LEVELS OF EVIDENCE

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Not all therapeutic recommendations are based on evidence of equal quality. The following can be used to grade the quality of evidence which is submitted for a given medical intervention. This simple grading system is based solely on the design of the clinical study.

In this grading scheme, scientific evidence can range from level 1, which is the most scientifically valid, to level 5, which is the weakest form of evidence. The guidelines are summarized in the Table.

### Table. The Hierarchy of Published Evidence for Interventional Studies

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Description</th>
<th>Study example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Randomized clinical trial with low study errors or a meta-analysis</td>
<td>Optic neuritis treatment trial¹</td>
</tr>
<tr>
<td>2</td>
<td>Randomized clinical trial with high study errors; usually “underpowered” (high type II error)</td>
<td>Scatter laser photocoagulation for occult choroidal neovascularization²</td>
</tr>
<tr>
<td>3</td>
<td>Clinical trial with a control group, with nonrandom treatment allocation</td>
<td>Thrombolytic therapy for acute retinal arterial occlusion³</td>
</tr>
<tr>
<td>4</td>
<td>Intervention case series</td>
<td>Macular translocation surgery for the treatment of CNVM and AMD⁴</td>
</tr>
<tr>
<td>5</td>
<td>Interventional case report</td>
<td>Removal of a choroidal neovascular membrane⁵</td>
</tr>
</tbody>
</table>

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### Level 1 Evidence

Level 1 evidence can come in one of 2 forms: a randomized clinical trial, which is associated with low study errors (low P value, confidence interval which excludes 1, or a “negative” result associated with a power of over 80%), or a meta-analysis. A meta-analysis refers to a study that statistically synthesizes the results of numerous “underpowered” randomized clinical trials and increases the confidence in an overall summary result. Unfortunately, limitations of meta-analyses include heterogeneity and publication bias. The Optic Neuritis Treatment Trial¹ is an example of a randomized clinical trial which contains level 1 evidence.

### Level 2 Evidence

Level 2 evidence is also derived from randomized clinical trials. These trials compare the outcome of those in the treatment group to those who receive no treatment. The treatment allocation in these trials is random in nature. With random treatment allocation, theoretically, known and unknown confounders are equally distributed between the two groups. Results of randomized clinical trials are classified as level 2 evidence when they are associated with an unacceptably high type I (alpha) or II (beta) study error. A type I error is the possibility of demonstrating a treatment effect when none exists. A type II error is the failure to detect a treatment effect when one, in fact, exists. Most of the clinical trials classified as level 2 evidence are “underpowered.” This means that not enough patients may have been enrolled in the study to detect a significant difference. A very large treatment effect can sometimes be ruled out, but a smaller one that is still clinically relevant may still exist. In a “pilot” study, Bressler et al.² noted that patients with subfoveal neovascularization fared no better after scatter laser photocoagulation than those who received no treatment. Assuming that 40% of patients with no treatment will develop severe visual loss, an alpha of 0.05, and a beta of 0.20, 83 patients would have been necessary in each treatment arm to detect a 50% reduction in severe visual loss. With only 29 patients in the treatment arm and 26 in the control group, the negative result in this study may have been related to the trial’s limited sample size.

### Level 3 Evidence

Level 3 evidence is derived from non-randomized, controlled clinical trials. In
these studies, patients who receive an intervention are compared to a control group. Authors may detect a statistically significant and clinically relevant outcome, but the reader is unsure of whether the outcome differences are caused by the treatment or some other factor which was not balanced between the two groups. Schmidt et al. were able to demonstrate an improvement in visual acuity in patients who received thrombolytic therapy as compared to those who did not receive this therapy. However, despite the impressive treatment effect observed in this trial, the reader is unsure of how the two groups compared in terms of possible known confounders, such as ipsilateral carotid disease, ocular hypertension, and possible unknown confounders.

Level 4 Evidence
Level 4 evidence, the case series, comes in the form of a group of patients subjected to a medical intervention or surgical procedure. In this study type, authors report on how a series of patients responds to a given intervention. The inherent limitation in this study is that the reader is unsure of how patients subjected to this procedure compare to those who are untreated or receive an alternate form of therapy. It should be noted that these studies do play a very important role as they often result in hypothesis generation; therefore, they are a necessary precursor to an analytic study. No one can argue against the importance of the level 4 evidence submitted by Meyer-Schwickerath and Schott, who described the first series of patients who received laser treatment for the management of diabetic retinopathy.

Level 5 Evidence
Interventional case reports can be classified as level 5 evidence. In an interventional case report, a single patient is subjected to an intervention. These studies often serve to report a novel intervention. As an example of an interventional study which can be classified as level 5 evidence, Connor et al. revealed that surgical removal of an extrafoveal choroidal neovascular membrane resulted in an improvement of visual acuity from 20/200 to 20/25. The primary limitation of a case report is that the reader is unsure of how the next patient who is subjected to the procedure will respond.

Two important points should be made about the levels of evidence pertaining to interventional studies. First, these levels of evidence are based on the study design and nothing else. It may be argued that there are other variables that strengthen a study’s validity (i.e., the reputations of the researchers, prospective versus retrospective designs, how patients and controls were selected in nonrandomized studies). Although this is true, we adopted the present scheme because it is simple, user-friendly, and it incorporates the essentials of the scientific process. Second, although we urge clinicians to practice ophthalmology based on studies of the highest quality, a randomized clinical trial or meta-analysis does not always exist to answer a specific therapeutic treatment. In these situations, there are two possible actions that can be taken: offer no treatment until level 1 evidence becomes available, or offer treatment based on the next highest level of evidence. Clearly, in this situation, a given patient’s input is a necessity.

References