous regarding the effects of corticosteroids with bacteria of varying virulence. Clinical data supports that eyes infected with less virulent organisms (such as *Staphylococcus epidermidis* or *Propionibacterium acnes*) have better outcomes when intravitreal triamcinolone is added as an adjuvant to antibiotics, but also suggests equally good outcomes with more virulent streptococcal strains.²²

However, in preclinical rabbit models, the ultimate course of infection caused by cytolytic strains of *Enterococcus faecalis* did not differ between those that received triamcinolone and those that did not receive triamcinolone.¹¹ In contrast, rabbits infected with specifically attenuated, non-cytolytic strains responded well to the antibiotics augmented by anti-inflammatory therapy. These results underscore the importance of bacterial toxins in infectious diseases of the eye and suggest that in cases of endophthalmitis caused by toxin-producing bacteria, significant improvement in the clinical outcome will require specific therapeutic targeting of the toxins involved. While corticosteroids are effective, their effectiveness hinges on an effective antibiotic. This reiterates the importance of corticosteroids as an adjuvant to antibiotics.

A literature review by Bui and Carvounis²³ probably offers most details in the assessment of bacteria of varying virulence. This article reviewed *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Bacillus cereus*, *Pseudomonas aeruginosa*, and other endophthalmitis models, with mixed conclusions. In *S. epidermidis* models of rabbits, intravitreal dexamethasone decreased the intraocular inflammation (in terms of vitreous culture, clinical examination of media clarity, and histopathology) in three studies after 5 days, 5 days, and 7 days, respectively.^{12,24,25} A fourth study showed no beneficial effect but the histopathologic examination in this study was also performed at an earlier time (2 days after intravitreal injection of drugs) when the beneficial effect of the corticosteroid may not have yet been fully realized.²⁶ In *S. aureus* models of rabbits, intravitreal dexamethasone also decreased intraocular inflammation in two studies^{27,28} but one study with a much higher concentration of microorganisms found a harmful effect cautioning against the use of

corticosteroids in severe endophthalmitis.²⁹ *Bacillus cereus* models of rabbits found improvement in clinical grading of the anterior segments and histopathologic grading of the posterior segments in two studies,^{19,30} but in sterile endophthalmitis induced by crude *Bacillus* exotoxins, one study found no improvement.³¹ This finding is somewhat surprising considering that ocular tissue necrosis in the setting of endophthalmitis is likely a direct effect of bacterial virulence factors in addition to host inflammatory response. *Pseudomonas aeruginosa* models of rabbits found that the timing of corticosteroid administration may be critical. A study by Graham and Peyman showed that dexamethasone significantly decreased inflammation but the beneficial effect was lost when dexamethasone was delayed more than 5 h following the establishment of endophthalmitis, and in fact, after 10 h, the inflammation was so intense that the retina was completely necrotic, even though the infection was controlled.³²

The Effect of Intravitreal Corticosteroids in Fungal Endophthalmitis

The role of intravitreal corticosteroids in fungal endophthalmitis is controversial because of the detrimental effects of corticosteroids, such as their *in vitro* properties of impairment of the efficacy of antifungal drugs, as well as interference with the immunogenic response that potentially results in contrary fungal proliferation.

Contrary to popular belief, Coats and Peyman found no evidence that the addition of intravitreal dexamethasone impaired antifungal activity or enhanced fungal proliferation in a rabbit model of exogenous *Candida albicans* endophthalmitis.³³ They found that on the fourth day, eyes treated with only amphotericin B or amphotericin B and dexamethasone had clearer vitreous than controls, and in fact, on the seventh day, eyes receiving amphotericin B and amethasone had significantly clearer vitreous in comparison to eyes receiving only amphotericin B ($p = 0.0017$). Although a small number of rabbits were used ($n = 8$ and $n = 8$), there were controls for comparison ($n = 4$). However, the observation period could be extended to monitor for steady improvement or deterioration after initial improvement.

Subsequently, a retrospective study by Majji et al. suggested that intravitreal dexamethasone promotes faster recovery of inflammation in fungal endophthalmitis.³⁴ However, the good recovery of inflammation was irrespective of fungal growth; hence, the sensitivity of the fungi to antifungals, dose and timing of steroids, and institution of effective anti-fungals prior to the use of steroids are essential factors that need to be examined further in a prospective manner. In terms of visual outcome, a greater percentage of patients in the group with dexamethasone showed a favorable visual outcome than the group without dexamethasone. The patients were followed-up to at least 2 months and some patients were followed-up to 24 months. However, the sample sizes are small ($n = 13$ and $n = 7$) and the difference was not statistically significant ($p = 0.64$). Strikingly, two out of four patients with *Aspergillus flavus* endophthalmitis in the group with dexamethasone required evisceration after 2 months. This is a significant number of patients because of the very small sample size, and because the risk of evisceration itself is grave (and potentially avoidable in the absence of adjunctive steroids).

In several *in vitro* studies, Grasso and colleagues showed suppression of phagocytosis of yeasts by dexamethasone-treated macrophages.^{35–38} Diamond showed similar effects of

dexamethasone on human monocytes *in vitro* and also showed facilitation of fungal proliferation by dexamethasone.³⁹ However, the purpose of this article is to analyze the role of corticosteroids as an adjuvant and not as a mainstay, and in these studies, no antifungals were used simultaneously to test whether dexamethasone facilitates fungal proliferation even in the presence of effective antifungals.

In summary, our review suggests that additional experimental and human studies of larger sample size and longer observation period need to be done to draw definitive conclusions about the effect of intravitreal corticosteroids in fungal endophthalmitis.

The Effect of Different Corticosteroids in Endophthalmitis

The studies and trials discussed in this review thus far mostly evaluated intravitreal dexamethasone. The roles of hydrocortisone, prednisolone, and triamcinolone acetate are less understood compared with dexamethasone in the management of endophthalmitis.

Intravitreal triamcinolone has been more extensively evaluated in the management of endophthalmitis. Two preclinical studies investigated the effect of intravitreal triamcinolone in rabbit eyes with *Staphylococcal epidermidis* endophthalmitis.^{40,41} Intravitreal triamcinolone in the absence of antibiotics resulted in higher culture-positive rate and higher degree of inflammation, suggesting an impaired ocular immune response and greater susceptibility to infection. However, in the presence of antibiotics, triamcinolone appeared to suppress the ocular inflammatory response without impairing the therapeutic effect. In one of the studies, a reduction in histologic inflammation of vitreous aspiration was observed in all the rabbit eyes that were treated with triamcinolone.¹²

Although prednisolone is often used as an adjuvant to antibiotics in the treatment of bacterial, fungal,⁴² and tuberculous endophthalmitis,²⁰ prednisolone was administered topically, orally, or systemically in these studies. The only study reporting the use of intravitreal prednisolone is one on diabetic macular edema,²¹ where statistically significant visual improvement was observed after intravitreal prednisolone. More definitive studies on the role of intravitreal prednisolone in endophthalmitis are lacking.

Thus far, no studies have employed hydrocortisone in the treatment of endophthalmitis, either intravitreally or by other modes of administration. This is hardly unusual in clinical practice too, conceivably due to its mild nature⁴³ that may render it minimally effective in the hostile environment of endophthalmitis.

Besides intravitreal dexamethasone, intravitreal triamcinolone may be optimal for endophthalmitis treatment because it delivers a high initial dose with slow, prolonged self-tapering as needed to treat severe inflammatory conditions in the eye.⁵ The low intracular solubility of triamcinolone could be the reason for the sustained effect.⁴⁴ In this article, we analyzed the role of intravitreal corticosteroids as an adjuvant to antibiotics in treating infectious endophthalmitis. Our review of the literature showed conflicting results on the use of intravitreal corticosteroids.

In conclusion, the role and effect of intravitreal corticosteroids as an adjuvant to antibiotics in infectious endophthalmitis can be drawn theoretically, experimentally and clinically.

Many organisms produce potent toxins that contribute to virulence of intraocular infection. The treatment of infections with these organisms is problematic because even after the intraocular spaces are sterilized with appropriate antibiotics, a significant amount of bacterial debris and potentially toxic products linger to account for the treatment failure. Hence, the most advantageous approach to the treatment of endophthalmitis should be simultaneously directed to control both infection and inflammation, thus allowing sufficient anti-inflammatory response to clear bacteria and bacterial debris while minimizing secondary host toxicity.

The only randomized trial in our review suggests that there is some benefit in the use of intravitreal corticosteroids; however, there is enough question that there is likely not sufficient support in the current literature to recommend intravitreal corticosteroids as a standard of care. Another comparative trial, which was not included in our review as its main measure of outcome was improvement in visual acuity between cases of infectious endophthalmitis that did or did not receive intravitreal dexamethasone, provides no support for intravitreal corticosteroids in view of a significantly reduced likelihood of obtaining a three-line improvement in visual acuity in patients who received intravitreal dexamethasone.⁴⁵ In the EVS study, all the patients received both intravitreal antibiotics and oral and topical steroids, and no patient received intravitreal steroids.

However, more preclinical trials have been done. They appear to suggest that intravitreal corticosteroids do not affect, and even prolong the presence of antibiotics at the site of infection. The roles of both early and delayed intravitreal corticosteroids seem unequivocal in infectious endophthalmitis in reducing concurrent inflammation and preventing flare, respectively. The role of intravitreal corticosteroids in fungal endophthalmitis is less understood due to the lack of adequate experimental and human studies in terms of sample size and observation period. Lastly, although intravitreal dexamethasone is the steroid most examined and used, intravitreal triamcinolone acetonide appears suitable in infectious endophthalmitis.

On the basis of our review of the literature, we believe that the burden of proof is on those who advocate the use of intravitreal corticosteroids. Any definitive recommendations to use intravitreal corticosteroids as an adjuvant to antibiotics in infectious endophthalmitis must await the results of additional experimental and human studies, including larger, well-designed randomized control trials.

In the future, we also propose clinical interest targeted studies on post-traumatic endophthalmitis, post-therapeutic endophthalmitis, and endophthalmitis associated with corneal infection.

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