Postoperative Endophthalmitis and Toxic Anterior Segment Syndrome Prophylaxis: 2020 Update

Jesse D. Sengillo[1], Ying Chen[1], Diley Perez Garcia[1], Stephen G. Schwartz[1], Andrzej Grzybowski[2,3], Harry W. Flynn Jr[1]

[1]Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, FL, USA; [2]Department of Ophthalmology, University of Warmia and Mazury, Olsztyn, Poland; [3]Institute for Research in Ophthalmology, Foundation for Ophthalmology Development, Poznan, Poland

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Correspondence to: Stephen G. Schwartz. Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, 3880 Tamiami Trail North, Naples, FL 34103, USA. Email: sschwartz2@med.miami.edu.

Abstract: Improved surgical techniques have led to an increase in the number of outpatient ophthalmic procedures. In spite of decreased surgical times and overall improved outcomes, endophthalmitis remains one of the most severe complications of ophthalmic surgery. Although there are well known risk factors for postoperative endophthalmitis, some prophylaxis strategies remain controversial. A category of noninfectious postoperative inflammation, known as toxic anterior segment syndrome (TASS), is a rare but important complication of cataract surgery. While several worldwide outbreaks of TASS have occurred, it is challenging to identify an etiology in order to reduce the risk of further cases. Endophthalmitis and TASS cannot be prevented completely, but their rates may be decreased through risk reduction strategies supported by peer-reviewed evidence. This review highlights the current evidence in the prevention strategies for postoperative endophthalmitis and TASS.

Keywords: Endophthalmitis; toxic anterior segment syndrome (TASS); prophylaxis

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Introduction

In the last few decades, there has been a large increase in the number of ophthalmic procedures performed worldwide. With improved surgical techniques and new technologic advances, surgical outcomes continue to improve. However, postoperative endophthalmitis and toxic anterior segment syndrome (TASS) remain important challenges. Both endophthalmitis and TASS can present as severe postoperative inflammation, and clinical characteristics may be used to differentiate between the two (*Table 1*). Without prompt treatment, both may lead to poor visual outcomes. Although these entities cannot be prevented completely, their rates may be decreased through risk reduction strategies supported by peer-reviewed evidence.

Postoperative endophthalmitis

Background

Acute-onset postoperative endophthalmitis is generally defined as endophthalmitis presenting within six weeks of intraocular surgery. Visual outcomes after endophthalmitis are often poor. The Endophthalmitis Vitrectomy Study (EVS) reported final visual acuity of worse than 20/100 in 36% of patients (2). In the European Society of Cataract and Refractive Surgeons (ESCRS) randomized clinical trial, 14% of patients had final visual acuity worse than or

Table 1 Clinical characteristics of endophthalmitis and toxic anterior segment syndrome (TASS)

Clinical characteristic	TASS	Endophthalmitis
Timing	12–24 hours (early)	3–7 days (can have slight delay)
Pain	None to mild discomfort	Moderate to severe
Visual acuity	Mild decrease	Moderate to severe decrease
Intraocular pressure	Normal to increased	Normal
Corneal edema	Severe (limbus-to-limbus)	Variable extent
Fibrin	Mild or absent	Typically present
Vitreous cell	Mild or absent	Typically present
Hypopyon	Minimal or absent	Often present

Adapted from Hernandez-Bogantes *et al.* (1).

equal to 20/200 (3), and one review of the US Medicare population reported a similar outcome in 34% of patients with endophthalmitis (4). The reported rates of acute-onset postoperative endophthalmitis after cataract surgery vary widely, but range from about 0.02% to 0.2% (5,6). Recent evidence suggests a decline in the incidence of this complication over the last two decades, partially attributed to the refinement of surgical techniques, smaller incisions, antisepsis with povidone-iodine, and possibly the use of intracameral antibiotics by some surgeons (7-9).

Risk factors

Risk factors for endophthalmitis include preoperative, intraoperative, and postoperative factors. Preoperative factors include uncontrolled blepharitis or other ocular surface disease, diabetes mellitus, an immunocompromised state, infectious foci near the surgical site, and advanced age (5,10-12). Intraoperative factors include large-incision extracapsular cataract extraction, clear cornea incision, posterior capsule rupture with or without vitreous loss, and a less experienced surgeon (3,10-13). Some authors report the non-use of intracameral antibiotics as a risk factor, but the overall benefit of intracameral antibiotics remains controversial, especially in the US (14-16). Postoperative factors include early wound leak (17,18).

Microbiology

The most common causative organisms causing acute-onset postoperative endophthalmitis are gram-positive bacteria, accounting for 94.2% of culture-positive cases in the EVS. Within this group, coagulase-negative staphylococci were more common than *Staphylococcus aureus* and streptococci (70% *vs.* 9.9% and 9%, respectively) (2). Subsequent large series generally corroborate these rates (13,19,20). Of the remainder, gram-negative species account for approximately 5% which includes Proteus, *Haemophilus influenzae*, and *Pseudomonas* (2,21). Given the high frequency of gram-positive isolates, it is generally agreed that the main source of organisms is the ocular surface; however, *Staphylococcus aureus*, a highly virulent microorganism, can be found most often in the anterior nares, nasopharynx, skin, perineum, axillae, and gastrointestinal tract in asymptomatic patients (22). In the EVS, approximately 30% of patients were culture negative (21).

Prophylaxis of postoperative endophthalmitis

Although endophthalmitis cannot be prevented completely, many preoperative, intraoperative, and postoperative strategies are helpful in prophylaxis. Common practices include antisepsis with povidone-iodine and prophylactic topical antibiotics. The use of routine intracameral antibiotics has become more common in many areas of the world, although this usage remains controversial.

Topical prophylaxis

Povidone-iodine

Preoperative antisepsis with povidone-iodine significantly decreases the rate of bacterial endophthalmitis and is a worldwide accepted strategy (5,23-26). Following

conjunctival cul-de-sac irrigation with 5% povidone-iodine prior to surgery, the conjunctival flora undergoes a reported ~60% reduction, especially of coagulase-negative staphylococci (20,27). The additional advantages of using this agent are low cost, no known bacterial resistance, and rapid bactericidal action (27,28). For *skin* disinfection, however, 10% povidone-iodine is generally recommended; one study reported that preoperative skin disinfection with a lower concentration of povidone-iodine was associated with an increased incidence of endophthalmitis (29). For the *ocular surface*, lower concentrations of povidone iodine administered as frequent applications during surgery are also shown to be effective in preventing contamination of the anterior chamber. Shimada *et al.* reported 0.25% povidone-iodine to be effective in this regard, in conjunction with antibiotic prophylaxis (20,26,30).

Topical povidone-iodine may cause toxicity to the corneal epithelium. Ridder *et al.* reported that corneal staining was present for up to one day following povidone-iodine administration, associated with temporarily decreased visual acuity and contrast sensitivity (31).

When povidone-iodine cannot be used for cataract surgery (although true allergy is rare), the use of topical chlorhexidine gluconate may be considered, although this agent may be toxic to the cornea (20,32).

Topical antibiotics

Although there is no conclusive evidence supporting the use of topical antibiotic prophylaxis, these agents are very widely used. For example, the 2014 American Society of Cataract and Refractive Surgery (ASCRS) survey reported that 90% of respondents used topical perioperative antibiotics and 97% of respondents used topical postoperative antibiotics (33). Many studies report a significant reduction of conjunctival flora with the use of topical antibiotics, but it is uncertain if this reduction actually decreases endophthalmitis rates (34). In the ESCRS trial, there was no significant difference in endophthalmitis rates among patients who received perioperative topical levofloxacin compared with patients who did not (3). A systematic review and meta-analysis of randomized controlled trials and observational studies performed failed to find any evidence supporting the use of postoperative topical antibiotics after ocular surgery (35). Nevertheless, these agents remain very widely used (36).

Intracameral antibiotics

Intracameral antibiotics may be used in irrigating fluids or injected as a bolus at the conclusion of surgery (37), and their use for routine prophylaxis varies widely around the world (38). In the 2014 ASCRS member survey, 47% of respondents used or planned to use intracameral antibiotics, with estimates suggesting the number would be higher if an approved, packaged commercial formulation were available in the US (38).

The ESCRS conducted a randomized clinical trial among 24 ophthalmology centers in nine different countries. Of the 16,603 patients who were recruited, 29 were diagnosed with endophthalmitis; the non-use of intracameral cefuroxime, clear corneal incisions, and silicone intraocular lenses were identified as risk factors (3). Criticisms of the ESCRS trial include the relatively high rates of endophthalmitis in patients not randomized to receive intracameral cefuroxime (approximately 0.2%), which may have biased the results in favor of cefuroxime, as well as the use of topical levofloxacin rather than more efficacious later-generation fluoroquinolones. A recently published single-site randomized clinical trial in Brazil reported a significantly decreased rate of endophthalmitis associated with intracameral moxifloxacin (0.5% bolus) compared to no intracameral antibiotic (39). Again, the rate of endophthalmitis in eyes not treated with intracameral antibiotics was high (0.38%) which may have biased the results in favor of intracameral moxifloxacin.

In addition to these two randomized clinical trials, many retrospective series have compared endophthalmitis rates in cohorts not treated with intracameral antibiotics versus cohorts treated with intracameral antibiotics. In most of these studies, the authors reported their rates after initiating routine intracameral antibiotics, and compared these patients with the patients operated before making this change. Therefore, the non-treated cohorts generally contained patients operated earlier in time than the patients in the treated cohorts, so the decreased rates of endophthalmitis in the (later) treated cohorts could have been due to factors other than the antibiotics, such as improved surgical techniques, newer lens implants, etc. Haripriya *et al.*, in one of the largest retrospective studies, reported a 3.5-fold reduction in the overall rate of endophthalmitis using intracameral moxifloxacin (40),

and one study from Northern California reported a 22-fold decline in the rate of clinical endophthalmitis (19). Similar results were reported from many other nations (8,13,33). Not all series reported a benefit associated with intracameral antibiotics, however. Two studies, one from Canada and another from India, reported that intracameral antibiotics were not associated with a decreased rate of endophthalmitis (41,42). Moreover, series from Japan (6) and Singapore (personal communication, Dr. Tat Keong Chan) have reported very low rates (≤0.02%) of endophthalmitis with no intracameral antibiotics (43).

Intracameral antibiotics are associated with various adverse outcomes. Inadvertent overdoses of cefuroxime have known ocular toxicity and may cause TASS (44-46). There is currently no approved, packaged formulation of intracameral antibiotics in the US, and as a result, these agents must be prepared by compounding pharmacies, with associated risks of overdose, underdose, and contamination. In Europe there is a commercially available intracameral cefuroxime (Aprokam, Thea Pharmaceuticals), which alleviates some of these concerns. However, the common use of cefuroxime in Sweden has led to an increased number of cefuroxime-resistant enterococcal cases (47). This increased rate of enterococcal infections has led to the practice, in same day bilateral surgery in Sweden, of using intracameral ampicillin plus cefuroxime (13).

Intracameral vancomycin is associated with hemorrhagic occlusive retinal vasculitis (HORV) (48), and retinal toxicity is also associated with cefuroxime at high (49,50) and standard intracameral doses (51).

TASS

Background

TASS is a non-infectious postoperative inflammation that occurs most commonly after cataract surgery but also may occur following keratoplasty and posterior segment procedures (52-55). It was first described in 1980 when nine eyes with intraocular lenses containing residual polishing compound on their surface developed sterile hypopyon (56,57). The incidence of TASS is difficult to estimate as it is uncommon and manifests both sporadically and in clustered outbreaks. The incidence following cataract surgery is likely around 1 in 1,000 (1,58).

Although the pathophysiology remains elusive, TASS typically represents an inflammatory response to a noninfectious substance introduced into the eye during surgery. Culprit substances leading to major outbreaks include intraocular lens contamination with small heavy metals, balanced salt solution containing endotoxin, viscoelastic, and intracameral antibiotics (59-64), although sometimes a cause is not identified (*Table 2*) (58,100,101).

Clinical outcomes of TASS are better with prompt diagnosis and treatment with topical corticosteroids and possibly cycloplegics. Typical presentations include blurred vision within 12–48 hours of surgery without salient complaints of pain; in general, TASS patients present sooner than do patients with endophthalmitis. “Limbus-to-limbus” corneal edema is characteristic of TASS and is uncommon for endophthalmitis. Other non-specific signs of anterior segment inflammation are common in both entities, such as anterior chamber cellular reaction, fibrin, and hypopyon (102).

Prophylaxis of TASS

Perioperative sterilization considerations

Similar to endophthalmitis, TASS cannot be prevented completely but the rate may be reduced. Minute amounts of foreign substances may incite inflammation, and the large number and variety of surgical instruments used, as well as their different sterilization processes, make prevention challenging. Proper cleaning of surgical instruments and sterilization remain important for reducing rates of TASS (102).

Cutler Peck *et al.* retrospectively queried data from site visits and questionnaires from surgical centers that reported cases of TASS between 2007 and 2009. Several risk factors associated with TASS were identified, with inadequate flushing of the phacoemulsification and irrigation/aspiration handpieces after surgery being the most common (72). Eighty-nine percent of centers visited were found to be deficient in this practice. Strict adherence to manufacturer directions for equipment sterilization is important. In addition, handpieces should be wiped with lint-free cloth or immersed in sterile water prior to flushing (103). This reduces the risk of retained debris on an instrument entering the anterior chamber of subsequent patients (104). Another identified process associated with TASS was ultrasonic bathing, with 63% of facilities utilizing this practice (72). Employed mainly for dislodging dried debris from the surface of surgical tools, this can lead to an accumulation of heat-stable endotoxins from bacteria harbored in the bath water. It is now generally

Table 2 Etiologies of Toxic Anterior Segment Syndrome (TASS)

Category	Cause	Associated References (PMID)
Antibiotics	Cefuroxime	(44-46,50)
	Gentamicin	(65,66)
Solutions	Heavy metals	(61,67,68)
Preservatives	Benzalkonium chloride	(69-71)
	Balanced salt solution	(59)
Perioperative	Powdered gloves	(72-74)
	Enzymatic detergents	(72,75-77)
	Autoclave	(78,79)
	Ultrasonic baths	(78,80,81)
	Reused tools	(53)
	Glutaraldehyde	(82)
Intravitreal injections	Bevacizumab	(83-88)
	Aflibercept	(89-92)
	Triamcinolone acetonide	(93)
	Silicone oil	(94)
Intraocular dyes	Trypan blue	(95)
	Indocyanine green	(96)
Ointments	Gentamicin sulfate	(97)
	Betamethasone	(97)
Other	Viscoelastic substance	(62,63,98,99)
	Polishing compound	(56)

Adapted from Hernandez-Bogantes *et al*. (1).

recommended to avoid ultrasonic baths as proper flushing should eliminate the need for further dislodgment of surface debris (72,103,105).

Impurities in steam sterilization systems are also associated with TASS. Poorly maintained autoclave generators with impurities in steam moisture were suspected to be the cause of eight TASS cases reported by Hellinger *et al.* (78). Investigators in this study found impurities such as sulfates, copper, zinc, nickel, and silica to be present in autoclave steam moisture in the setting of suboptimal equipment reprocessing and personnel changes. The incidence of TASS has subsequently decreased following removal of steam moisture impurities. Another outbreak was also resolved with improved autoclave maintenance, after identifying gram-negative bacteria and endotoxin in autoclave reservoirs (106).

Enzymatic detergents in the processing of surgical instruments are also associated with TASS (72,107,108), with incomplete rinsing thought to leave residual detergent that can become introduced intraocularly. *In vitro* experiments support this as a likely cause. Endothelium of paired rabbit corneas were perfused with enzymatic detergent as compared to corneas perfused with BSS (109). A dose-related response in corneal swelling was observed, and similarly confirmed in human corneas. Thus, ASCRS and the American Society of Ophthalmic Administrators (ASOA) recommend diligent observation of instructions pertaining to proper dilution and disposal of enzymatic solutions according to the manufacturer. Extensive rinsing with copious volumes of water are used to remove all the detergent, and treating the volumes designated by the manufacturer as if they are a minimum

needed. The final rinse should be with sterile water (105).

Bodnar *et al.* sought to assess how risk factors have changed for TASS over a decade, specifically before and after 2009. Their findings suggest that education and increased awareness of TASS may have improved preoperative sterilization practices (104).

Materials, medications, and solutions implicated in TASS

Numerous other agents are associated with TASS. Awareness of historical causes of TASS is helpful in reducing the risk of future outbreaks.

Gloves

Contacting an intraocular lens with a gloved hand is not a rare event (104), and talc containing surgical glove powders are known to be associated with ocular toxicity (73,74). Interestingly, powder-free gloves are also associated with TASS, as gloves can retain residue from chemicals used during the extraction process in their manufacturing (1,74). Avoiding direct contact between gloved hands and lens implants is advised where possible.

Preservatives

Although most surgeons have abandoned intracameral use of agents containing preservatives, inadvertent administration of these preservatives may result in TASS. Benzalkonium chloride is a frequently cited offender, and care should be taken to ensure medications instilled intracamerally do not contain this preservative (69-71). This agent not only causes dose-related inflammation to extraocular structures like the conjunctiva, it is also reported to make structural alterations to the endothelium even at exceedingly low concentrations (110). It is generally recommended to avoid the intraocular use of medications and solutions that contain benzalkonium chloride, thimerosal, eidetic acid, and sodium bisulfite (111).

Intravitreal injections

Anterior segment surgery with phacoemulsification is the most commonly implicated in TASS, but posterior surgical procedures and even intravitreal injections are frequently reported to cause a sterile inflammatory reaction. Both bevacizumab and aflibercept have been reported in past outbreaks (83-87), although it is not always clear if toxicity is inherent to the drug itself, the solution it is dissolved in (the vehicle), or the syringe used for injection (1). In one retrospective case series, the irritant was identified to be endotoxin contaminating three vials of counterfeit bevacizumab. Similarly, in a non-counterfeit lot of bevacizumab, elevated levels of endotoxin and silicone oil residues contributed to a Canada-wide TASS outbreak (85). It is important to note that bevacizumab is used off-label for various ocular conditions, and the levels of both endotoxin and silicone oil in the lot met industry standards for intravenous use at that time. Despite the severity of intraocular inflammation in the setting anti-VEGF injections, the prognosis is often favorable (89).

Aluminum and heavy metals

One of the most widespread TASS outbreaks was from aluminum toxicity related to the use of HOYA iSert one-piece intraocular lenses, (HOYA Co Ltd, Tokyo, Japan) (61,67). Six cases were also subsequently identified to cause late-onset TASS (68). A review of manufacturing practices revealed residual metallic particles on these intraocular lenses as the cause.

Ointments

Investigators at one center found an ointment containing gentamicin and betamethasone as a likely cause of eight TASS related cases, performed by the same surgeon. Mass spectrometry identified a mixed chain hydrocarbon compound on both the intraocular lens extract and within the ointment used post-operatively. The authors suggested that wound integrity and tight eye patching that was used may have contributed to the ointment gaining access into the anterior chamber.

Case illustration of TASS in the setting of uncomplicated cataract surgery

A 73-year-old man presented one day after uncomplicated cataract extraction with intraocular lens implant in the right eye. He described blurred vision without pain, instead describing mild irritation. On exam, best corrected visual acuity was 1/200 with an intraocular pressure of 10 mmHg. Slit lamp examination revealed diffuse Descemet's folds and limbus to limbus corneal edema (*Figure 1A*). The anterior chamber exhibited a 4+ inflammatory cell reaction without hypopyon (*Figure 1B*). The intraocular lens appeared centered with trace fibrin on the anterior surface. There was a poor view of the posterior pole due to the anterior segment inflammation, but no frank evidence of vitritis.

Treatment with topical methylprednisolone every hour and polymyxin B sulfate/trimethoprim every four hours to

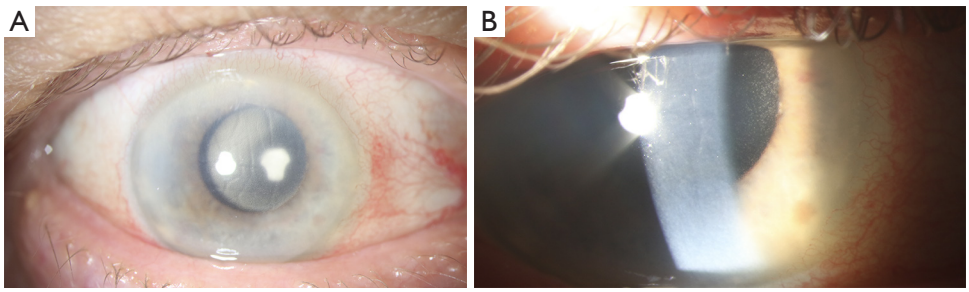

Figure 1 Slit lamp photograph of a patient with TASS. (A) Diffuse Descemet's folds and limbus to limbus corneal edema; (B) an anterior chamber 4+ inflammatory cell reaction without hypopyon.

the affected eye was initiated. By post-operative day five, visual acuity had improved to 20/60 and a slow taper of the topical steroid was initiated. At post-operative week six, visual acuity had improved to 20/30 in the affected eye.

As with all cases of post-operative inflammation following cataract surgery, endophthalmitis must be considered. In the case presented here, there was a lower suspicion for endophthalmitis as symptoms were very acute in onset—within 24 hours of surgery, and the inflammation was predominantly anterior without evidence of vitritis. An additional characteristic of TASS includes limited description of pain from the patient; blurry vision predominates. Importantly, there is commonly not a source identified for TASS, as in this case. Institutional awareness and prompt reporting of TASS should be a priority upon diagnosis.

Conclusions

Knowledge of clinical features and risk factors for post-operative endophthalmitis and TASS has increased. For both entities however, identifying the best methods of prevention remains important for improving visual outcomes after ophthalmic surgery.

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Footnote

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to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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