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Medical Retina

With 91 Figures, Mostly in Colour
and 13 Tables

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Chapter 5

Intravitreal Injections: Techniques and Sequelae

5

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Core Messages

- Through the introduction of new treatment strategies for exudative age-related macular degeneration, the number of intravitreal injections has increased dramatically over the past few years. It is likely that this form of therapy will become the most common surgical intervention in ophthalmology within a short period of time.
- Although severe ocular adverse events associated with intraocular injections are rare, the rate can increase significantly if certain standards for intraocular interventions are not followed. Several guidelines on the technique for intravitreal injections have been published in recent years. Strict adherence to these guidelines is advisable.
- Endophthalmitis is the most feared complication of intravitreal injections. It is usually caused by bacterial contamination during or immediately after the injection and occurs in about 0.1% of injections and in about 1% of patients with repeated injections.
- Ocular hypertension and cataract development are not typically seen after anti-VEGF therapy.
- Based on the studies and data currently available, no major difference in the risk profile of the anti-VEGF drugs used at present can be seen.
- Triamcinolone is associated with a higher rate of secondary ocular hypertension (40%) and need for glaucoma surgery (1%) than anti-VEGF agents. It also has a higher rate of cataract progression in about 40% of patients within the first year of treatment.

5.1 Introduction

The introduction of new drugs for the treatment of age-related macular degeneration (AMD) has led to a significant change in ophthalmological practice. Until a few years ago, intravitreal injections were reserved for a small number of rare diseases (e.g., endophthalmitis, viral retinitis). Within a short period of time, the numbers of injections have increased and are now second only to cataract surgery as the most common treatment in most tertiary centers across Europe and the United States. It is likely that intravitreal injections with the anti-vascular endothelial growth factor (VEGF) type of action will soon become the most common intraocular procedure performed worldwide. With intravitreal injection we can obtain a high intraocular concentration of a drug, with minimal systemic exposure.

This tremendous and rapid change indicates a significant challenge for ophthalmological units; a tidal wave of intraocular injections, re-injections, and follow-up examinations has to be integrated into daily routine without compromising patients' safety. It is therefore mandatory to maintain essential safety standards for all injections whilst avoiding unnecessary and costly examinations and safety measures. In order to maximize

the number of patients that can be treated, the workload associated with each patient has to be minimized within the treating unit; therefore, it is likely that more and more pre- and postoperative examinations will be shifted to places outside the centers where the injections are performed. In a relatively short period of time, ophthalmologists and optometrists who are currently not performing intraocular injections will be confronted with a larger number of patients following intravitreal injections. In this chapter, the techniques, complications, and guidelines for intravitreal injections are reviewed. Because of the recent shift in the application of intravitreal drugs, the chapter focuses on studies of anti-VEGF substances and triamcinolone.

5.2 Complications of Intravitreal Injections

With an appropriate technique, the intravitreal injection of a drug is a straightforward surgical procedure that carries a low rate of serious complications (Table 5.1). Yet, the first published multicenter study showed that the disregard

Table 5.1 Complications of intravitreal injections

Complication	Peri-operative	Early (>7 days)	Late (>7 days)	Incidence	Related to injected substance
Conjunctival hemorrhage	X	X		~20–40%	–
Conjunctival scarring			X		
Punctate keratitis	X	X		~30%	–
Pain	X	X		~30%	
Traumatic cataract	X	X	X	<1%	–
Cataract progression			X	First year: ~15% ~40% (triamcinolone)	X
Central retinal artery occlusion	X	X		<1%	–
Vitreous reflux	X	X		~20%	–
Vitreous hemorrhage	X	X	X	<1%	–
Vitreous floaters	X	X	X	~30%	X
Intraocular inflammation	X	X		~20%	X
Uveitis/pseudo-endophthalmitis		X		~1%	X
Endophthalmitis		X	X	~0.15% per injection ~1% per patient with multiple injections	X
Retinal detachment		X	X	<1%	–
Ocular hypertension	X	X	X	Triamcinolone ~40%	X

of basic standards for intraocular surgery can quickly increase the rate of complications to unacceptable levels. In the initial stages of the VISION trial, the rates of bacterial endophthalmitis were more than 4-fold higher than those after routine cataract surgery [8, 14]. Serious adverse events occurred in 19% of patients (169 out of 892), although serious adverse events were also noted in 15% of patients (45 out of 298) with sham treatment [8]. These figures underline that intravitreal injections should be treated as intraocular surgery and conducted according to the standards applied to all intraocular procedures, e.g., asepsis of the operating field and a sterile technique throughout the process. Even with the greatest care, complications associated with intravitreal injections will never be avoided completely; however, as demonstrated in the recent large prospective trials, in only very few cases will these complications lead to a long-term reduction in visual acuity or discontinuation of the treatment if dealt with in a timely and appropriate fashion [4, 8, 14, 29].

5.2.1 Methodology

In this chapter, the complications associated with intraocular injections are reviewed. A methodological review is flawed by several problems:

1. The most serious side effects of intravitreal injections (e.g., endophthalmitis, retinal detachment, glaucoma, cataract) are rare following anti-VEGF treatment and occur in less than 1% of injections and in about 1–2% of patients undergoing repeated injections. Only randomized prospective trials with large patient numbers are able to reflect the true rate of complications associated with the drug examined and the treatment protocol applied. Such trials have been published for pegaptanib and ranibizumab (Table 5.2) [4, 8, 14, 29].
2. For the two other currently most commonly used drugs, bevacizumab and triamcinolone, such studies do not exist and it is unlikely that this will be the case in the near future.
3. Other important, potentially sight-threatening complications of injections are intraocular inflammation, cataract development, and a rise in intraocular pressure (IOP). The examination methods, time points, and definitions for the detection of these complications vary from study to study.
4. Different protocols for the performance of intravitreal injections have been used. The differences in the injection technique (e.g., subconjunctival anesthesia, perioperative drug treatment, etc.) can have a significant influence on the complication rate.

5.2.2 Perioperative Complications

Complications following intravitreal injections can be divided according to their occurrence into perioperative, early postoperative, and late (Table 5.1). Furthermore, complications from the intraocular injection procedure itself have to be distinguished from possible biological side-effects of the injected substance.

5.2.2.1 Conjunctival Hemorrhage

Conjunctival hemorrhage is related to the trauma caused by manipulations during the injection, e.g., forceps or needle injuries. Obviously, when subconjunctival anesthesia is used, the need for two injections increases the risk of this complication. In one series, subconjunctival hemorrhages could be seen in 18% of patients with intravitreal injections and topical anesthesia versus 40% in patients with subconjunctival anesthesia [22]. Nevertheless, even with topical anesthesia, hemorrhage can be seen in up to 37% of patients [7].

In the vast majority of cases, conjunctival hemorrhages is more cosmetically disturbing than harmful. They clear spontaneously within 7–14 days and do not require any therapy. Very rarely, they can progress to cause significant anterior segment problems that require surgical intervention. The risk of significant conjunctival hemorrhage seems to be increased in patients with anticoagulant therapy, e.g., warfarin [15]. In contrast to their relative insignificance in the majority of cases, conjunctival hemorrhage is often perceived as a serious side-effect from the patients' point of view. Particularly in an outpatient setting without a scheduled short-term follow-up examination, patients have to be instructed about

Table 5.2 Ocular adverse events in studies of pegaptanib and ranibizumab

	Follow-up (months)	Number of patients	Number of injections	Endophthalmitis (*n*)	Per patient (%)	Per injection (%)
Pegaptanib						
VISION [14]						
0.3 mg		295				
1.0 mg		301				
3.0 mg		296				
First year	12	892	7,545	12	1.3	0.16
Second year		374	4,091	4	1.0	0.1
Ranibizumab						
MARINA [29]						
0.3 mg	24	238	NA	2	0.8	
0.5 mg	24	240	NA	3	1.2	
Total		478	10,443	5	1.0	0.05
ANCHOR [4]	12					
0.3 mg	12	137	1,507	0	0	0
0.5 mg	12	140	1,568	2	0.14	
Total		277	3,075	2	0.07	0.006
Control groups						
VISION (sham injection)	24	298				
ANCHOR (PDT)	12	140			0	
MARINA (sham injection)	24	238			0	

Inflammation (%)	Uveitis (%)	Cataract (%)	Cataract surgery (%)	Glaucoma (%)		Retinal detachment (%)
16		Split in different grades, highest grade 17%		>35 mmHg 9		
14		18		9		1
13		22		15		0.3
			<1			
						1.6
17	1.2	15	5.1	>30 mmHg 13.0	>40 mmHg 2.3	–
21	1.2	15	7.2	17.6	2.3	–
19	1.2		6.1			–
12		11	5.3	>30 mmHg 8.8	>40 mmHg 2.9	0.7
8		12.9	1.2	8.6	2.9	–
						0.3
16		26	18			
3		7.0	0	>30 mmHg 4.2	>40 mmHg 0.7	0.7
12	0	15.7		>30 mmHg 3.4	>40 mmHg 0	0.4

their appearance and natural course. Strategies to minimize their incidence include the use of topical versus subconjunctival anesthesia and the use of a cotton bud for conjunctival manipulation instead of forceps.

5.2.2.2 Conjunctival Scarring

Repeat injections, especially when combined with subconjunctival anesthesia, will lead to conjunctival scarring. Significant conjunctival scarring or ocular surface disorders as a result of multiple intravitreal injections have not been reported in larger studies to date. However, if repeated injections are necessary, it is recommended to record the position of the injection and to avoid repeated injection in the same location if possible.

5.2.2.3 Pain

Pain can be related to the anesthesia, the needle entry through the conjunctiva and sclera, and the rise in IOP associated with the injection. When subconjunctival anesthesia is used, patients experience pain associated with the subconjunctival injection, but less pain when the needle enters the posterior segment. In the VISION trial, 34% of patients (subconjunctival anesthesia and intravitreal injection) versus 28% of the controls (subconjunctival anesthesia and sham injection) experienced pain [8]. When topical anesthesia is used, the pain associated with the subconjunctival injection is avoided; however, the intravitreal injection is more painful [22]. Overall, the patients' expected levels of pain and discomfort are usually greater than those from the actual experience [30].

5.2.2.4 Punctate Keratitis and Corneal Edema

Punctate keratitis was detected in 32% of patients in the VISION trial versus 27% of controls [8]. It has not been noted as a complication in other trials. The most likely cause is a combination of the anesthesia of the ocular surface, a reduced blink reflex after corneal anesthesia, flushing of the corneal surface with antiseptic solution, the prolonged exposure of the cornea for the duration of the injection, and irregularities of the ocular surface after the injection. A combination of these factors and the intermittent rise in IOP can also cause corneal edema; this was noted in 9% of patients in the VISION trial [8]. However, to date there are no suggestions that the corneal surface or the corneal endothelium can be affected through a direct toxic effect of the injected substances. To avoid damage to the corneal epithelium, the exposure time following topical anesthesia should be minimized. Alternatively, ocular lubricants can be applied following the procedure.

5.2.2.5 Vitreous Reflux

The intravitreal injection of 0.1 ml of fluid is associated with a rise in IOP to around 45 mmHg [3]. During removal of the needle, vitreous, liquefied vitreous or fluid can exit the posterior segment through the needle path into the subconjunctival space or transconjunctivally to the ocular surface. This phenomenon can be observed in about 20% of injections [3]. Two problems can be associated with a vitreous prolapse:

1. A substantial amount of the injected drug can be misplaced.
2. A "vitreous wick" can serve as an entry site for bacteria from the ocular surface and may significantly increase the risk of postoperative endophthalmitis [5].

The rate of vitreous reflux is dependent on the needle, the injected volume, the consequential rise in IOP, and the injection technique used. Vitreous reflux can be avoided using sharp small-gauge needles (e.g., 27-, 30- or 31-gauge) and/or a short scleral tunnel for injection by pulling the conjunctiva over the injection site and using a slightly angled scleral path with the injection needle.

5.2.2.6 Traumatic Cataract

With the appropriate training of surgeons carrying out the injection and the injection technique, the rate of traumatic cataract should be minimal. Yet, sudden head movements of the patient or ac-

cidental moving of the needle tip toward the lens can never be fully avoided, and even intralenticular injections have been reported [19].

In the VISION trial, the rate of traumatic cataract was 0.07% (5 out of 892) [8]. The importance of the appropriate injection technique is underlined by the fact that, in this trial, 2 of the 5 lens injuries occurred on the same day in one center [8]. In the MARINA trial, lens damage was noted in 0.2% (1 out of 477) [29]. In the ANCHOR trial, no lens damage was noted during the first year in 277 patients with multiple injections [4].

5.2.2.7 Cataract Progression

Any intraocular manipulation is likely to be associated with an increase in cataract formation over time. The analysis of this complication is made difficult by several factors:

1. Different systems for grading and diverse definitions of "cataract progression" have been used in studies on intravitreal injections.
2. The systems for cataract grading currently used are still biased by subjective differences in the grading of lens opacities by different examiners.
3. The majority of published studies are retrospective in nature and a precise recording of cataract progression does not seem to be achievable with such study designs.
4. A difference in cataract progression may only be seen after several years of follow-up. To date, most studies cannot provide the necessary data because follow-ups are limited to 1 or 2 years.
5. A significant amount of cataract progression is likely to occur in the age group of patients with AMD unrelated to any intervention.

The latter is underlined by the rates of cataract progression that were noted in the control groups of prospective trials. These were 16% in the MARINA trial (sham injection), 7% in the ANCHOR trial (photodynamic therapy + sham injection), and 26% in the VISION trial (sham injection) [4, 8, 14, 29]. In comparison, similar or slightly higher rates of cataract progression could be noted in the treatment groups (MARINA 15%, ANCHOR 11–13%, and VISION 17–22%) [4, 8, 14, 29]. Very few patients underwent cataract surgery during the trial periods in these studies. Overall, there seems to be little or no cataractogenicity of repeated intraocular injections with anti-VEGF substances compared with their respective control groups within the first 2 years.

In contrast to the intravitreal application of anti-VEGF substances, intravitreal triamcinolone is associated with a higher rate of cataract development. By and large, cataract surgery has been performed in 20–45% of patients within the first year of the initial injection [21, 33]. The rate of cataract formation and consecutive surgery is time-dependent. In a prospective 2-year trial, cataract surgery was performed in 54% of patients (15 out of 28) with diabetic macular edema treated with intravitreal triamcinolone compared with 0% (0 out of 21) in the control group [12].

The cataractogenicity of local and systemic steroids has long been established; yet, the precise mechanisms are not clearly understood [20]. In the majority of cases, steroid use is associated with posterior subcapsular cataract formation. In addition, cortical cataracts and, to a lesser extent, nuclear cataract progression can also be seen following intravitreal triamcinolone injection [11, 33]. Interestingly, there seems to be a highly significant association of the second major complication of intravitreal triamcinolone, the rise in IOP, with the progression of subcapsular posterior and cortical cataracts [11]. A higher rate of cataract progression should therefore be expected in patients who are classified as steroid responders according to a rise in IOP following the injection.

5.2.2.8 Retinal Perforation

Entering the posterior segment with a sharp instrument carries the potential risk of retinal injury. This can occur when the entry site is too posterior (>5 mm), the needle is too long and advanced too far, the needle is pointed in the wrong direction or detached retina or choroid are in the way of the needle. No such retinal injuries have been reported in recent multicenter trials [4, 8, 14, 29]. Inspection of the retinal periphery before and after the injection should be included in the routine injection procedure. With appropriate training of surgeons, retinal injuries should be avoidable.

5.2.2.9 Vitreous Floaters

Vitreous floaters are commonly noticed by patients following intravitreal injections. In the VISION trial, they were perceived in 33% of patients in the treatment group versus 8% of patients with sham injections [14]. Due to the crystalline structure of the injected substance, floaters are more prevalent following triamcinolone injections. Floaters usually subside within the first week without the need for additional therapeutical measures.

5.2.2.10 Vitreous Hemorrhage

Vitreous hemorrhage is another potential complication of intravitreal injections. It can be caused by the injection itself during which the needle penetrates the choroids to reach the posterior chamber as well as by post-injection changes within the vitreous, leading to vitreous traction with preretinal hemorrhage. Its incidence, however, is relatively low; furthermore, the diseases most commonly treated with intravitreal injections, e.g., exudative AMD or diabetic retinopathy, are frequently associated with vitreous hemorrhage not related to surgical interventions.

In the VISION trial, the rate of vitreous hemorrhage was 0.21% (16 out of 7,545) [8]. However, only 9 of the 16 incidents were judged to be associated with the injection procedure. In the MARINA trial, the rates of vitreous hemorrhage were 0.4% (2 out of 477) in the treatment group versus 0.8% (2 out of 236) in the group with sham treatment [29]. Usually, no treatment is required for vitreous hemorrhage secondary to intravitreal injections. Pars plana vitrectomy can be considered in advanced cases or those without spontaneous regression.

5.2.2.11 Retinal Toxicity

Retinal toxicity is a potential complication of intravitreally applied drugs. Such toxicity, can lead to changes in the electroretinogram, may cause visible changes through alterations of the fundus pigmentation and can lead to gross photoreceptor and macular malfunction. Cases of retinal toxicity or presumed toxicity have been documented following intravitreal application of tissue plasminogen activator, methotrexate, amikacin and hyaluronidase [6, 17, 35].

So far, there have been no reports of presumed toxicity of anti-VEGF drugs, including bevacizumab, in vivo or in vitro with the currently used dose regimen [4, 8, 10, 29]. However, some concerns remain that constant VEGF suppression might increase the long-term risks of toxicities for retinal tissue [25].

The question of possible toxicity of triamcinolone has been raised in in vitro studies on rabbits and on cultured human retinal pigment epithelial (RPE) cells [32, 36]. This toxicity has been linked to the concentration of the drug, the preservative in commercial preparations or the direct contact of the triamcinolone crystals with the retina [21, 32, 36]. In clinical series, no evidence of triamcinolone toxicity has been reported so far [21].

5.2.2.12 Intraocular Inflammation

Anti-VEGF substances are humanized antibodies, or aptamers, that potentially can cause an intraocular immune reaction. Clinical studies have therefore specifically looked at intraocular inflammation following their intravitreal application. Intraocular inflammatory cells, however, can also be seen after any manipulation of the eye or the ocular adnexa, including intravitreal injections or sham injections.

A dose-related increase in intraocular inflammation has been documented for two drugs after intravitreal application, ranibizumab and hyaluronidase. Early phase I/II studies of ranibizumab were associated with a relatively high rate of low-grade to moderate intraocular inflammation in up to 78% of patients [16]. This might have been due to the lyophilized preparation of the antibody. In a further dose-escalating study, Rosenfeld et al. found a dose-dependent response; injections up to 500 μg of ranibizumab seem to be well tolerated, but higher doses were accompanied by more intraocular inflammation [28]. In the large prospective clinical trials of ranibizumab (up to 500 μg) and pegaptanib (up to 3 mg), the rates of (mostly low-grade) anterior and posterior chamber inflammation were

significantly lower and were seen in up to 20% within the treatment groups. There was no correlation between the level of intraocular inflammation and the injected drug dose and a comparable rate and severity of events could be seen in the respective control groups [4, 8, 14, 29]. Typically, intraocular inflammations following ranibizumab and pegaptanib can be seen on day 1 after the injection and usually subside without treatment within 14 days. Anti-inflammatory treatment is not necessary in most cases. There does not seem to be an increased risk of more severe inflammation with repeated injections that would indicate an amplification of the immune response as a reaction to the injected proteins. In contrast, lower intraocular inflammation scores were seen following repeated injections in a dose-escalating study with more frequent and higher dosed injections compared with the currently recommended doses of ranibizumab [28].

Another drug that was documented to cause a biological reaction following intravitreal injection is bovine hyaluronidase. Increased intraocular inflammatory responses with a dose relationship could be seen. The rates of moderate or severe iritis in the study by Kupperman et al. were 0% (observation) and 8% (saline injection) in the control groups versus 20% (7.5 IU hyaluronidase), 37% (55 IU), and 40% (75 IU) [24] in the treatment groups.

Intraocular inflammatory reactions (with the exception of pseudo-endophthalmitis or endophthalmitis, see Sect. 5.2.2.13) do not seem to be a particular problem following intravitreal triamcinolone [21]. When injected into the anterior chamber and capsular bag following routine cataract surgery, there is a dose-related reduction of the anterior chamber inflammatory response [13]. In one series of 759 consecutive intravitreal injections, no significant anterior chamber reaction could be noted [23]. This is probably due to the immunosuppressive effect of the drug.

5.2.2.13 Uveitis and Pseudo-endophthalmitis

The vast majority of inflammatory reactions in the anterior and posterior chamber following intravitreal injections are of low grade and do not require any treatment. They are usually thought to be associated with the injection procedure. Occasionally, severe intraocular inflammatory reactions can be seen. In these rare cases it is important, although sometimes extremely difficult, to differentiate a sterile inflammatory process from an inflammatory reaction associated with infectious endophthalmitis. To complicate things further, the term "pseudo-endophthalmitis" has been introduced. This has almost exclusively been used for severe intraocular inflammations following intravitreal triamcinolone injections.

Low-grade inflammatory reactions following intravitreal injections are thought to be a reaction to the injection procedure, whereas severe, noninfectious reactions might be caused by the drug itself (or its solvent) [29]. To distinguish low-grade inflammation from clinically significant inflammatory reactions, the latter are often classified as uveitis. In a phase I/II study of ranibizumab, one case of a severe recurrent uveitis was noted [16]; the uveitis recurred after each injection of the drug, underlining the likelihood of a biological reaction to the injected antibody. In the larger prospective studies of ranibizumab, uveitis could be seen in 1 of the 277 cases in the ANCHOR trial and in 1.2% of cases (6 out of 478) in the MARINA trial. In the Bevacizumab Safety Survey, 10 cases of uveitis out of a total of 5,228 patients (0.19%) were reported [10]. No severe intraocular inflammations other than endophthalmitis were reported to occur following pegaptanib injection in the VISION trial [14].

Pseudo-endophthalmitis (synonyms: sterile, noninfectious or toxic endophthalmitis) is characterized by intraocular changes or a severe inflammatory reaction mimicking the clinical picture of infectious endophthalmitis. This reaction is almost exclusively seen following intravitreal injection of unaltered, commercially available triamcinolone. Three different paths can lead to its manifestation:

1. Immune reaction to the vehicle of the injected drug, leading to severe intraocular uveitis.
2. Collection of triamcinolone crystals in the anterior chamber, mimicking the picture of a hypopyon. This can particularly seen in eyes with previous vitrectomy and defects in the lens capsule or zonular fibers, or when part

of the injected triamcinolone is misdirected alongside the anterior vitreous surface.
3. The crushing of triamcinolone crystals in small-gauge cannulae (30- or 31-gauge), leading to an almost immediate and dense vitreous haze following the injection.

There is no unambiguous clinical sign to differentiate pseudo-endophthalmitis from infectious endophthalmitis. However, some clinical features are more commonly associated with pseudo-endophthalmitis:
1. Clinical signs develop within the first few hours of the injection. This does not exclude infectious endophthalmitis, but newly diagnosed intraocular inflammation days after the injection should is more indicative of infectious endophthalmitis and rather than pseudo-endophthalmitis.
2. Pain, periorbital swelling and photophobia are usually absent in pseudo-endophthalmitis. However, it should be kept in mind that pain is also absent in about 20% of infectious endophthalmitis.
3. Dense vitreous infiltrates and pseudo-hypopyon seen in pseudo-endophthalmitis are accompanied by a relatively low-grade anterior chamber reaction (e.g., very few anterior chamber cells above the crystals).
4. Anterior chamber taps or vitreous biopsies fail to isolate bacterial or fungal organisms.

Some authors advocate purification of commercially available triamcinolone before intravitreal injection in order to eliminate the vehicle and to lower the occurrence of toxic reactions. With this technique, only one case of pseudo-endophthalmitis could be seen after 759 injections in a series by Kreissig et al. [23]. In contrast, in a series of 922 injections without removal of the vehicle, 8 cases of pseudo-endophthalmitis were seen (0.87%) [26].

Pseudo-endophthalmitis usually subsides without any specific therapy over 7–14 days. In contrast, infectious endophthalmitis can progress extremely quickly without appropriate treatment with potentially devastating consequences. Weighing the potential risks of treating a case of pseudo-endophthalmitis with intraocular antibiotics against delaying treatment of infectious endophthalmitis, it seems justified to recommend treatment with intraocular antibiotics in uncertain cases.

5.2.2.14 Endophthalmitis

Infectious endophthalmitis is the most feared complication of intravitreal injections and has been reported after application of all currently used preparations. The prevention of postoperative endophthalmitis is one of the key issues influencing the organization and implementation of intravitreal injections on a larger scale. The first large multicenter studies of intravitreal anti-VEGF treatment revealed several problems that need to be considered when integrating this type of therapy into routine practice:
1. The endophthalmitis rates per patient following repeated intraocular injections are significantly higher than rates reported after routine cataract surgery. This underlines the importance of appropriate hygiene standards and techniques for intraocular injections.
2. The rate of endophthalmitis can be lowered by adherence to certain standards, e.g., sterile environment, and appropriate disinfection [8]. This, in return, has a major impact on the costs and the logistics of patient treatment.
3. With timely and appropriate treatment, devastating outcomes can be avoided and the majority of patients will go on and continue the therapy if more injections are needed [8].

Prevention and timely treatment are key issues to lower the rates of post-injection endophthalmitis and its potentially devastating outcomes. This concerns not only the injection itself, but also the pre-operative examination and postoperative care of the patient:
1. Patients with acute or chronic infections of the anterior segment and ocular adnexa, e.g., conjunctivitis or blepharitis, should first undergo treatment of the infectious disease before proceeding to the injection.
2. The preparation of the ocular surface should aim to minimize the bacterial contamination during the injection. Additional measures, e.g., sterile drapes and the use of a lid speculum, have been associated with a decrease in postoperative endophthalmitis in one study [8].

3. The preparation of drugs and any modification processes (e.g., separation from the solvent of commercially available triamcinolone) have to be performed under sterile conditions.
4. Patients at higher risk of endophthalmitis (e.g., those post-filtering surgery, with immunosuppression, with diabetes) have to be identified, informed about their increased risk and monitored more closely.
5. Patients have to be informed about possible signs and symptoms of endophthalmitis.
6. Patients should be provided with clear instructions and pathways of whom to contact and where to be examined if symptoms or signs of endophthalmitis develop.
7. Ophthalmologists performing intravitreal injections should be familiar with the current treatment recommendations for postoperative endophthalmitis and should be able to perform an injection of intravitreal antibiotics in cases of presumed infectious endophthalmitis. Any delay in initiation of treatment can lower the chances of a successful treatment outcome.
8. Patients with routine topical eye medications (e.g., glaucoma drops or artificial tears) should discard their old eye drop bottles and resume with new bottles due to the possibility of bacterial contamination of old opened bottles.

Currently, it is unclear whether or not scheduled follow-up visits can lower the rate of devastating outcomes in cases of infectious endophthalmitis, e.g., by detecting clinical signs of endophthalmitis before patients become symptomatic and seek medical attention. The necessity of follow-up visits, the extent of these examinations, their frequency and timing would depend on such information, and this would have a major impact on the costs and logistics of routine application of intravitreal drugs. No universally accepted guidelines have been established on this matter so far and recommendations regarding postoperative follow-up examinations differ significantly between studies and current guidelines (Table 5.1).

In the three major trials published on intravitreal anti-VEGF therapy, endophthalmitis rates were between 0.006% and 0.16% per injection and between 0.07% and 1.3% per patient [4, 8, 14, 29]. There were a total of 19 cases of presumed infectious endophthalmitis, with 11 out of 19 being culture-positive. The most commonly isolated organism was *Staphylococcus aureus*. In the Bevacizumab Safety Survey, 1 case of endophthalmitis in 5,228 patients with 7,113 injections has been reported [10]. However, these data come from a self-reporting survey with the potential of under-reporting serious adverse events.

Post-injection endophthalmitis has been a particular concern in conjunction with the intravitreal use of triamcinolone. In a review of 922 patients treated at different institutions with intravitreal triamcinolone, 8 patients with infectious endophthalmitis were identified, leading to an endophthalmitis rate of 0.87% [26]. In contrast, Kreissig et al. observed only 1 case of endophthalmitis following 759 injections (0.1%) in 645 eyes (0.1%) [23]. There are differences between infectious endophthalmitis following intravitreal injection of triamcinolone and that after anti-VEGF therapy or other intravitreally applied drugs:

1. There seems to be a higher risk of infectious endophthalmitis following triamcinolone injection. This is likely to be due to the immunosuppressive steroid effect of the drug. Also, more patients at higher risk of endophthalmitis are usually included in the populations treated with triamcinolone (e.g., those with diabetes).
2. Severe pain associated with the onset of endophthalmitis seems to be less common.
3. The clinical course is often prolonged, but more foudroyant, and the rate of eyes with total visual loss, phthisis or enucleation may be higher compared with other causes of infectious post-injection endophthalmitis.
4. The spectrum of cultured organism shows a greater variation of different bacterial species causing endophthalmitis.
5. The histology of enucleated globes demonstrates differences with regard to the morphology of the inflammatory infiltrations, possibly due to local variation in the triamcinolone concentration and its immunosuppressive effects.

The current first-line treatment for infectious endophthalmitis is intravitreal injection of antibiotics and/or pars plana vitrectomy in advanced cases. The choice of antibiotic depends on the

suspected organism. Usually, a broad spectrum antibiotic is chosen because in most cases, therapy has to be initiated before culture results are available. Because the majority of cultured species are gram-positive bacteria, vancomycin (1 mg/0.1 ml) has been the most commonly used agent. Cephalosporins, e.g., ceftazidime (2.25 mg/0.1 ml), cover some gram-negative bacteria as well. Aminoglycosides, e.g., amikacin (0.4 mg/0.1 ml), have a broad gram-negative coverage, but have been associated with retinal toxicity [35].

Reported outcomes of endophthalmitis following intravitreal injections with pegaptanib have been surprisingly good compared with postoperative endophthalmitis of other etiology. In the VISION trial, only 1 out of 12 cases of endophthalmitis suffered a significant visual loss and 8 were within 10 letters of visual loss compared with baseline [8]. In contrast, 5 out of 8 cases with bacterial endophthalmitis following triamcinolone injection had a significant decrease in visual acuity, with 3 eyes losing light perception [26]. One of the reasons for the good outcomes of endophthalmitis in the VISION trial might be the intensified instructions and methodical follow-up examinations of patients participating in such well-conducted clinical trials. It underlines the importance of these aspects to routine intravitreal therapy in day-to-day practice.

Summary for the Clinician

- Infectious endophthalmitis following intravitreal injections typically occurs within the first week of injection.
- About two thirds of cases are culture-positive, e.g., *Staphylococcus aureus*.
- Clinical signs are periocular pain, swelling, redness, photophobia, decrease in visual acuity.
- There is a good outcome in the majority of cases when treated promptly.
- Treatment is with intravitreal injections of antibiotics, e.g., vancomycin (1 mg/0.1 ml) or ceftazidime (2.25 mg/0.1 ml).

5.2.2.15 Retinal Artery and Vein Occlusion

Central retinal artery occlusions can be observed in patients with an acute and extreme increase in IOP immediately after the injection. It is an unusual finding if a volume of 0.5 ml is injected. In the VISION trial, 4 cases out of 7,545 injections were reported [8]. All cases resolved after paracentesis without long-term complications. Checking the visual acuity should be performed immediately after the injection. Patients with central retinal artery occlusion usually have no light perception. Most current guidelines also recommend performing ophthalmoscopy to check perfusion of the retinal artery after the injection.

Retinal artery or vein occlusions outside the immediate postoperative course are even rarer. One case of a central retinal artery occlusion has been reported in the Bevacizumab Safety Survey [10]. Single cases of retinal arterial emboli and vein occlusion were reported by Heier et al. following ranibizumab injections [16]. No other retinal vascular occlusion has been described in the larger studies of anti-VEGF therapy. Few cases of retinal vascular occlusion have been reported following intravitreal injection of other drugs, mainly antiviral agents [17]. Based on the data currently available, there does not seem to be an increased risk of retinal vascular disease following intravitreal injections with the exception of acute central retinal artery occlusion during or immediately after the injection.

5.2.2.16 Retinal Detachment

Surgical manipulations in the posterior segment carry the risk of inducing retinal detachment or its precursors. This is also true for intravitreal injections, as they can lead to vitreous reflux that might result in increased vitreous traction. Furthermore, initiation of posterior vitreous detachment might also be caused through repeated surgical manipulations in the posterior segment with low-grade inflammations. The injection of gas, for example, induces posterior vitreous detachment in a high number of cases [27]; this is one of the major events preceding rhegmatogenous retinal detachment.

Several cases of retinal detachment have been seen after intravitreal anti-VEGF treatment. However, the detachment rates were lower than expected and no major differences from the control groups were seen. In the MARINA trial, no retinal detachment and 2 retinal breaks were found in 477 eyes with intravitreal Lucentis therapy versus 1 detachment and no breaks in 236 eyes of the control group [29]. In the ANCHOR trial, 1 detachment was seen in 277 treated eyes as well as in 143 eyes of the control group treated with photodynamic therapy [4]. In the VISION trial, 4 cases of rhegmatogenous retinal detachment were seen in the first year of follow-up of 892 patients, with an additional two detachments in 374 patients during the second year; no detachments were noted in the control group [8]. Three cases of retinal detachment were reported in 5,228 summarized in the Bevacizumab Safety Survey [10]. Jonas observed no cases of retinal detachment in 348 patients treated with intravitreal triamcinolone [21]. In summary, the risk of the development of a retinal detachment seems to be low with the drugs currently used for intravitreal injections.

In contrast to the results of the studies of anti-VEGF therapy and triamcinolone, a high rate of 9.5% of patients with post-injection retinal detachment (128 out of 1,344) was seen in the controls as well as in the treatment group in two trials on the intravitreal use of hyaluronidase for vitreous hemorrhage [24]. However, this is most likely due to the high incidence of retinal detachment in the study population (patients with vitreous hemorrhage), including the high number of tractional retinal detachments in this cohort.

5.2.2.17 Acute Rise in Intraocular Pressure

Intraocular injections will lead to a rise in the IOP in relation to the injected volume. During the injection, the rise in the IOP is related to the force applied to the plunger and the diameter of the needle. This is sometimes difficult to judge and one case of globe rupture has been reported following intraocular injection of triamcinolone [34].

Immediately following the injection of 0.1 ml, IOP reaches 46 mmHg on average if no vitreous reflux is noted. This will quickly return to the normal values within the first 30 min [3]. Between 3 and 24 h after injection, the IOP is comparable to baseline values [9].

The injected volume of ranibizumab is 0.05 ml, bevacizumab is usually approximately 0.05 ml, and the volume of pegaptanib is 0.09 ml of fluid. With this volume, IOP measurements are on average 4–5 mmHg higher at 30 min post-injection and 2–4 mmHg at 60 min compared with the baseline [28, 29]. IOPs above 30 mmHg were noted in up to 17% of patients after ranibizumab injection [29]. The rate of paracentesis for release of acutely elevated IOP in the VISION trial was low (3% in the first year and 4% in the second year) and seem to be possibly due to the preferred practice pattern in a participating center rather than a significantly elevated IOP [8]. In addition, pegaptanib is delivered through an incorporated needle that is quite large, allowing for the possibility of spontaneous reflux through the needle track. To avoid major increases in IOP during or immediately after the injection, care must be taken to remove excess fluid or air from the syringe and needle before injection and to ensure that no additional resistance, e.g., blocking of the needle or plunger, is present before entering the globe with the needle.

In addition to the purely volume-related increases in IOP, relatively early and clinically significant rises in IOP within the first week of the injection of intravitreal triamcinolone have been reported [31]. This could either be due to an early steroid-associated effect of IOP rise or a presumed blockade of the trabecular meshwork outflow by triamcinolone crystals.

5.2.2.18 Ocular Hypertension and Glaucoma

Sustained rises in IOP following intravitreal injections can either be due to a pharmacological effect of the injected agent or vehicle, structural changes within the globe following the injections, secondary effects of singular or repetitive intraocular inflammations after one or more injections, or an aging process independent of the treatment

performed. The data currently available demonstrate that only drug-related effects seem to play a significant role and that a sustained rise in IOP is almost exclusively associated with triamcinolone injections.

Regarding anti-VEGF therapy, data of three major prospective randomized trials with a follow-up of up to 2 years are available [4, 8, 14, 29]. IOP rises have specifically been addressed in these studies. No significant differences in sustained rises in IOP were seen compared with control groups, and no pressure-lowering surgical interventions have been reported. In the Bevacizumab Safety Survey, no cases of ocular hypertension or secondary glaucoma were identified [10].

The induction of secondary ocular hypertension after intravitreal triamcinolone injection has been well documented. In summary, the following observations can be made [21]:

1. A sustained rise in IOP can be observed in about 40% of treated patients.
2. About 9% will have IOPs above 30 mmHg.
3. About 1% of patients will have insufficient lowering of IOP with medical treatment and will have to undergo glaucoma surgery.
4. Following a first injection, a comparable reaction and rise in IOP can be expected with repeated injections.
5. In most cases, increased IOP values can be detected about 1 week after the injection, with a peak incidence between 1 and 2 months.
6. The duration of the pressure increase seems to be dose-dependent (about 3–4 months with 4 mg and about 7–9 months with 20–25 mg).
7. Higher doses of injected triamcinolone do not cause greater elevation of IOP, but prolonged pressure elevation.
8. Pre-existing glaucoma or ocular hypertension does not seem to increase the risk of increased pressure.
9. Younger patients seem to have a higher rate of secondary ocular hypertension.
10. There does not seem to be any significant difference in the responses to various groups of glaucoma medications.

Summary for the Clinician

- Perioperative complications include conjunctival hemorrhage (20–40%), pain (30%), punctate keratitis (30%), vitreous reflux (20%), vitreous floaters (20%), traumatic cataract (<1%), a rise in IOP (average IOP 46 mmHg if 0.1 ml is injected), and central retinal artery occlusion (<1%).
- Postoperative complications include intraocular inflammation (20%), cataract progression (7–26% within first year), endophthalmitis (0.15% per injection, 1% in patients with multiple injections), and retinal detachment (<1%).
- Complications associated with intravitreal triamcinolone injections include a higher rate of cataract progression (20–45% within the first year), ocular hypertension (about 40% of all patients, about 1% requiring filtration surgery), "pseudo-endophthalmitis" (suspected immune reaction to vehicle or drug, <1%), and a possibly higher rate of infectious endophthalmitis (0.8% per injection).

5.3 Surgical Technique for Intravitreal Injection

Intravitreal injections are relatively straightforward intraocular procedures with a low rate of severe ocular side effects. However, based on treatment strategies that are currently are transferred into daily practice, the number of patients who will receive up to 12 intravitreal injections per year over the next few years is likely to increase exponentially—and with it the number of severe adverse ocular events. Because patient safety is a key issue in all surgical interventions, it is therefore necessary to incorporate this expected high number of future patients into the daily routine of operating theaters and outpatient clinics with acceptable safety standards.

Many recommendations regarding several aspects of the procedure are not evidence-based. Some parts can be transferred from studies and practice patterns of routine cataract surgery.

Other features have been conceived from recently conducted and published studies. In most cases, guidelines represent a consensus statement of authorities in the field.

5.3.1 Guidelines and Preferred Practice Survey

The synopsis of three major guidelines is displayed in Table 5.3. The consensus statement of mainly US-based retinal specialists was published in Retina in 2004 and is based on a review of more than 15,000 injections [1, 17]. The recommendations of the German Ophthalmological Society, the Retinological Society, and the Association of Ophthalmologists in Germany was published in 2005 [18]. The guidelines of the Royal College of Ophthalmologists became available on the internet in 2006 (http://www.rcophth.ac.uk/). The display of guidelines is accompanied by a survey of the preferred practice patterns for intravitreal triamcinolone injections of 562 ophthalmologists performing intravitreal injections in the UK in 2004 [2].

5.3.2 Preoperative Assessment and Preparation

5.3.2.1 Concomitant Eye Diseases

Bacterial infections of the anterior segment and ocular adnexa increase the risk of endophthalmitis and should be treated before performing an intravitreal injection. Patients with glaucomatous diseases should have adequately controlled IOP before injection. Although the risks and the amount of postoperative rises in IOP is higher for patients with glaucoma, it is not seen as a contraindication for intravitreal injections including triamcinolone. The value of a pre-injection provocation test with steroid eye drops is questionable and this is usually not performed.

5.3.2.2 Preoperative Assessment

A thorough preoperative assessment including funduscopy should be performed before any intravitreal injection to confirm the need for the injection and to rule out possible contraindications or to detect conditions that might complicate the injection, e.g., retinal detachment, vitreous hemorrhage or increased IOP. Measurement of the IOP immediately before the injection is recommended by the Royal College guidelines.

5.3.2.3 Preoperative Medication

The value of preoperative topical antibiotics to reduce the number of bacteria on the ocular surface is a point of debate. It has been optional in some of the major trials of anti-VEGF therapy and is sometimes advocated in patients with a presumed allergy to iodine. The disadvantage of the uncritical application of broad-spectrum antibiotics is the induction of resistance of bacteria to antibiotic treatment. There seems to be no advantage of topical antibiotics over disinfection with povidone-iodine. In the guidelines, the use of preoperative antibiotics is optional.

5.3.2.4 Location

In the USA the vast majority of injections are given in the outpatient clinic. The German guidelines recommend performing the injection in an operating theater according to the standards for day-case surgical interventions. The Royal College guidelines recommend alternatively a dedicated room in the outpatient department. The preferred practice pattern survey showed that the majority of injections in the UK were carried out in operating theaters.

5.3.2.5 Preparation of the Eye and Ocular Adnexa

The standard for preoperative disinfection of the ocular surface and eyelids is povidone-iodine 5% and 10% (skin). A forceful scrubbing of the lid margins is not recommended to avoid expression of bacteria from the lid glands. Pupillary dilatation is recommended by all guidelines in all routine cases except for those with contraindications. Although subconjunctival anesthesia has

Table 5.3 Current guidelines and preferred practice survey for intravitreal injections

Guidelines				Preferred practice survey
	German Ophthalmological Society	Consensus Statement Retina	Royal College of Ophthalmologists http://www.rcophth.ac.uk/	Royal College of Ophthalmologist Specialist register
Country, year	Germany, 2005 [18]	USA, 2004 [1]	United Kingdom, 2006	United Kingdom, 2006 [2]
Preparation				
Location	Operating theater	–	Operating theater or dedicated room in outpatients clinic	77% operating theater 19% outpatients
Removal of vehicle (triamcinolone)	Recommended	–	–	5.8%
Pretreatment antibiotics	Recommended in high-risk cases	Optional	Optional	
Mydriatics	Yes	Yes	Yes	78%
Topical anesthesia	Yes		Yes	
Subconjunctival anesthesia	Optional	Optional	Optional	
Conjunctival disinfection	10 ml povidone-iodine 5%	Povidone-iodine	5% povidone-iodine drops 3 min before injection	94% povidone iodine
Lid disinfection	Povidone-iodine 10%	Povidone-iodine No scrubbing of lid margins	Povidone-iodine 10%	
Hand disinfection	Yes	–	Yes	
Gloves	Yes	Yes	Yes	86%
Sterile drape	Yes	Optional	Yes	63%
Lid speculum	Yes	Yes	Yes	
Preoperative intraocular pressure measurement			Yes	

Table 5.3 *(continued)* Current guidelines and preferred practice survey for intravitreal injections

Guidelines				Preferred practice survey
Injection				
Cannula	27- or 30-gauge	27-gauge or smaller length 12.7 to 0.15.75 mm	27- to 30- gauge length 12.7 to 15.75 mm	54% 27-gauge 22% 30-gauge
Distance to limbus	3.5 mm	Pseudophakic 3.5 mm Phakic 4.0 mm	Pseudophakic 3.0 to 3.5 mm Phakic 3.5 to 4.0 mm	
Conjunctival shift	Yes	–	–	
Needle positioning	Advance 6–7 mm	Advance at least 6 mm	–	
Injection	Not too quickly	Moderately slow	Slowly and carefully	
Blockade sclerotomy	Yes	Yes		
Paracentesis	Optional, not routinely recommended	Optional, not routinely recommended	Optional, not routinely recommended	11% before (sometimes) 40% after (sometimes)
Antibiotic drops immediately after injection	–	–	Yes	
Postoperative care				
Visual acuity check	Yes	Yes	Yes	
Ophthalmoscopy	Yes	Yes	No	
Slit-lamp examination	No	No	Yes	
Intraocular pressure check	30–60 min	Monitor pressure after injection	Within 30 min	26% same day 23% next day
Topical antibiotics	Optional for 3 days	Optional	For 3 days	58%
Follow-up examination	First day post-injection	To be contacted by physician's office within 1 week	–	

been used in some of the major studies, standard practice is topical anesthesia with eye-drops with or without a pledget. Paracentesis before injection is not recommended unless higher volumes are injected (≥0.2 ml).

5.3.2.6 Preparation of the Surgeon

A hand-wash and disinfection according to routine standards for surgical interventions as well as wearing of surgical gloves are recommended as per universal precautions. However, surgical gowns or face masks are not worn in the majority of centers.

5.3.2.7 Preparation of the Drug

Most drugs for intravitreal injections are provided in syringe and needle packets ready for injection. When the injectable volume is drawn from larger vials (e.g., bevacizumab or triamcinolone), sterile conditions have to be ensured throughout the preparation of the drug. Removal of the solvent before triamcinolone injections has been associated with a lower rate of intraocular inflammation and is recommended by the German guidelines.

5.3.3 Injection

5.3.3.1 Syringe and Needle

Twenty-seven or 30-gauge needles measuring between 12.7 and 15.75 mm long are usually recommended. In every case, air within the syringe and needle should be removed before the injection. Testing that no major resistance is present (e.g., clogging of the needle with triamcinolone crystals or the rigid plunger of the syringe) before injection is also recommended. When injecting triamcinolone it is helpful to have a syringe with a Luer lock, so that the needle does not become detached from the syringe during injection.

5.3.3.2 Position of the Injection

The injection should be positioned between 3.0 and 4.0 mm posterior to the limbus, depending on the lens status. Usually, the first injection is performed temporally and inferiorly. In most cases of repeated injections, previous injection sites are avoided because of fibrotic reactions in this area. The exact position of an injection should be noted within the patient's notes. However, given the need for monthly injections for some medications it will be virtually impossible to avoid a site inferiorly that has not been injected before.

5.3.3.3 Entry Path

The German guidelines recommend pulling the conjunctiva over the entry site in order to achieve a step-like entry path and to lower the risk of vitreous reflux. Usually, a straight needle path, pointing at the center of the eyeball is recommended. With relatively large needles that sometimes are pre-installed from the manufacturer and cannot be exchanged, a slightly angled scleral entry path is needed in order to avoid vitreous reflux.

5.3.3.4 Advancement of Needle and Injection

The needle should be advanced 6–7 mm toward the center of the eyeball to avoid injection along the anterior vitreous surface. Checking the position of the needle tip with indirect ophthalmoscopy or with the operating microscope is not recommended because these manipulations may increase the risk of unintentional movements of the needle tip and iatrogenic trauma. The injection should be carried out in one slow but steady movement. Caution should be used if increased resistance is felt at the beginning or during the injection. The needle should be withdrawn in one movement with a cotton applicator covering the injection site and replacing the conjunctiva in order to avoid vitreous reflux and a vitreous wick.

5.3.4 Postoperative Assessment

5.3.4.1 Assessment Immediately Following the Injection

Immediately after the injection, the visual function (hand movements and light perception)

should be checked. In addition, funduscopy should be performed to rule out central retinal artery occlusion, retinal detachment or vitreous hemorrhage. If central retinal artery occlusion is present and does not resolve spontaneously within the first few minutes, paracentesis should be performed. Paracentesis is not recommended routinely. The IOP should be checked within the first 60 min of injection. The Royal College guidelines also recommend a slit-lamp examination following the injection.

5.3.4.2 Topical Therapy

The value of postoperative topical antibiotics is debatable and recommendations vary among the different guidelines. Again, the reduction in number of bacteria on the ocular surface has to be measured against the relatively low incidence of endophthalmitis when appropriate standards for the injection are used and the definite induction of resistance to antibiotics by routine application of broad-spectrum antibiotics. Recommendations concerning the type of drug to be used also vary.

Summary for the Clinician

- Exclude patients with suspected bacterial infections of the anterior segment (e.g. blepharitis, conjunctivitis).
- Provide a designated treatment room or operating theater.
- Use preoperative antisepsis with 10% povidone-iodine (lids) and 5% povidone-iodine (conjunctiva).
- Carry out hand disinfection and wear gloves.
- Use a sterile drape and lid speculum.
- Use preoperative mydriatics.
- Use topical anesthesia.
- Use a 27- or 30-gauge cannula.
- Ensure the injection site is 3.5–4.0 mm from the limbus, preferably in the temporal inferior quadrant.
- Carry out conjunctival shift.
- Ensure needle advancement of 6–7 mm.
- Carry out moderately slow injection.

Summary for the Clinician

- Check vision and assess central retinal artery perfusion immediately post-injection.
- Perform paracentesis only if the central retinal artery is occluded.
- Carry out an IOP check within 30–60 min.
- Administer topical antibiotics for 3 days.

5.3.4.3 Follow-up Examinations

There is some variation regarding the necessity of follow-up examinations. In addition, regional variations in the availability of such examinations also play a role. The German guidelines advocate a full examination on the first day after the injection. Since most cases of endophthalmitis occur several days after injection, examination 1 day post-injection may miss a true infection. The US consensus statement recommends (telephone-based) contact between the patient and the treating institution. In any case, patients should be well informed about possible symptoms and signs of severe ocular events, e.g., pain, decrease in vision, inflammation and photophobia, and the means of contact and emergency treatment should such situations arise.

References

1. Aiello LP, Brucker AJ, Chang S et al (2004) Evolving guidelines for intravitreous injections. Retina 2004;24 [5 Suppl]:S3–19
2. Anijeet DR, Hanson RJ, Bhagey J et al (2006) National survey of the technique of intravitreal triamcinolone injection in the United Kingdom. Eye (in press)
3. Benz MS, Albini TA, Holz ER et al (2006) Short-term course of intraocular pressure after intravitreal injection of triamcinolone acetonide. Ophthalmology 2006;113(7):1174–1178
4. Brown DM, Kaiser PK, Michels M et al (2006) Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 355(14):1432–1444

5. Chen SD, Mohammed Q, Bowling B et al (2004) Vitreous wick syndrome—a potential cause of endophthalmitis after intravitreal injection of triamcinolone through the pars plana. Am J Ophthalmol 137(6):1159–1160; author reply 1160–1161
6. Chen SN, Yang TC, Ho CL et al (2003) Retinal toxicity of intravitreal tissue plasminogen activator: case report and literature review. Ophthalmology 110(4):704–708
7. Costa RA, Jorge R, Calucci D et al (2006) Intravitreal bevacizumab for choroidal neovascularization caused by AMD (IBeNA Study): results of a phase 1 dose-escalation study. Invest Ophthalmol Vis Sci 47(10):4569–4578
8. D'Amico DJ, Patel M, Adamis AP et al (2006) Pegaptanib sodium for neovascular age-related macular degeneration: two-year safety results of the two prospective, multicenter, controlled clinical trials. Ophthalmology 113(6): 992–1001.e6
9. Dwinger MC, Pieper-Bodeewes I, Eter N et al (2005) [Variations in intraocular pressure (IOP) and necessity for paracentesis following intravitreal triamcinolone injection]. Klin Monatsbl Augenheilkd 222(8):638–642
10. Fung AE, Rosenfeld PJ, Reichel E (2006) The International Intravitreal Bevacizumab Safety Survey: using the internet to assess drug safety worldwide. Br J Ophthalmol 90(11):1344–1349
11. Gillies MC, Kuzniarz M, Craig J et al (2005) Intravitreal triamcinolone-induced elevated intraocular pressure is associated with the development of posterior subcapsular cataract. Ophthalmology 112(1):139–143
12. Gillies MC, Sutter FK, Simpson JM et al (2006) Intravitreal triamcinolone for refractory diabetic macular edema: two-year results of a double-masked, placebo-controlled, randomized clinical trial. Ophthalmology 113(9):1533–1538
13. Gills JP, Gills P (2005) Effect of intracameral triamcinolone to control inflammation following cataract surgery. J Cataract Refract Surg 31(8):1670–1671
14. Gragoudas ES, Adamis AP, Cunningham ET Jr et al (2004) Pegaptanib for neovascular age-related macular degeneration. N Engl J Med 351(27):2805–2816
15. Gupta R, Negi A, Vernon SA (2005) Severe sub conjunctival haemorrhage following intravitreal triamcinolone for refractory diabetic oedema. Eye 19(5):590–591
16. Heier JS, Antoszyk AN, Pavan PR et al (2006) Ranibizumab for treatment of neovascular age-related macular degeneration: a phase I/II multicenter, controlled, multidose study. Ophthalmology 113(4):633–642.e4
17. Jager RD, Aiello LP, Patel SC et al (2004) Risks of intravitreous injection: a comprehensive review. Retina 24(5):676–698
18. Jaissle GB, Szurman P, Bartz-Schmidt KU (2005) [Recommendation for the implementation of intravitreal injections—statement of the German Retina Society, the German Society of Ophthalmology (DOG) and the German Professional Association of Ophthalmologists (BVA)]. Klin Monatsbl Augenheilkd 222(5):390–395
19. Jalil A, Chaudhry NL, Gandhi JS et al (2007) Inadvertent injection of triamcinolone into the crystalline lens. Eye 21(1):152–154
20. Jobling AI, Augusteyn RC (2002) What causes steroid cataracts? A review of steroid-induced posterior subcapsular cataracts. Clin Exp Optom 85(2):61–75
21. Jonas JB, Kreissig I, Degenring R (2005) Intravitreal triamcinolone acetonide for treatment of intraocular proliferative, exudative, and neovascular diseases. Prog Retin Eye Res 24(5):587–611
22. Kaderli B, Avci R (2006) Comparison of topical and subconjunctival anesthesia in intravitreal injection administrations. Eur J Ophthalmol 16(5):718–721
23. Kreissig I, Degenring RF, Jonas JB (2006) [Intravitreal triamcinolone acetonide. Complication of infectious and sterile endophthalmitis]. Ophthalmologe 103(1):30–34
24. Kuppermann BD, Thomas EL, de Smet MD et al (2005) Safety results of two phase III trials of an intravitreous injection of highly purified ovine hyaluronidase (Vitrase) for the management of vitreous hemorrhage. Am J Ophthalmol 140(4):585–597
25. Michels S (2006) Is intravitreal bevacizumab (Avastin) safe? Br J Ophthalmol 90(11):1333–1334

26. Moshfeghi DM, Kaiser PK, Scott IU et al (2003) Acute endophthalmitis following intravitreal triamcinolone acetonide injection. Am J Ophthalmol 136(5):791–796
27. Ochoa-Contreras D, Delsol-Coronado L, Buitrago ME et al (2000) Induced posterior vitreous detachment by intravitreal sulfur hexafluoride (SF6) injection in patients with nonproliferative diabetic retinopathy. Acta Ophthalmol Scand 78(6):687–688
28. Rosenfeld PJ, Schwartz SD, Blumenkranz MS et al (2005) Maximum tolerated dose of a humanized anti-vascular endothelial growth factor antibody fragment for treating neovascular age-related macular degeneration. Ophthalmology 112(6):1048–1053
29. Rosenfeld PJ, Brown DM, Heier JS et al (2006) Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 355(14):1419–1431
30. Roth DB, Scott IU, Gulati N et al (2006) Patient perceptions of discomfort and changes in vision and functional status associated with intravitreal triamcinolone injection. Am J Ophthalmol 142(3):492–494
31. Singh IP, Ahmad SI, Yeh D et al (2004) Early rapid rise in intraocular pressure after intravitreal triamcinolone acetonide injection. Am J Ophthalmol 138(2):286–287
32. Szurman P, Kaczmarek R, Spitzer MS et al (2006) Differential toxic effect of dissolved triamcinolone and its crystalline deposits on cultured human retinal pigment epithelium (ARPE19) cells. Exp Eye Res 83(3):584–592
33. Thompson JT (2006) Cataract formation and other complications of intravitreal triamcinolone for macular edema. Am J Ophthalmol 141(4):629–637
34. Ung T, Williams CP, Canning CR (2006) Globe rupture as a complication of intravitreal injection of triamcinolone. Eye (in press)
35. Widmer S, Helbig H (2006) Presumed macular toxicity of intravitreal antibiotics. Klin Monatsbl Augenheilkd 223(5):456–458
36. Yu SY, Damico FM, Viola F et al (2006) Retinal toxicity of intravitreal triamcinolone acetonide: a morphological study. Retina 26(5):531–536