Discussion and debate:

Use of topical antibiotics with intravitreal injections

Professor Anat Loewenstein
Dr. Paisan Ruamviboonsuk
Session aims

- To debate and discuss evidence ‘for’ and ‘against’ the use of topical antibiotics with IVT injections
- To provide a summary of the Vision Academy’s Viewpoint on the use of topical antibiotics with intravitreal injections
  - The Viewpoint can be found in your symposium pack
Debate:
Is there a case FOR topical antibiotics with intravitreal injections?

Professor Anat Loewenstein
Tel Aviv Sourasky Medical Center, Israel
## Financial and other disclosures

<table>
<thead>
<tr>
<th>I have the following financial interests or relationships to disclose</th>
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<tbody>
<tr>
<td>Allergan, Bayer, ForSight Labs, Notal Vision, Novartis</td>
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</tr>
</tbody>
</table>

C, consultant
Risk of endophthalmitis with IVT injections

- Endophthalmitis is an uncommon, potentially devastating complication of IVT injection
  - Occurrence of endophthalmitis ranges from 1 in 1000 to 1 in 5000 injections
  - 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

IVT, intravitreal.
Endophthalmitis After Intravitreal Injections: Incidence, Presentation, Management, and Visual Outcome


Incidence and clinical features of post-injection endophthalmitis according to diagnosis

Rayess N. BJO 2016; 100: 1058–1061

LOW ENDOPHTHALMITIS RATES AFTER INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR INJECTIONS IN AN OPERATION ROOM
A Retrospective Multicenter Study

Freiberg FJ et al. Retina 2017; 0: 1–6

Post-intravitreal anti-VEGF endophthalmitis in the United Kingdom: incidence, features, risk factors and outcome

Lyall D. Eye 2012; 26: 1517–1526

VEGF, vascular endothelial growth factor.
# Precautions for endophthalmitis prevention

<table>
<thead>
<tr>
<th>General consensus on:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meticulous preparation</td>
</tr>
<tr>
<td>Avoidance of needle contact with eyelashes</td>
</tr>
<tr>
<td>Eyelid speculum</td>
</tr>
<tr>
<td>Drapes</td>
</tr>
<tr>
<td>Careful attention paid to aseptic technique</td>
</tr>
<tr>
<td>Povidone-iodine use</td>
</tr>
<tr>
<td>On ocular surface, in conjunctival cul-de-sac</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lack of consensus on:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of sterile gloves</td>
</tr>
<tr>
<td>Movement of conjunctiva over injection site</td>
</tr>
<tr>
<td>Use of pre- or post-injection antibiotics</td>
</tr>
</tbody>
</table>
2014 ASRS PAT survey:
Percentage of physicians using topical antibiotics with IVT injections*

*Total percentage of physicians who prescribe topical antibiotics only in selected patients, or at any stage of the intravitreal injection process.

ASRS, American Society of Retina Specialists; IVT, intravitreal; PAT, Preferences and Trends.

Rezaei KA et al. 2014 Global Trends in Retina Survey. American Society of Retina Specialists; Chicago, IL, USA.
2015 ASRS PAT survey: Percentage of physicians using topical antibiotics with IVT injections*

*Total percentage of physicians who prescribe topical antibiotics only in selected patients, or at any stage of the intravitreal injection process.

ASRS, American Society of Retina Specialists; IVT, intravitreal; PAT, Preferences and Trends.

Stone TW et al. 2015 Preferences and Trends Membership Survey. American Society of Retina Specialists; Chicago, IL, USA.

USA 9%
Rest of the world 59.8%
Regional considerations

Possible reasons for regional variations

- Perceived as the standard of care in some regions
- Personal preference
- Medico-legal considerations
- Mandated by label in some regions (e.g., Japan)
- Resources and conditions vary between countries
Regional considerations

Possible reasons for regional variations

- Perceived as the standard of care in some regions
- Personal preference
- Medico-legal considerations
- Mandated by label in some regions (e.g., Japan)
- **Resources and conditions vary between countries**
IVT injection technique and monitoring: Updated guidelines from an expert panel

- The dramatic increase in the number of IVT injections has been accompanied by a comparable increase in evidence surrounding IVT practice patterns and techniques.
- An expert panel of ophthalmologists performed a review of the literature regarding IVT injections and concluded that:

IVT, intravitreal.
Avery RL et al. Retina 2014; 34: S1–S18.
IVT injection technique and monitoring: Updated guidelines from an expert panel

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- An expert panel of ophthalmologists performed a review of the literature regarding IVT injections and concluded that:
  - There was a lack of evidence to support the routine use of pre-, peri-, and post-injection antibiotics to reduce the risk of endophthalmitis.
  - There was a lack of evidence to support the role of aerosolized droplets containing oral contaminants from the patient and/or providers as a potential source of infection.

- The panel emphasized the continued importance of applying povidone-iodine and avoiding eyelid contact with the intended injection site and needle.
The dramatic increase in the number of IVT injections has been accompanied by a comparable increase in evidence surrounding IVT practice patterns and techniques.

An expert panel of ophthalmologists performed a review of the literature regarding IVT injections and concluded that:

- There was a lack of evidence to support the routine use of pre-, peri-, and postinjection antibiotics to reduce the rate of endophthalmitis.
- There was a lack of evidence to support the role of aerosolized droplets containing oral contaminants from the patient and/or providers as a potential source of infection.
- They are not against antibiotics!

The panel emphasized the continued importance of applying povidone-iodine and avoiding eyelid contact with the intended injection site and needle.

IVT, intravitreal.
Avery RL et al. Retina 2014; 34: S1–S18.
Is there a case for using topical antibiotics with IVT injections?

<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>
</tr>
</thead>
<tbody>
<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>
</tr>
<tr>
<td>Bhavsar et al. 2012</td>
<td>8027</td>
<td>DME and PDR</td>
<td>0.13%</td>
<td>0.03%</td>
<td>Not significant</td>
</tr>
<tr>
<td>Bhavsar et al. 2015</td>
<td>18,839</td>
<td>Multiple</td>
<td>0.005%</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Cheung et al. 2012</td>
<td>15,895</td>
<td>Multiple</td>
<td>0.061–0.084%</td>
<td>0.038%</td>
<td>Not significant</td>
</tr>
<tr>
<td>Falavarjani et al. 2013</td>
<td>5901</td>
<td>Multiple</td>
<td>0.10%</td>
<td>0%</td>
<td>Not significant</td>
</tr>
<tr>
<td>Falavarjani et al. 2015</td>
<td>8037</td>
<td>Multiple</td>
<td>0.01%</td>
<td>0%</td>
<td>Not significant</td>
</tr>
<tr>
<td>Meredith et al. 2015</td>
<td>18,509</td>
<td>Neovascular AMD</td>
<td>0.04–0.08%</td>
<td>0.15%</td>
<td>Not significant</td>
</tr>
<tr>
<td>Park et al. 2013</td>
<td>17,332</td>
<td>Multiple</td>
<td>0%</td>
<td>0.035%</td>
<td>Not significant</td>
</tr>
<tr>
<td>Porteous et al. 2014</td>
<td>6957</td>
<td>Not specified</td>
<td>Not applicable</td>
<td>0.04%</td>
<td>Not significant</td>
</tr>
<tr>
<td>Ramel et al. 2014</td>
<td>11,450</td>
<td>Not specified</td>
<td>0.03%</td>
<td>0.23%</td>
<td>p=0.024</td>
</tr>
<tr>
<td>Storey et al. 2014</td>
<td>117,171</td>
<td>Multiple</td>
<td>0.049%</td>
<td>0.032%</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

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

- A meta-analysis and consensus paper did not find any harm in prescribing antibiotics, and in some analyses, a lower risk for endophthalmitis was demonstrated.
- On a large-scale basis, and in various societies with diverse sanitary conditions, the need for antibiotics may vary and should still be considered.
Debate:
Topical antibiotics **SHOULD NOT** be used alongside intravitreal injections

Dr. Paisan Ruamviboonsuk
*Rajavithi Hospital, Thailand*
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<td>Novartis, Bayer</td>
<td>S</td>
</tr>
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</table>

C, consultant; S, grant support.
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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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 bacterial colony counts¹

- This benefit does not appear to translate to the use of topical antibiotics administered before an IVT 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%)⁴

*When given in addition to povidone-iodine.
IVT, intravitreal.
Pooled incidence of endophthalmitis

Review

POOLED ESTIMATES OF INCIDENCE OF ENDOPHTHALMITIS AFTER INTRAVITREAL INJECTION OF ANTI–VASCULAR ENDOTHELIAL GROWTH FACTOR AGENTS WITH AND WITHOUT TOPICAL ANTIBIOTIC PROPHYLAXIS

MICHELE REIBALDI, MD, PhD,* ALFREDO PULVIRENTI, PhD,† TERESIO AVITABILE, MD,* VINCENZA BONFIGLIO, MD, PhD,* ANDREA RUSSO, MD, PhD,* CESARE MARIOTTI, MD,‡ CLAUDIO BUCOLO, PhD,§ RODOLFO MASTROPASQUA, MD,§ GUGLIELMO PARISI, MD,* ANTONIO LONGO, MD, PhD*

Purpose: To assess the effect of topical antibiotic prophylaxis on postoperative endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents. Methods: A systematic literature search was performed from inception to March 2016 using PubMed, Medline, Web of Science, Embase, and the Cochrane Library, to identify articles that reported cases of endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents. We used a pooled analysis to estimate the incidence of cases of endophthalmitis who developed after injections performed with and without topical antibiotic prophylaxis. We used regression analysis to explore the effects of study characteristics on heterogeneity.

Results: From our search of electronic databases, we identified and screened 4,561 unique records. We judged 60 articles to have reported findings for cohorts of patients who met our inclusion criteria, (12 arms of randomized clinical trials, 11 prospective cohort studies, and 37 retrospective cohort studies), which included 244 cases of endophthalmitis and 639,391 intravitreal injections of anti–vascular endothelial growth factor agents. The final pooled estimate endophthalmitis proportions were 9/10,000 (95% confidence interval, 3.4–28.8; 19/10,000) in the antibiotic–prophylaxis group and 8/10,000 (95% confidence interval, 2.7–27.2).
The review paper by Reibaldi et al. identified and screened 4561 records; 60 articles met the inclusion criteria (12 arms of RCTs, 11 prospective cohorts, and 37 retrospective cohorts) and included 244 cases of endophthalmitis and 639,391 IVT injections of anti-VEGF.

The final pooled estimate of endophthalmitis proportions were:
- 9 / 10,000 (95% CI, 7 / 10,000–12 / 10,000) in the antibiotic-treated group
- 3 / 10,000 (95% CI, 2 / 10,000–5 / 10,000) in the untreated group

CI, confidence interval; IVT, intravitreal; RCTs, randomized controlled trials; VEGF, vascular endothelial growth factor. Reibaldi M et al. Retina 2018; 38 (1): 1–11.
Use of antibiotics can interfere with models of care

- For patients on a PRN regimen with monthly monitoring, a requirement for pre-injection antibiotics would mean that IVT injections could not take place during the monitoring visit\(^1\)
  - 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 year\(^2\)

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**Burden on the patient**
Additional clinic visits may affect adherence to treatment

**Burden on clinic capacity**
Increased clinic visits require resources and clinician time

**Burden on the healthcare system**
Increased costs of delivering IVT therapy

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IVT, intravitreal; PRN, pro re nata (as needed).
Use of topical antibiotics increases antibiotic resistance

**Percentage of patients with ocular colonies resistant to fluoroquinolones**

<table>
<thead>
<tr>
<th>No post-injection antibiotics</th>
<th>With post-injection fluoroquinolone</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 3 intraocular injections with post-injection antibiotics**

<table>
<thead>
<tr>
<th>Bacterial Isolates</th>
<th>Before antibiotic treatment (n=23)</th>
<th>After antibiotic treatment (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ofloxacin</td>
<td>p=0.003</td>
<td>85</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>p=0.003</td>
<td>52</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>p=0.009</td>
<td>39</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>p&lt;0.001</td>
<td>34</td>
</tr>
</tbody>
</table>

Use of povidone-iodine alone with IVT injections does not lead to bacterial resistance

IVT, intravitreal.
Lack of antibiotic penetration into the vitreous

- A prospective randomized study demonstrated that topical antibiotic administration leads to effective levels in the aqueous but not in the vitreous.
  - The concentrations in the vitreous did not exceed the MIC$_{90}$ for the most common bacterial pathogens causing acute postoperative endophthalmitis.

<table>
<thead>
<tr>
<th>Topical antibiotic</th>
<th>Mean vitreous concentration ± SD (μg/mL)</th>
<th>MIC$_{90}$ (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3-day pre-surgery regimen* (n=3)</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin 0.5%</td>
<td>0.011 ± 0.008</td>
<td></td>
</tr>
<tr>
<td>Gatifloxacin 0.3%</td>
<td>0.008 ± 0.006</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1-hour pre-surgery regimen† (n=3)</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin 0.5%</td>
<td>0.012 ± 0.011</td>
<td></td>
</tr>
<tr>
<td>Gatifloxacin 0.3%</td>
<td>0.001 ± 0.0003</td>
<td></td>
</tr>
</tbody>
</table>

MIC$_{90}$, minimum inhibitory concentration for 90% of isolates; SD, standard deviation.

*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.

What is the Vision Academy’s position?
Vision Academy Viewpoint:
Use of topical antibiotics with intravitreal injections

Based on an extensive literature search, the Vision Academy **does not** recommend the use of topical antibiotics alongside IVT injections.

- **There is no evidence** for the prevention of infection\(^1\)
- **There is no evidence** for a reduction in infection-related morbidity\(^2\)
- Repeated use of antibiotics is proven to **increase** the occurrence of **antibiotic resistance** and can potentially increase virulence\(^1\)
- **There is an additional and unnecessary cost and burden** to patients, physicians, and healthcare systems\(^1\)

IVT, intravitreal.
Vision Academy Viewpoint: Use of topical antibiotics with intravitreal injections

Topical antibiotic use **prior to** IVT 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** IVT injection

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

Vision Academy Viewpoint:
Use of topical antibiotics with intravitreal injections

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\(^3\)

Vision Academy Viewpoint:
Use of topical antibiotics with intravitreal injections

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

- Significant regional differences
- Challenge in changing clinical practice

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

IVT, intravitreal.
Summary

The Vision Academy does not recommend the use of topical antibiotics alongside IVT 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 IVT medications should be updated to reflect this recommendation and to remove barriers to clinicians wishing to change their practice