

## Review

# Do You Still Use Topical Antibiotics after Intravitreal Injections?

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### ABSTRACT

Nowadays intravitreal drug injection is the most frequent treatment for retinal diseases. Despite widely use endophthalmitis is already most feared complication of every intravitreal injection in each patient. In clinical setting topical antibiotics have been widely used as a precaution to prevent endophthalmitis however recent published evidence showed it to be unnecessary. Furthermore repeated use of topical antibiotics might give rise to antibiotic resistance in conjunctival flora and thus more aggressive endophthalmitis. Strict asepsis has been awarded as the main rule for endophthalmitis prophylaxis intravitreal injection.

### Keywords

Intravitreal injection; Steroid; Anti-vascular endothelial growth factor (VEGF); Topical antibiotic; Endophthalmitis; Antibiotic resistance.

### INTRODUCTION

Intravitreal injections have become the main treatment modality for retinal diseases all over the world. Anti-vascular endothelial growth factor (VEGF) drugs and to a lesser extent steroid implants have made intravitreal injection the most frequent procedure in ophthalmology. The anti-VEGF era began in 2004 with the approval of the first pharmacologic agent for inhibition of VEGF.<sup>1,2</sup> Till that time the intravitreal injection was an uncommon procedure and many guidelines were advising the use of pre- and post-injection topical antibiotics to prevent endophthalmitis which was the most feared complication.<sup>3</sup> The initial randomized clinical trial protocols evaluating the efficacy of anti-VEGF agents mandated also topical antibiotics following intravitreal drug injection. Additionally, product informations of anti-VEGF agents included recommendations for topical antibiotic use as well.<sup>4</sup> However, the exponential increase in the number of intravitreal injections evidenced a lower incidence of endophthalmitis than expected ranging between 0.01-0.26% in several studies.<sup>5-12</sup> This raises questions about the necessity of pre- or post-injection topical antibiotic use.

The practice of using topical antibiotics was actually adopted from other intraocular procedures like cataract surgery. In

surgical procedures there exists a surgical wound that may not be completely sealed. However, in intravitreal injections there isn't such a wound as a 30-gauge or at the largest 27-gauge needle is used. This was probably the main reason for the lower endophthalmitis rate.

### PRE-INJECTION ANTIBIOTIC USE

Most endophthalmitis cases related to intravitreal injections showed that the causative organism in post-injection endophthalmitis is usually inoculated at the time of injection rather than subsequent entry to the eye. Therefore, needle penetration into a nutrient-rich body cavity warrants pre-cautions that should be taken during the procedure to avoid contamination.<sup>13</sup> Pre-injection antibiotic use was found logical until studies showed that povidone-iodine immediately prior to injection revealed less positive bacterial cultures compared to pre-treatment antibiotic use.<sup>14,15</sup> Two studies also revealed higher risk for endophthalmitis in patients using prophylactic antibiotics. The mechanism has been thought to be the increased ratio of antibiotic-resistant surface bacteria or the detrimental effect of repeated fluoroquinolone use on ocular surface health.<sup>6,16</sup>

## POST-INJECTION ANTIBIOTIC USE

As mentioned above post-injection topical antibiotic use was also a query. First in 2004 Aeillo et al<sup>3</sup> postulated that post-injection antibiotics did not decrease endophthalmitis incidence. Recently the outcome of numerous large retrospective studies evaluating thousands of injections presented in Table 1 showed no benefit to prevent endophthalmitis.<sup>6,8,11,12,16</sup> In contrast, some of them found higher rates of endophthalmitis in patients using topical antibiotics.<sup>5,6,9,17,22</sup> A [www.DRCR.net](http://www.DRCR.net) study reported endophthalmitis rate to be 0.13% in the group receiving topical antibiotics and 0.03% in the group without antibiotic.<sup>18</sup> This was attributed to resistant organisms due to antibiotic overuse.<sup>23</sup> The comparison of age-related macular degeneration treatments trials (CAT) study also showed no significant difference in endophthalmitis rates between groups with and without antibiotic use.<sup>24</sup>

**Table 1. Summary of Studies Evaluating Endophthalmitis Group**

Study	Prophylaxis	Drug	Endophthalmitis Rate	
			With AB	Without AB
Meyer <sup>45</sup>	Post-injection	Anti-VEGF,TA	2/860	0/984
Bhatt <sup>18</sup>	Post-injection	Anti-VEGF,TA	5/2287	5/2480
Cheung <sup>19</sup>	Post-injection	Anti-VEGF,TA	5/8259	4/7636
Falavarjani <sup>20</sup>	Post-injection	Anti-VEGF	6/3975	0/1926
Casparis <sup>46</sup>	Post-injection	Anti-VEGF	2/13234	1/26777
Ramei <sup>47</sup>	Post-injection	Anti-VEGF,TA	3/10144	3/1306
Stranak <sup>48</sup>	Pre+post-injec.	Anti-VEGF,TA	2/2651	1/2355
Li <sup>28</sup>	Pre+post-injec.	Anti-VEGF,TA, Dex, Ocriciplasmin	6/16984	11/53345
Falavarjani <sup>49</sup>	Post-injection	Anti-VEGF	1/2771	0/5266
Meredith <sup>24</sup>	Pre+post-injec.	Anti-VEGF	8/16509	3/2000
Pachuo <sup>50</sup>	Post-injection	Anti-VEGF	0/310	0/310
Bhavsar <sup>51</sup>	Pre+post-injec.	Anti-VEGF,TA	6/11565	3/17208
Storey <sup>21</sup>	Post-injection	Anti-VEGF	28/57654	24/89825

## STERIOD INJECTION

Among intravitreally injected drugs steroids have distinctive features than anti-VEGFs. The most frequently used steroid-dexamethasone intravitreal implant (Allergan, Inc., Irvine, CA, USA) has a 22-Gauge needle and additionally steroids give rise to the tendency for infections.<sup>25</sup> Therefore, steroid injections are expected to require a different approach than anti-VEGF drugs. However, retrospective studies and meta-analysis were surprising. A retrospective study evaluating 3593 dexamethasone implant injections without pre- or post-antibiotic use suggests that an endophthalmitis is a rare event as anti-VEGF injections.<sup>26</sup> Another meta-analysis evaluating 13 studies and approximately 350,000 injections assessed that type of antibiotic, type of drug injected or antibiotic prophylaxis regimen neither influence endophthalmitis rate nor reduce its incidence.<sup>27</sup> A significant number of triamcinolone and dexamethasone injections were enrolled in this meta-analysis.

Many retrospective studies also reported similar endophthalmitis risks for both anti-VEGF and steroid implants. However, most of them evaluated a smaller number of steroid injections compared to anti-VEGF injections.<sup>9,28</sup> This should be kept in mind when evaluating this outcome.

## WHY ARE TOPICAL ANTIBIOTICS UNNECESSARY?

The distinctive feature of intravitreal injections compared to other invasive ophthalmic procedures is the repeated application. The ocular surface was thought to be sterile for years due to the presence of lysozyme, antimicrobial peptides, immunoglobulin A (IgA) complement and other substances. Local bacteria on the ocular surface maintain ocular immunity but transient disruption of bacteria *via* antibiotics results in a reduction in immune-related mechanisms.<sup>29</sup> Additionally, the repeated use of short term topical antibiotics increases the resistance of the ocular surface organism to antibiotics.<sup>19,30</sup> This has been clearly demonstrated in the study of Kim et al.<sup>31</sup> After 1-year monthly intravitreal injection, the treated eyes using topical antibiotics had increased bacterial resistance compared to untreated fellow control eyes.<sup>31</sup> Moss et al<sup>15</sup> reported the rate of positive bacterial culture as 8% in patients using pre-operative antibiotic and povidone-iodine and 4% in the group receiving povidone-iodine only. Another study compared conjunctival cultures of the injected eye following the use of several topical antibiotics with the fellow untreated eye. Cultures proved multi-drug resistance of coagulase-negative staphylococci between 67.5-81.8% to antibiotics used. As conjunctival flora is presumed the source of post-injection endophthalmitis, this outcome has severe implications.<sup>23</sup> The drug resistance caused by repeated antibiotic use is not only limited to the eye. It has also impact on the drug resistance in nasopharyngeal flora which may give rise to soft tissue infections and pneumonia.<sup>31</sup>

A confounding factor related to antibiotic use is its limited penetration to vitreous. Only about 1/100,000<sup>th</sup> of the drug observed in tear fluids reaches the retina and choroid.<sup>32</sup> So it is impossible to reach the minimum inhibitory concentration in vitreous required to prevent microorganism proliferation after intravitreal injection.<sup>33</sup>

## MEASURES TO PREVENT ENDOPTHALMITIS

Certainly, some prophylactic measures are warranted to minimize the risk of endophthalmitis following intravitreal injection. Recent evidence shows the use of povidone-iodine installation as the safest way for ocular surface preparation before injection.<sup>34</sup> Povidone-iodine is a disinfectant and antiseptic agent commonly used for pre-operative preparation in ophthalmic procedures and provides broad-spectrum fast-acting microbicidal activity. It is applied to lids and lashes in 5% concentration. In contrast to repeated topical antibiotics ocular surface preparation using povidone-iodine 5% without antibiotic use does not promote bacterial resistance.<sup>35</sup> A study evaluating daily use of povidone-iodine for peritoneal dialysis exit sites reported no resistance.<sup>36</sup> Hsu et al<sup>34</sup> also reported no antibiotic resistance even no significant alteration resulting from povidone-iodine 5% for ocular preparation. Povidone-iodine is ad-

viced to be instilled as the last drop before injection and should be allowed to stay for at least 30-seconds or more.<sup>37</sup> Dropping it after lid retraction has been shown to decrease the risk of endophthalmitis 7 folds.<sup>38</sup> Povidone-iodine with 10% showed no significant difference with povidone-iodine 5% in endophthalmitis risk and it may cause greater corneal toxicity and discomfort (Table 2).<sup>39</sup>

Table 2. Precautions Before Intravitreal Injection Procedure
<b>Use of Povidone-iodine for Intravitreal Injection</b>
%5 concentration preferred
Last drop before injection
Put a drop after lid retraction
Wait at least for 30-seconds or more

## CONCLUSION

In light of these informations most of the authorities are trending away from topical antibiotic use following intravitreal injections.<sup>40</sup> The [www.DRCR.net](http://www.DRCR.net) and CATT advice to abandon the use of topical antibiotics as frequent use of antibiotics appear to promote the emergence of microbial resistance.<sup>24,41</sup> American Academy of Ophthalmology (AAO) and also Royal College of Ophthalmology (RCOphth) also discourage the use of antibiotics after intravitreal injections in their guidelines.<sup>42-44</sup> These are strong scientific evidence to justify a jury that antibiotics are no longer required post-injection if an injection-related endophthalmitis would be brought to a court of law as a medicolegal suit. Using povidone-iodine 5% without topical antibiotic appears to be the safest approach to avoid the widespread problem of increasing antibiotic resistance. We have to keep in mind to instill it as the last drop possibly after lid retraction and wait for at least 30-seconds.

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