Viewpoint:
Use of topical antibiotics with intravitreal injections
Objectives

To review the current use of topical antibiotics with intravitreal injections

To highlight areas where current evidence could better inform clinical practice

To present the recommendations of the Vision Academy on this topic

The Vision Academy provides ophthalmic specialists with a forum to share existing skills and knowledge, build best practice, and lead the wider community in the drive towards optimized, compassionate patient care.

Through their collective expertise, the Vision Academy seeks to provide guidance for best clinical practice in the management of retinal disease, particularly in areas with insufficient conclusive evidence.

What are the challenges surrounding the use of topical antibiotics?
Background
The use of topical antibiotics with intravitreal injections to prevent infection is largely historical, based on surgical practice and protocols from the initial clinical trials of anti-VEGF.

As a result, initial product information / drug labels included a recommendation for topical antibiotic use, leading to routine use by many, despite evidence to suggest that this does not represent best practice.

Further, the low incidence of infectious endophthalmitis means that RCTs are not feasible, so we must rely on data from phase III / IV studies and large retrospective series.

**CLINICAL CHALLENGE**

Evidence-based guidelines on the use, or otherwise, of topical antibiotics during intravitreal injection procedures are lacking.

**Intravitreal injections**

Intravitreal injections are increasing in frequency due to the widespread adoption of anti-VEGF therapies for the management of retinal diseases. However, serious complications of intravitreal injections include infectious endophthalmitis.

**Current use of topical antibiotics with intravitreal injections is based on historical protocols**

What is the significance of endophthalmitis?

• Endophthalmitis is an uncommon, potentially devastating complication of intravitreal injection
  – Occurrence of endophthalmitis ranges from 1 in 1000 to 1 in 5000 injections
  – Commonly caused by coagulase-negative *Staphylococcus* and *Streptococcus*
  – Despite appropriate and prompt therapy, visual outcomes are often poor

• Risk reduction strategies for the prevention of endophthalmitis are particularly important for improving overall patient outcomes

### Worldwide experience highlights low incidence of endophthalmitis

<table>
<thead>
<tr>
<th>Country</th>
<th>Article title</th>
<th>Citation</th>
<th>Overall incidence of post-injection endophthalmitis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>🇺🇸</td>
<td>Endophthalmitis After Anti-VEGF Injections</td>
<td>Klein KS et al. <em>Ophthalmology</em> 2009; 116 (6): 1225.e1</td>
<td>0.049</td>
</tr>
<tr>
<td>🇺🇸</td>
<td>Incidence and Clinical Features of Post-injection Endophthalmitis According to Diagnosis</td>
<td>Rayess N et al. <em>Br J Ophthalmol</em> 2016; 100 (8): 1058–1061</td>
<td>0.038</td>
</tr>
<tr>
<td>🇬🇧</td>
<td>Post-intravitreal anti-VEGF endophthalmitis in the United Kingdom: incidence, features, risk factors, and outcomes</td>
<td>Lyall D et al. <em>Eye</em> 2012; 26: 1517–1526</td>
<td>0.025</td>
</tr>
</tbody>
</table>

VEGF, vascular endothelial growth factor.
Approaches to prevent endophthalmitis
Endophthalmitis prevention strategies

<table>
<thead>
<tr>
<th>Meticulous preparation</th>
<th>Careful attention paid to aseptic technique</th>
<th>Povidone-iodine use</th>
<th>Reduce aerosolized droplets containing oral contaminants</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Avoidance of needle contact with eyelashes</td>
<td>• Use of sterile gloves</td>
<td>• On ocular surface, in conjunctival cul-de-sac</td>
<td></td>
</tr>
<tr>
<td>• Eyelid speculum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Drapes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Prevent movement of conjunctiva over injection site

Use of topical antibiotics

Postpone injections in patients with active external infections

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g., eye pain, redness of the eye, photophobia, and blurring of vision) without delay.
Evidence on the use of topical antibiotics with intravitreal injections
<table>
<thead>
<tr>
<th>Title</th>
<th>What is the rationale for the use of topical antibiotic prophylaxis for intraocular procedures?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Details</td>
<td>For incisional surgery where there is an external surgical wound that may not always be completely sealed (e.g., sutureless phaco), there is a sound theoretical rationale for topical antibiotic prophylaxis.</td>
</tr>
<tr>
<td></td>
<td>However, such a wound is seldom present when intravitreal injections are given, especially when using a 30-gauge needle (at the largest, 27-gauge).</td>
</tr>
<tr>
<td></td>
<td>A major factor that sets intravitreal injections apart from other invasive procedures is the repeated nature of the injections in many cases.</td>
</tr>
</tbody>
</table>

Pre-injection antibiotics are not associated with lower bacterial loads at the injection site

- The use of topical antibiotics (combined with povidone-iodine) before cataract surgery has been shown to result in reduced colony counts\(^1\)

- This benefit does not appear to translate to the use of topical antibiotics administered before an intravitreal injection

- **There is no additional benefit of pre-injection antibiotic use** when combined with povidone-iodine
  - Povidone-iodine reduces the number of bacterial colonies by 91\(^3\)
  - Povidone-iodine lowers the risk of endophthalmitis to 0.06% (vs. 0.24% with silver protein solution)\(^4\)


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**CHALLENGE REQUIRING VISION ACADEMY GUIDANCE**

Should topical antibiotics be used with intravitreal injections?

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**Percentage of patients with conjunctival culture positivity with and without pre-injection antibiotics**

<table>
<thead>
<tr>
<th>Culture collection timepoint</th>
<th>Povidone-iodine alone (n=136)</th>
<th>Povidone-iodine + gatifloxacin for 3 days prior to injection (n=137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day of injection, before povidone-iodine</td>
<td>47.8</td>
<td>21.2</td>
</tr>
<tr>
<td>After all patients have been given povidone-iodine</td>
<td>4.4</td>
<td>8.0</td>
</tr>
<tr>
<td>Needle (immediately following procedure)</td>
<td>1.5</td>
<td>2.2</td>
</tr>
</tbody>
</table>
Post-injection antibiotics have no effect on the rate of endophthalmitis

• Large studies have shown that the use of post-injection antibiotics does not reduce the incidence of endophthalmitis\(^1-4\)

• A similar outcome was also reported in one of the largest (316,576 injections), retrospective, nationwide studies conducted in France\(^5\)

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**Percentage of patients developing endophthalmitis after intravitreal injection**

- **Storey et al.\(^*1\)**
  - No post-injection antibiotics: 0.027%
  - With post-injection antibiotics: 0.049%
  - N=172,096\(^6\)
- **Cheung et al.\(^1,2\)**
  - No post-injection antibiotics: 0.038%
  - With post-injection antibiotics: 0.066%
  - N=15,895\(^6\)
- **Bhavsar et al.\(^1,3\)**
  - No post-injection antibiotics: 0.03%
  - With post-injection antibiotics: 0.13%
  - N=8027\(^6\)
- **Bhatt et al.\(^4\)**
  - No post-injection antibiotics: 0.2%
  - With post-injection antibiotics: 0.22%
  - N=4767\(^6\)

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**CHALLENGE REQUIRING VISION ACADEMY GUIDANCE**

Should topical antibiotics be used following intravitreal injections?

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\*For the Post-Injection Endophthalmitis Study Team. \(^1\)8259 patients were given antibiotics for 5 days after injection; 2370 patients received antibiotics immediately after injection. \(^2\)For the Diabetic Retinopathy Clinical Research Network. \(^3\)Injections.
Higher incidence of endophthalmitis WITH antibiotics

• This paper identified and screened 4561 records:
  - 60 articles met the inclusion criteria (12 arms of RCTs, 11 prospective cohorts, and 37 retrospective cohorts)
  - 244 cases of endophthalmitis
  - 639,391 intravitreal injections of anti-VEGF

The final pooled estimate of endophthalmitis proportions was higher in the antibiotic-treated group:

- 0.09% (95% CI, 0.07–0.12) in the antibiotic-treated group
- 0.03% (95% CI, 0.02–0.05) in the untreated group

CHALLENGE REQUIRING VISION ACADEMY GUIDANCE

Should topical antibiotics be used with intravitreal injections?
The majority of studies do not show a difference in endophthalmitis rates with antibiotic use

<table>
<thead>
<tr>
<th>Study</th>
<th>Injections</th>
<th>Retinal diseases treated</th>
<th>Endophthalmitis rate with topical antibiotics</th>
<th>Endophthalmitis rate without topical antibiotics</th>
<th>Statistical significance</th>
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<tr>
<td>Bhatt et al. 2011</td>
<td>4767</td>
<td>Multiple</td>
<td>0.22%</td>
<td>0.20%</td>
<td>Not significant</td>
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<tr>
<td>Falavarjani et al. 2013</td>
<td>5901</td>
<td>Multiple</td>
<td>0.10%</td>
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<td>Falavarjani et al. 2015</td>
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<td>Multiple</td>
<td>0.01%</td>
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<td>Meredith et al. 2015</td>
<td>18,509</td>
<td>Neovascular AMD</td>
<td>0.04–0.08%</td>
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<tr>
<td>Park et al. 2013</td>
<td>17,332</td>
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<td>0%</td>
<td>0.035%</td>
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<tr>
<td>Porteous et al. 2014</td>
<td>6957</td>
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<td>Ramel et al. 2014</td>
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CHALLENGE REQUIRING VISION ACADEMY GUIDANCE
Should topical antibiotics be used with intravitreal injections?

AMD, age-related macular degeneration; DME, diabetic macular edema; PDR, proliferative diabetic retinopathy.


The majority of studies do not show a difference in endophthalmitis rates with antibiotic use.

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Many large series have reported that topical antibiotics do not decrease, and may in fact increase, the rate of endophthalmitis.

CHALLENGE REQUIRING VISION ACADEMY GUIDANCE
Should topical antibiotics be used with intravitreal injections?

AMD, age-related macular degeneration; DME, diabetic macular edema; PDR, proliferative diabetic retinopathy.
Antibiotics do not penetrate the vitreous humor

- A prospective randomized study demonstrated that topical antibiotic administration leads to effective levels in the aqueous but not in the vitreous humor
  - Concentrations in the vitreous humor did not exceed the MIC\textsubscript{90} for the most common bacterial pathogens causing acute postoperative endophthalmitis

<table>
<thead>
<tr>
<th>Topical antibiotic</th>
<th>3-day pre-surgery regimen\textsuperscript{*} (n=3)</th>
<th>1-hour pre-surgery regimen\textsuperscript{†} (n=3)</th>
<th>Staphylococcus aureus</th>
<th>Staphylococcus epidermidis</th>
<th>Streptococcus pneumoniae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxifloxacin 0.5%</td>
<td>0.011 ± 0.008</td>
<td>0.012 ± 0.011</td>
<td>0.064</td>
<td>0.047</td>
<td>0.125</td>
</tr>
<tr>
<td>Gatifloxacin 0.3%</td>
<td>0.008 ± 0.006</td>
<td>0.001 ± 0.0003</td>
<td>0.11</td>
<td>0.09</td>
<td>0.22</td>
</tr>
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\textsuperscript{*}Four doses per day for 3 days prior to surgery (patient-administered; 100% patient compliance); \textsuperscript{†}One drop every 15 minutes for a total of three doses administered 1 hour prior to surgery. MIC\textsubscript{90}, minimum inhibitory concentration for 90% of isolates; SD, standard deviation.

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<th>Mean vitreous concentration ± SD (μg / mL)</th>
<th>MIC\textsubscript{90} (μg / mL)</th>
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**CHALLENGE REQUIRING VISION ACADEMY GUIDANCE**

Should topical antibiotics be used with intravitreal injections?

*Four doses per day for 3 days prior to surgery (patient-administered; 100% patient compliance); †One drop every 15 minutes for a total of three doses administered 1 hour prior to surgery. MIC\textsubscript{90}, minimum inhibitory concentration for 90% of isolates; SD, standard deviation. Costello P et al. Retina 2006; 26 (2): 191–195.
Use of topical antibiotics increases antibiotic resistance

Percentage of patients with ocular colonies resistant to fluoroquinolones

- No post-injection antibiotics
- With post-injection fluoroquinolone

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>N=22</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>87.5</td>
</tr>
</tbody>
</table>

Percentage of conjunctival bacterial isolates resistant to fluoroquinolones, before and after three intraocular injections with post-injection antibiotics

<table>
<thead>
<tr>
<th>Percentage of resistant isolates (%)</th>
<th>Prior to antibiotic treatment (n=23)</th>
<th>After antibiotic treatment (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ofloxacin</td>
<td>57</td>
<td>34</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>52</td>
<td>34</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>39</td>
<td>67</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>34</td>
<td>77</td>
</tr>
</tbody>
</table>

p=0.003 p=0.003 p=0.009 p<0.001

CHALLENGE REQUIRING VISION ACADEMY GUIDANCE
What is the impact of the use of topical antibiotics on antibiotic resistance?

Use of topical antibiotics increases antibiotic resistance

Percentage of patients with ocular colonies resistant to fluoroquinolones⁴

Use of povidone-iodine alone with intravitreal injections does NOT lead to bacterial resistance³

Percentage of conjunctival bacterial isolates resistant to fluoroquinolones, before and after three intraocular injections with post-injection antibiotics²

CHALLENGE REQUIRING VISION ACADEMY GUIDANCE

What is the impact of the use of topical antibiotics on antibiotic resistance?

Antibiotic-resistant strains may become more virulent

Rabbit models have demonstrated that antibiotic-resistant strains of *Staphylococcus epidermidis* tend to cause earlier and more severe inflammation compared with antibiotic-susceptible strains.

It has been hypothesized that resistant strains are more capable of surviving in the intraocular compartment and colonizing ocular tissues, causing tissue damage or eliciting a damaging immune response:

- These features and the resistant genes may then be transferred to the next generation.

**CHALLENGE REQUIRING VISION ACADEMY GUIDANCE**

What is the impact of the use of topical antibiotics on antibiotic resistance?

Use of antibiotics can interfere with models of care and increase costs

• For patients on a PRN regimen with monthly monitoring, a requirement for pre-injection antibiotics would mean that intravitreal injections could not take place during the monitoring visit, in cases where treatment is only decided at the time of consultation, meaning that treatment has to be deferred rather than given on the day the decision is made¹
  – Increased burden of appointments for patients and clinics

• Post-injection antibiotics have been estimated to increase the financial burden on the US healthcare system by an additional $64 million per year²

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Despite the appealing theoretical rationale for topical antibiotic prophylaxis in the prevention of endophthalmitis, there is a distinct lack of evidence in its favor and growing evidence against its use.

- There is a lack of evidence that the use of topical antibiotics with povidone-iodine provides any additional benefits to the patient.
  - Povidone-iodine has been shown to be safe and highly effective in the prevention of endophthalmitis.

- The use of topical antibiotics is associated with antibiotic resistance, with the potential for these resistant strains to become virulent.

- The use of topical antibiotics may not only increase the burden on both the clinic and the patient, but it is also associated with high costs, which may have an impact on healthcare systems.
Which regions are using topical antibiotics and why?
Results from ASRS PAT surveys indicate a reduction in the use of antibiotics in the US

Percentage of survey respondents using pre- and post-injection antibiotics

<table>
<thead>
<tr>
<th>Year</th>
<th>Pre-injection</th>
<th>Post-injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Practice habits are highly variable according to region and country

Do you prescribe topical antibiotics for use with intravitreal injections?

**US**
- Yes 11%
- No 89%

**Central / S. America**
- Yes 86%
- No 13%

**Europe**
- Yes 81%
- No 18%

**Asia-Pacific**
- Yes 84%
- No 15%

**Africa / Middle East**
- Yes 79%
- No 18%

In 2014, 84% of physicians from the Asia-Pacific region said they used topical antibiotics, compared with only 11% of US physicians.
Until recently, some guidelines continued to recommend the use of topical antibiotics.

**UK guidelines (2009 / 2018):**
- The Royal College of Ophthalmologists guidelines for intravitreal injection procedures in 2009 noted that the use of post-injection topical antibiotics is recommended.
- However, when updated in 2018, the guidelines stated that the use of peri-injection antibiotics is no longer recommended.

**US guidelines (2014):**
- In December 2014, an expert US panel of 16 HCPs with expertise in various aspects of the intravitreal injection procedure convened to review and revise intravitreal injection guidelines.
- An agreement was reached: “There is insufficient evidence to support the routine use of pre-, peri, or post-injection antibiotics to reduce the rate of endophthalmitis.”

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Clinical challenges
**Clinical challenges requiring guidance**

**Use of topical antibiotics**
- Is the use of topical antibiotics with intravitreal injections warranted?

**Antibiotic resistance**
- What is the impact of the use of topical antibiotics on antibiotic resistance?

**Guidelines**
- Do guidelines sufficiently address the use of topical antibiotics?
Vision Academy recommendations
Use of topical antibiotics prior to, alongside, or after intravitreal injections is not recommended

**Topical antibiotic use prior to intravitreal injection**

- Most infections result from inoculation of organisms at the time of injection
- No prospective studies demonstrating that pre-injection antibiotics reduce the risk of endophthalmitis

**Topical antibiotic use concurrent with or after intravitreal injection**

- No additional benefit of post-injection antibiotics in preventing endophthalmitis

Available evidence does not support a reduction in the risk of endophthalmitis with use of topical antibiotics

There is a growing body of evidence detailing increased antibiotic resistance in patients receiving topical antibiotics.

**Antibiotic resistance**

- Several studies have demonstrated increasing resistance of conjunctival flora to topical antibiotics.\(^1,^2\)
- Resistance to fluoroquinolones, the most commonly used topical antibiotics in many regions, may have serious ramifications in other procedures (e.g., cataract surgery).

**Antibiotic penetration**

- Topical administration leads to effective antibiotic levels in the aqueous but not in the vitreous humor.\(^3\)

Evidence suggests an increase in antibiotic resistance with use of topical antibiotics.

Topical antibiotics should not be used alongside intravitreal injections.

General consensus

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Product information for intravitreal medications and local / professional society guidelines should be updated

Significant regional differences

- Reasons for continued use of topical antibiotics with intravitreal injections include:
  - Personal preference
  - Peer pressure
  - Medico-legal concerns

- Changes in practice habits may be achieved through the revision of drug labels and the amendment of local and professional society guidelines

Regional differences exist in the continued use of topical antibiotics with intravitreal injections

Revision of product information and guidelines is required to enable physicians to change their practice
Summary

The Vision Academy does not recommend the use of topical antibiotics alongside intravitreal injections

There is a lack of evidence supporting any benefit for topical antibiotic prophylaxis against post-injection endophthalmitis

There is a growing body of evidence detailing increased antibiotic resistance in patients receiving topical antibiotics

Product information for intravitreal medications and local / professional society guidelines should be updated to reflect this recommendation and to remove barriers to clinicians wishing to change their practice

- Ophthalmologists should avoid inappropriate use of topical antibiotics
- Emphasis should be placed on antisepsis and aseptic technique, which are the major proven methods of endophthalmitis prevention, rather than antibiotics

The Viewpoint ‘Use of topical antibiotics with intravitreal injections’ can be downloaded from: https://www.visionacademy.org/resource-zone/treatment-best-practices