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Clinical Practice Update: Management of Infectious Endophthalmitis After Intravitreal Anti-VEGF Injection

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Abstract

Although infectious endophthalmitis after intravitreal antivascular endothelial growth factor injections is rare, it is the most feared and potentially devastating complication of this procedure. There is no high-level evidence to provide definitive guidance on the management of endophthalmitis occurring after intravitreal injection (IVI). This clinical practice update reviews the published literature regarding post-IVI endophthalmitis and highlights areas in which further research is needed to better guide its management.

Keywords

endophthalmitis, intravitreal injection, vascular endothelial growth factor

Intravitreal injection (IVI) is the most common vitreoretinal procedure, and its use continues to rise as the availability of and indications for intravitreal therapeutics increase. US Medicare Part B data show that between 2000 and 2014, there was an 89 563% increase in IVIs.[1] Antivascular endothelial growth factor (anti-VEGF) agents comprise the vast majority of IVIs. The incidence of post-IVI endophthalmitis has been reported to range from 0.028% to 0.056% per injection in large reviews and meta-analyses,[2–4] although some series quote lower rates.

Although intravitreal antibiotics are well established as the cornerstone of treatment for infectious endophthalmitis in general, much of the management of post-IVI endophthalmitis is based on literature reporting endophthalmitis that occurred after cataract surgery, which differs in several respects. There have been no randomized controlled studies of the treatment for post-IVI endophthalmitis, and the results of the seminal Endophthalmitis Vitrectomy Study (EVS),[5] on which many treatment decisions for endophthalmitis after cataract surgery are still based, were published 27 years ago. The extent to which the EVS results can be extrapolated to the management of post-IVI endophthalmitis remains unclear, and it must be kept in mind that the majority of patients screened for the EVS were ineligible for randomization into the study.

This paper summarizes the published literature relevant to post-IVI endophthalmitis and suggests areas for further research specific to this complication.

Distinguishing Infectious From Noninfectious Endophthalmitis

Endophthalmitis after intravitreal anti-VEGF injection can be infectious or noninfectious in etiology, and distinguishing between the 2 forms can be clinically challenging. Noninfectious endophthalmitis might present with less pain, visual acuity disturbance, conjunctival injection, corneal edema, anterior chamber cells/flare/fibrin, and vitreous cells, whereas infectious endophthalmitis is more likely to be associated with more pain, greater loss of vision, and hypopyon.[6] Unfortunately, none of these characteristics can be used to definitively distinguish between the 2 entities.

Given the potential for severe irreversible loss of vision if treatment for infectious endophthalmitis is delayed, a low threshold for performing a vitreous tap and injection (tap/inject) of intravitreal antibiotics is prudent. Although less inflammation might point toward a noninfectious etiology, it might also indicate a pathogen of lower virulence or a lower bacterial load.

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The distinction between the 2 entities is further blurred when one considers that a large proportion of cases of presumed infectious endophthalmitis are culture negative.

True sterile endophthalmitis is an inflammatory response to the agent, vehicle, or other contaminants, and cases often occur in clusters. Noninfectious endophthalmitis has been reported after administration of bevacizumab,[7–10] aflibercept,[11,12] and ranibizumab. Although some authors have suggested that sterile inflammation is less common with ranibizumab,[13] numerous studies found no difference in the incidence of infectious endophthalmitis between the 3 agents.[6,14,15] There has been significant concern regarding the risk for intraocular inflammation and occlusive retinal vasculitis associated with vision loss after treatment with brolucizumab.[16,17] Sterile endophthalmitis has also been associated with the use of biosimilars.[18]

The culture-positive rate in various reports of postinjection endophthalmitis ranges from 30% to 60%.[3,19–23] Even with the use of additional techniques, such as polymerase chain reaction (PCR), there is a significant proportion of culture-negative cases, as discussed below. It is also possible that some culture-negative cases might be the result of nonbacterial pathogens.[24]

Initial Management

Suspected infectious endophthalmitis is an ophthalmic emergency. Early diagnosis and prompt intravitreal antibiotic administration, with or without pars plana vitrectomy (PPV), are essential. Although there is a relative paucity of data specific to post-IVI endophthalmitis, it is likely that most clinicians treat it in a fashion similar to the treatment of endophthalmitis after cataract surgery.[25] The most common initial treatment is a tap/inject of intravitreal antibiotics.[20,26,27] Considerations in initial management include sampling and culture of specimens, the choice of intravitreal and possibly systemic antibiotics, the role of early vitrectomy, and the use of corticosteroids (intravitreal or oral).

Sampling and Culture

The highest microbiological yield is obtained with a vitreous sample.[5,28,29] This can be performed with a needle (tap) or a vitrectomy cutter (vitreous biopsy). In the case of a dry vitreous tap, an aqueous sample can be obtained. This serves the dual purpose of (1) creating sufficient space to accommodate the volume of the intravitreal antibiotic injections and (2) providing fluid for culture (albeit with a lower yield than vitreous sampling).[5,28,29] Alternatively, a vitreous biopsy can be performed. Some clinicians obtain both vitreous and aqueous samples, as required by the EVS protocol.[5] EVS data show no significant difference in microbiological yield between a vitreous tap and a vitreous biopsy with a vitreous cutter.[30] The culture-positive rate in various reports of postinjection endophthalmitis was lower than that in the EVS, ranging from 30% to 60%.[3,19–22]

Xu et al[26] reported the results of a survey of practice patterns of endophthalmitis treatment of members of the American Society of Retina Specialists (ASRS). Most respondents (489 of 652 [75%]) routinely performed a vitreous tap, 187 (29%) routinely performed an anterior chamber (AC) tap (with or without vitreous tap), and 155 (24%) routinely performed an AC tap if the vitreous tap yielded no sample. Aqueous taps have a significantly lower rate of microbiological yield,[28,29,31] and it is even lower in post-IVI endophthalmitis than in postsurgical endophthalmitis.[3,19–22]

As with culture results, Gram stains were positive far more often from vitreous samples (43.1%) than from AC samples (18.9%) in the EVS.[28] As expected, a positive Gram stain was associated with a significantly higher incidence of a positive culture.[28] The probability of a positive vitreous culture from a vitreous sample with a positive Gram stain was 95%. Bhikoo et al[29] found that vitritis severe enough to obscure the fundus red reflex was strongly associated with a positive microbial culture result. The use of blood culture bottles can increase microbial identification rates compared with conventional plate cultures by amplifying the number of organisms before subculture on agar plates.[32–34] Although alternatives to conventional laboratory diagnosis, such as PCR and other molecular techniques, might increase the diagnostic yield, they have limitations, including cost and an increase in false positive results.[35]

Although specimens for culture are obtained in most cases to help differentiate infectious etiology from noninfectious etiology, allowing more targeted antimicrobial therapy and evaluation of local patterns of antimicrobial resistance, in practice culture results infrequently alter management.[25] Patel et al[22] looked specifically at changes in management based on vitreous culture results in post anti-VEGF IVI endophthalmitis. They found that changes in management were initiated based on declining vision and/or clinical worsening in both culture-positive cases and culture-negative cases; however, no additional interventions were initiated based on positive culture results alone. Patel et al[36] further suggest that it might be acceptable to perform an immediate injection of intravitreal antibiotics without a vitreous tap when microbiology facilities are not readily available.

Spectrum of Bacterial Isolates and Selection of Antibiotics

Similar to the EVS and other studies of postoperative endophthalmitis, the most common isolates in post IVI endophthalmitis are coagulase-negative staphylococci, ranging from 34% to 65% of positive culture results.[2,3,19,37] A major difference, however, is the frequency of streptococcal isolates, which are the second most common in several series and meta-analyses of post-IVI infections, with numbers ranging from 24% to 31% compared with 9% in the EVS.[2,3,19,21,37]

Endophthalmitis from oral flora, including *Streptococcus* species and *Enterococcus*, typically has a worse visual prognosis than endophthalmitis from most other organisms.[37–40]

Oral and nasal pathogens are more prevalent in post-IVI endophthalmitis; therefore, measures such as mask wearing and a "no-talking" policy have been suggested. There is some evidence that this might be having an impact. In 2 case series from the same Australian institution, an initial study (2007–2010) reported a 25% incidence of *Streptococcus* species in 53 post-IVI cases.[41] In 2012, national guidelines for performing intravitreal therapy were updated to include recommendations that a mask be worn by the injecting physician and the patient be instructed not to talk during the procedure.[42] A subsequent study (2012–2017) reported a 3.6% incidence of *Streptococcus* species in 141 post-IVI cases.[43] In a retrospective series from 2013 to 2019,[44] the Post-Injection Endophthalmitis (PIE) Study Group found no statistically significant difference in endophthalmitis rates among physicians who wore a face mask and those who did not wear a face mask but observed a no-talking policy. In that study, 16 cases of infectious endophthalmitis were attributable to oral flora in the no-talking group; however, there were no cases in the group wearing a face mask.

Hebert et al[45] compared the rate of endophthalmitis before and during the COVID-19 pandemic when routine patient masking was implemented in Canada. There was universal use of physician masks during both time periods. Despite concerns that patients wearing a mask could direct oral flora toward the eyes during intravitreal injection, they found no significant difference in the rate of endophthalmitis between the 2 time periods. The PIE group[44] also explored the effect of increased use of face masks during the COVID pandemic. Although they found no significant reduction in the overall rate of endophthalmitis with the universal wearing of masks, there were significantly fewer cases of culture-positive endophthalmitis in the universal-face-mask group than in no-face-mask group.[46]

The intravitreal antibiotics used in the EVS were vancomycin 1 mg/0.1 mL and amikacin 0.4 mg/0.1 mL. Vancomycin remains the agent of choice for gram-positive coverage.[47] There have been no reports of vancomycin-resistant organisms in post-IVI endophthalmitis, although there have been a few cases in endophthalmitis of other etiologies.[22] Although hemorrhagic occlusive retinal vasculitis has been reported after IVI of vancomycin,[48,49] the rarity of this complication and the absence of a similarly efficacious alternative in the context of a blinding condition such as endophthalmitis justify its continued use. Since the EVS, ceftazidime 2.25 mg/0.1 mL has largely replaced amikacin for gram-negative coverage. The 2 drugs have similar gram-negative coverage[47]; however, amikacin has been well documented to cause macular toxicity at doses as low as 0.2 mg/0.1 mL.[50] Although historically amikacin has been used in patients with a penicillin or cephalosporin allergy, Meyer et al[51] found that 53 such patients were administered intravitreal ceftazidime without adverse reactions.

To date, systemic antibiotics have been regarded as unhelpful in the management of presumed infectious endophthalmitis. The EVS found no additional benefit from the use of intravenous (IV) antibiotics. There are sound arguments against the use of systemic antibiotics, including cost, potentially severe adverse events, and that most patients requiring intravitreal therapy are elderly and have multiple comorbidities and concomitant medications. Newer agents that were not available during the EVS, including fourth-generation orally administered fluoroquinolones such as moxifloxacin, provide broad-spectrum gram-positive and gram-negative coverage, have good activity against atypical organisms, and achieve therapeutic aqueous and vitreous concentrations[52]; however, a 40% to 60% resistance to fluoroquinolones among coagulase-negative *Staphylococcus* endophthalmitis isolates has been reported.[53] Furthermore, although in general fluoroquinolones are well tolerated, there might be significant side effects from systemic administration.[54] Therapeutic vitreous concentrations have also been achieved with IV meropenem and oral linezolid.[55] Although empiric treatment with topical antibiotics is common practice, a recent retrospective case-control study found no benefit.[56]

In the absence of literature to support the use of systemic antibiotics in post-IVI (or post-cataract surgery) endophthalmitis, a future randomized controlled study should explore the use of systemic antibiotics as an adjunct to intravitreal antibiotics. Systemically administered antibiotics with good vitreous penetration, such as moxifloxacin, linezolid, and meropenem, could prolong antimicrobial activity in the vitreous after the concentrations of the injected antibiotics wane to subtherapeutic levels and thereby reduce the need for antibiotic reinjection.

Role of Vitrectomy

PPV can be performed at several stages in the management of endophthalmitis as follows: (1) as the initial intervention, (2) when there are signs of deterioration after initial treatment, or (3) once the acute infection has settled to treat vision-impairing conditions, such as vitreous opacity, retinal detachment (RD), and macular epiretinal membrane. There is ongoing controversy regarding the role and threshold for PPV with intravitreal antibiotics in the initial management of eyes with better than light perception (LP) vision on presentation.

The concept of early PPV in the management of endophthalmitis is defined variably in the literature, from within 6 hours[5] to within 1 week of presentation.[27,57] PPV performed beyond 36 hours from presentation is arguably not "early" because patients in the EVS initially randomized to the TAP group (vitreous tap or biopsy) could have PPV if the eye was doing poorly 36 to 60 hours after the initial procedure. The potential benefits of early PPV include collection of a greater volume of vitreous for microbiologic analysis; removal of bacteria and associated toxins, inflammatory mediators, and biofilms, which might hinder passage of intravitreal antibiotics; clearance of vitreous opacities and vitreous membranes; and possibly better distribution of intravitreal antibiotics. The disadvantages include a delay in treatment compared with a tap/inject procedure because of the need for operating room (OR)

availability, increased costs, anesthesia risks, and ocular risks, including RD.

In the EVS, *immediate vitrectomy* was defined as procedures performed within 6 hours of presentation. Importantly, eyes were ineligible for randomization if media clarity did not permit safe removal of 50% of the vitreous gel. The study found a benefit for early PPV only in patients presenting with LP vision. In cases in which there was no posterior vitreous separation, no attempt to induce a posterior vitreous detachment was made and the surgical goal was to remove at least 50% of the vitreous gel.[5] Since that study, several retrospective series comparing the results of early vitrectomy with initial tap/inject have been published, with varying results. These case series have small numbers and numerous biases; thus, their utility in guiding management is limited. With a single exception, these studies included endophthalmitis from multiple causes, with only a small minority post-IVI; therefore, the results might not be directly applicable.[58]

There is evidence that surgeons have a lower threshold for performing initial vitrectomy in eyes with endophthalmitis and better than LP vision.[27,59–61] In the 2016 ASRS Preferences and Trends Survey,[62] there was a marked difference between US and international respondents in their preferred management of a patient with endophthalmitis after IVI with hand motions (HM) vision. US respondents favored tap/inject in the office (68%) over PPV with antibiotic injection in the OR (30%), whereas international respondents favored PPV/antibiotics (73%) over tap/inject (25%). This represented a slightly higher proportion favoring PPV over tap/inject in both respondent groups for post-IVI endophthalmitis compared with the same scenario for endophthalmitis after cataract surgery.[62]

In a retrospective study of 47 patients, Kuhn and Gini[63] described "complete and early" vitrectomy to treat postoperative endophthalmitis in eyes in which no retinal detail was visible, the red reflex was poor, or there was no clinical improvement within 24 hours after intravitreal antibiotic injection. The protocol used media clarity and early clinical progress rather than a specific level of visual acuity (VA) to determine whether to perform PPV. The authors reported a final VA of 20/40 or better in 91% of cases. Unfortunately, no details were provided regarding presenting visual acuities. In a subsequent series of 62 patients with acute post-cataract endophthalmitis using the same criteria and technique, the final VA was 20/40 or better in 49 eyes (79%).[64] The authors compared this with EVS results (53% of eyes with 20/40 or better VA), although a retrospective case series cannot be directly compared with a randomized controlled trial that used different inclusion criteria. Neither of these retrospective studies included patients with post-IVI endophthalmitis, and the term *early* was not explicitly defined.

In a retrospective study of 171 cases of endophthalmitis that included 16 (9.4%) post-IVI cases, Choi et al[65] found early vitrectomy (within 24 hours of symptom onset) to be better than delayed vitrectomy. In a retrospective study of 64 cases of endophthalmitis that included 23 (36%) post-IVI cases, Ho et al[66] defined early PPV as occurring within 72 hours of presentation. The indication for early PPV in this study was a VA of counting fingers or worse at presentation. The authors found that eyes with HM or LP acuity achieved similar gains after PPV, concluding that early PPV might be beneficial for eyes with HM or LP acuity on presentation. In a retrospective review of 23 cases of post anti-VEGF injection endophthalmitis initially treated with tap/inject, Chaudhary et al[58] found that 90% of eyes receiving only tap/inject regained baseline VA compared with 46% of eyes receiving subsequent PPV. However, comparison of the 2 groups in this study is problematic given that the PPV group received PPV because of worsening clinical features after initial treatment in contrast to the group receiving tap/inject only.

A survey of practice patterns in Europe, Africa, Asia, and South America included 237 cases of endophthalmitis, 35 (14.8%) of which were postinjection.[27,57] Early vitrectomy (occurring within 1 week of presentation) was performed in 176 eyes (74.3%). Early PPV in this study was not shown to be predictive of favorable visual outcomes compared with tap/inject alone. The odds of performing PPV were 4-fold higher in eyes in which the disc and macula were not visualized. In a retrospective series of 40 cases of post-IVI endophthalmitis, Xu et al[23] found no statistical difference in the best-corrected VA (BCVA) at presentation or at the 6-month follow-up between the tap/injection group and the PPV group. The PPV group showed a nonstatistically significant trend toward worse BCVA on presentation and at the 6-month follow-up after treatment but also had greater improvement in vision when comparing the BCVA before endophthalmitis and the BCVA at the 6-month follow-up.

Since the EVS was performed in the early 1990s there have been major advances in vitrectomy surgery, including wide-angle viewing systems (which afford a superior view through hazy media), smaller gauge vitrectomy instrumentation, cannula port systems, and increased cutting speeds. Although initial vitrectomy (when technically feasible) with intravitreal antibiotics remains the gold standard for eyes with LP vision on presentation, unanswered questions regarding the role of initial PPV in eyes with post-IVI endophthalmitis and a presenting VA of HM or better should be addressed with a randomized controlled clinical trial. Additional emphasis on vitreous clarity (as opposed to VA only) seems warranted. Visual results would have to be interpreted in light of the preexisting macular pathology present in most post-IVI cases. Given that a significant delay might occur in performing initial PPV versus initial tap/inject and that even a delay of a few hours might be significant in severe cases with virulent organisms, it is recommended that all patients have a tap/inject on presentation even if immediate PPV is planned. Repeat intravitreal antibiotic injection can be performed at the time of PPV.

Use of Corticosteroids

The role of adjuvant corticosteroids in the management of infectious endophthalmitis is unclear. The chief theoretical benefit of corticosteroid therapy in this setting is to reduce inflammation and its associated tissue damage, including chronic

vascular leakage. In the EVS, participants were treated with a combination of oral, topical, and subconjunctival steroids; however, intravitreal steroids were not used.[5] There has been much interest in the role of intravitreal steroids subsequent to the EVS, motivated in part by the desire to spare patients the side effects of systemic corticosteroids. However, in a survey of ASRS members,[26] 60% of respondents reported never or rarely administering intravitreal dexamethasone in conjunction with intravitreal antibiotics. In the European Vitreo-Retinal Society Endophthalmitis Study,[27] only a quarter of eyes were treated with intravitreal corticosteroids. Neither of these surveys specifically addressed postinjection endophthalmitis.

In a Cochrane review, Kim and colleagues[67] found no studies examining the role of adjuvant corticosteroids in the management of post-IVI endophthalmitis. Numerous animal studies,[68] retrospective clinical series,[69–74] and randomized controlled clinical studies[75–79] have explored the role of adjuvant intravitreal corticosteroids in the management of endophthalmitis after surgery. The largest prospective study to date enrolled 167 eyes and randomized patients to intravitreal dexamethasone or a placebo in addition to intravitreal antibiotics.[79] The study found no difference in final VA between the dexamethasone group and placebo group.

In a retrospective review of 133 eyes with presumed infectious endophthalmitis, Robbins et al[80] examined the role of oral corticosteroids. Only 23 cases (17.3%) were post-IVI. In this nonrandomized series, the 33 cases (25%) that received oral corticosteroids were more likely to have VA improvement of 3 lines or more than those that did not. Interpretation of the results in this study are complicated by the nonstandardized use of topical and intravitreal corticosteroids in a subset of eyes. Similar issues apply to many other studies in which patients received corticosteroids via multiple routes.

It is plausible that the intraocular tissue destruction associated with infectious endophthalmitis often commences before steroids can be administered and that dexamethasone is cleared from the vitreous too quickly to have a clinically evident benefit.[68,81] Although further studies could be helpful in further understanding the role and timing of adjuvant oral and intravitreal corticosteroids in the management of post-IVI endophthalmitis, it is unlikely that a sufficiently large prospective randomized clinical trial will be performed to adequately address these questions.

Subsequent Interventions

The decision to perform further interventions after initial tap/inject or PPV/inject procedures is based on the clinical course and the judgment and preferences of the individual clinician. There is little specific guidance in the literature in this regard given the degree of variability in response and the relative priority given to different clinical features by each clinician. In the EVS, recommendations for further interventions (repeat intravitreal antibiotic injection or PPV/repeat intravitreal antibiotic injection) were based on assessment 36 to 60 hours after the initial intervention.[5] Specific clinical criteria were used; however, interventions could ultimately be performed (or not performed) if they were believed to be in the patient's best interests. In general, additional intervention is now considered at an earlier stage.[82] Leung et al[83] found that in eyes having a second tap/inject, those with positive cultures in the second tap grew organisms with the same antibiotic sensitivities as in the first tap in 94% of cases, and these eyes with persistently culture-positive endophthalmitis had very poor outcomes. Based on this finding, Clarke et al[82] recommended that the secondary intervention consist of PPV with repeat intravitreal antibiotic injection rather than repeat tap/inject.

Recommencement of Anti-VEGF Therapy

After treatment of endophthalmitis, anti-VEGF injections might have to be recommenced to treat the underlying disease. The decision to restart treatment is influenced by several factors, including the visual potential, the state of the fellow eye, the presence of intraocular inflammation, and the underlying disease process (age-related macular degeneration [AMD] vs retinal vascular disorders such as diabetic macular edema [DME] or retinal vein occlusion [RVO]). There is likely to be a reevaluation of the risk:benefit ratio by both the physician and the patient, and the treatment paradigm might shift from a treat-and-extend approach to an as-needed (PRN) approach in some circumstances, especially when the visual potential is poor. In a multicenter study of practice preferences after postinjection endophthalmitis, Chen et al[20] reported a reduction in injection frequency after endophthalmitis, with a shift toward lower frequency injection algorithms.

Several reports suggest regression or prolonged inactivity of neovascular AMD after endophthalmitis.[84–88] Although the explanation for this observation is unclear, possible mechanisms include a persistent antiangiogenic effect from the infective agent or inflammation, a reduction in angiogenic drive resulting from tissue destruction or corticosteroids, and increased vitreous cavity oxygen tension associated with vitrectomy, among others. We are unaware of any reports describing a change after endophthalmitis in exudation from retinal vascular diseases such as DME and RVO. In contrast to the aforementioned reports, Michalewska and Nawrocki[89] described 8 cases of post-IVI endophthalmitis in patients bring treated for neovascular AMD. Despite prompt vitrectomy within 12 hours of symptom onset, all their patients required recommencement of anti-VEGF injections and the frequency of treatment did not change.

Conclusion

Despite the increasing number of cases of post-IVI infectious endophthalmitis and the proliferation of scientific papers relating to this most feared complication, management of this condition continues to rely largely on extrapolation of results from studies of postsurgical, in particular post-cataract surgery, endophthalmitis. There is evidence of significant deviation from the recommendations of the EVS, especially in countries outside the US.

Specific guidance regarding post-IVI endophthalmitis is required. Despite the low incidence of post-IVI endophthalmitis on a per-procedure basis, the enormous volume of IVIs suggests that a randomized controlled clinical trial addressing remaining questions is feasible and should be explored. Although it is unlikely that a single trial could address all the unanswered questions, several key areas should be considered. These include the threshold at which the initial intervention should be PPV/injection as opposed to tap/inject, the potential adjunctive role of systemically administered antibiotics with adequate vitreous penetration, the role of corticosteroids via various routes of administration, and the timing and nature of secondary interventions.

Given the preexisting limitation on visual potential posed by the underlying macular pathology, emphasis should be placed on the final VA relative to the baseline VA at the time of the inciting injection. As always, the critical importance of preventive measures against infectious endophthalmitis cannot be overstated. In cases of suspected or presumed infectious endophthalmitis after IVI, IVI of antibiotics should occur as soon as possible as part of tap/inject or even if initial PPV is planned given the almost invariable delay in access to the OR for PPV.

Ethical Approval

Ethical approval was not sought for the present study because the article is based on review of previous literature and did not involve patient care or chart review.

Statement of Informed Consent

Informed consent was not sought for the present study because the article is based on review of previous literature and did not involve patient care or chart review.

Declaration of Conflicting Interests

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