Toxic anterior segment syndrome

Moudgil T¹, Bansal Y²

ABSTRACT

In this era of topical cataract surgeries, where patients come and get operated within 15-20 minutes and walk with 20/20 vision from the hospital, there is a nightmare for ophthalmologists which is called endophthalmitis and Toxic Anterior Segment Syndrome (TASS). Despite an uneventful surgery patient may land in ophthalmologist’s outpatient department with decreased vision the next day because of TASS. Mild cases respond to treatment but severe cases may end up losing vision and may require further intraocular surgeries. Thus, steps should be taken to prevent this monstrous disease from happening. This article reviews how to diagnose, treat and prevent TASS.

Key Words: Denatured OVDs, toxic anterior segment syndrome, corneal edema, endophthalmitis, uveitis

Introduction

Toxic anterior segment syndrome (TASS) is an acute, sterile anterior segment inflammation in which a noninfectious material from the surgical devices or implants enters the anterior segment and induces toxic damage to the intraocular tissues, following an uneventful cataract and anterior segment surgery. It is most commonly reported after cataract surgery, phakic IOL implantation, penetrating keratoplasty and glaucoma surgeries. There have been cases of hypopyon caused by toxic substances as well as anterior segment damage to various degrees. At first, these cases were referred to as sterile endophthalmitis or post-operative uveitis of unknown cause. However, with the symptoms of infection restricted to the anterior segments, Mondon et a¹ later renamed it “Toxic Anterior Segment Syndrome” or TASS. Furthermore, a condition termed toxic endothelial cell destruction (TECD) syndrome has been described and is now believed to be a variant of TASS.

Pathophysiology

TASS results from the inadvertent entry of toxic substances into the anterior chamber. This causes a marked inflammatory reaction that varies in intensity depending on the type and duration of the toxin.

Histopathology: Hallmark of TASS is toxic anterior segment damage. Cellular necrosis and/or apoptosis and extracellular damage occur, resulting in the severe acute inflammatory response. The corneal endothelium is often the most damaged structure because of its inability to regenerate and replace dead cells. Toxic agents specifically induce the acute breakdown of endothelial junctions with
loss of the barrier function. This results in the remaining viable endothelial cells to migrate and spread over the damaged areas in an effort to maintain the endothelial pumping system. If significant damage occurs, however, the remaining viable cells will not be able to sufficiently compensate the loss, with ensuing permanent corneal edema being the consequence.

Trabecular meshwork damage can also develop, resulting in decreased drainage, scarring, and peripheral anterior synechiae formation with a subsequent rise in intraocular pressure.

Prevalence

Data on the incidence of TASS are lacking. Clusters ranging from a few cases to up to 20 cases occur several times each year. Furthermore, in 2005, audience response during the American Academy of Ophthalmology Annual Meeting revealed that 52% of attendees had seen 1 case of TASS and 7% of attendees reported seeing more than 5 cases. [6]

Causes

Numerous noninfectious substances have been implicated to cause TASS:

- Talc from surgical gloves[7]
- Abnormal pH and osmolarity
- Anesthetic agents[6]
- Preservatives[9]
- Intraocular lenses[1]
- Irritants on the surfaces of surgical instruments (denatured OVDs)[10]
- Topical ophthalmic ointments[12]
- Inappropriately reconstituted intraocular preparations[13]
- Contaminated irrigating solutions (e.g., balanced salt solution contaminated with bacterial endotoxin).

One study shows that corneal toxicity from intracameral agents may be associated with the concentration of free radicals present in the agents. [14] Contaminants on the surfaces of intraocular surgical instruments that have accumulated as a consequence of inadequate or inappropriate instrument cleaning include the following:

- Denatured viscosurgical devices
- Enzymatic detergents
- Bacterial endotoxin contamination of ultrasound water bath cleaners
- Impurities of autoclave steam
- Oxidized metal deposits and residues

- Mitomycin-C: In addition, according to Pastor et al. Mitomycin C used during a trabeculectomy may decrease the endothelial cell count by 4.7-20%. [15]
- Sterilization of equipment: Bacterial endotoxin contamination during sterilization can be related to the development of TASS. Gram-negative bacteria may proliferate if the water reservoir in the phaco machine or inside the autoclave is not replaced on a regular basis. Gram-negative bacteria are typically destroyed during the autoclaving procedure; however, heat-stable lipopolysaccharide (LPS) endotoxin may remain behind. Endotoxin deposits are removed only by acetone or alcohol if operative instruments are dry. Currently, sterilization of surgical instruments is mostly done using an autoclave or EO gas. An autoclave has the disadvantage of potentially leaving rust inside devices with a small internal caliber. It may also wear down the instruments. However, the U.S. Centers for Disease Control and Prevention (CDC) pointed out that EO gas is a carcinogen and can be toxic to reproductive cells. [16] This indicates that sterilization using EO gas should be avoided whenever possible. Autoclaving should be the
technique of choice to sterilize surgical instruments. The use of disposable instruments will help make operative conditions safer for patients. In this study, the team found that all patients who developed TASS had surgeries which used instruments that were sterilized with EO gas. Therefore, it is highly likely that development of TASS was related to the sterilization technique. Smith et al. found that the chrome covering the inside of the cannula may be oxidized during plasma gas sterilization.

- Viscosurgical devices can be produced by gene-coded bacteria in a microbial fermentation process and may be contaminated by heat stable endotoxins. Endotoxins in OVDs must not exceed 0.50 endotoxin units/mL. The highest acceptable endotoxin concentration (EC), however, is yet to be established. In one study, Provisc had an EC under 1.2 endotoxin units/mL. Concern has been expressed regarding the presence of endotoxins in OVDs, which may be responsible for postoperative anterior chamber reactions. The use of pure OVDs is therefore recommended to prevent inflammatory reactions. One hypothesis might be that heat-stable endotoxins in the Provisc caused an anterior segment inflammatory reaction in a hypersensitive patient.

A study was conducted by Leder HA et al. to investigate whether enzymatic detergents used in cleaning ophthalmic surgical instruments can cause toxic anterior segment syndrome (TASS)-like responses in a rabbit model. It was a randomized, investigator-masked, controlled experimental animal study and it was concluded from the study that enzymatic detergents caused a severe but unusual response from the iris when injected intracameraly into rabbit eyes. This response has not been reported in humans with TASS. The time course of inflammation was faster (peak at 6 hours) and resolved more quickly (within 48 hours) than TASS. Simulated cleaning and extraction studies indicate that the level of residual detergent to which a patient could be exposed is significantly less than the lowest dose used in this study. Because that low dose caused no significant observations other than injection of the iris vessels, these results do not support residual enzymatic detergents on surgical instruments as a cause for TASS.

Because of the multiple causes and associations implicated, it is often difficult for the surgical center to isolate a cause directly. The TASS task force of the American Society of Cataract and Refractive Surgery (ASCRS) has developed a questionnaire to assist investigation of a TASS outbreak.

Clinical Features
The hallmark of TASS is its -

- Rapid onset, usually within 12-24 hours.
- Painless, however, if pain is present, it is mild.
- Decreased vision

Depending on the severity of the insult, the presentation can vary. Features that are unique to TASS include the following:

- Limbus-to-limbus corneal edema: the classic finding of TASS; however, not all cases have this finding.
- Anterior chamber reaction: moderate to severe with the presence of hypopyon and fibrin
- Pupil: dilated and non-reacting to light.
- Intraocular pressure: elevated secondary to trabecular meshwork damage.
- Cystoid macular edema may occur.
The following table summarizes the classic presentation of TASS and infectious endophthalmitis to help differentiate the two entities. (Table: 1) Differentiating Toxic Anterior Segment Syndrome and Infectious Endophthalmitis[^6]

**Management**

Patients who present with TASS should be assessed carefully and infectious endophthalmitis should be ruled out by:

- Anterior chamber aspirate
- A vitreous tap, and/or a vitreous biopsy for Gram stains and
- Microbiologic cultures
- B-scan ultrasound
- Specular microscopy
- Ultrasound bimicroscopy

**Conservative management**

Patients should be treated as infectious endophthalmitis if the clinical picture is unclear as to the exact etiology of the inflammation unless proved otherwise. Once TASS is confirmed, patients should be started on topical steroids.

- **Topical steroids**
  - Prednisolone acetate 1%: Strongest steroid of its group and best choice for uveitis. It decreases inflammation by suppressing migration of polymorphonuclear leukocytes and reversing increased capillary permeability. The usual regimen is 1 drop every 30-60 minutes for the first 3 days with gradual tapering.[^21]

- **Nonsteroidal Anti-inflammatory Drugs**
  - NSAIDs inhibit enzyme cyclooxygenase and also can be used in the prevention of cystoid macular edema (CME). NSAIDs are administered topically, usually for 3-4 months.

- **Anterior chamber washout**: No clear benefit has been demonstrated for immediate anterior chamber washout. In cases of a severe and refractory fibrin reaction due to TASS, intracameral recombinant tissue plasminogen activator (r-tPA) may be beneficial.

- **Intraocular lens exchange**: In cases where the intraocular lens is suspected to be the cause of the inflammation, an intraocular lens exchange may be needed if no response to medical treatment is demonstrated.

- **Corneal transplantation**: If corneal edema persists for more than 6 weeks despite medical treatment, the corneal decompensation is likely permanent and a corneal transplantation is required.

- **Glucoma filtration surgeries**: If intraocular pressure cannot be controlled medically, seton valve procedures may be required.

**Follow up**

Initially, patients should be examined on a daily basis to assess their response to treatment. Once the inflammation is resolved, patients need to be assessed carefully for corneal and/or trabecular meshwork damage.

**Prevention**

Recommended practices for cleaning and sterilizing intraocular surgical instruments from the American Society of Cataract and Refractive Surgery and the American Society of Ophthalmic Registered Nurses[^22] are as follows and divided into 2 sections -

- **General principles of cleaning and sterilization that must be addressed to prevent TASS**.
- **Specific recommendations for cleaning and sterilizing intraocular surgical instruments**.
General principles of cleaning and sterilizing intraocular surgical instruments

- To avoid drying of debris and OVD, the instruments should be kept moist until the cleaning process begins.
- All debris inclusive of OVD should be removed.
- Quality and volumes of water should be used as specified by manufacturer’s directions for use (DFU) for suspension of detergents and for cleaning and rinsing instruments.
- DFU for most intraocular instruments require or recommend sterile distilled or sterile deionized water for most cleaning steps. Sterile distilled or sterile deionized water are required for final rinsing.
- Follow detergent and instrument manufacturers’ DFU to ensure proper use of the detergent and to ensure compatibility with the instruments.
- Rinsing should remove all cleaning agents as well as all debris loosened during the cleaning process.
- The method of sterilization applied to instruments should be approved by both the manufacturer of the sterilizer and the manufacturer of the surgical instruments. Sterilizers should be maintained in accordance with the manufacturer’s recommendations.
- Procedures for instrument cleaning and sterilization should be developed and written for each healthcare facility.
- Adequate time should be provided to allow completion of all steps of cleaning and sterilization.
- Staff training, competency validation, and periodic performance review should be implemented for each healthcare facility.

Recommendations for cleaning and sterilizing intraocular surgical instruments

- Adequate time for thorough cleaning and sterilization of instrumentation should be established.
- Rigorous adherence to recommended procedures for cleaning and sterilizing surgical instruments should never be circumvented to save time or money.
- Inventory of instruments should be sufficient to meet surgical volumes and to provide adequate time for completion of cleaning and sterilization.
- Flash sterilization is designed to manage unanticipated, urgent needs for instruments. Flash sterilization should not be used to save time or as a substitute for sufficient instrument inventory.
- For each piece of equipment, the manufacturer’s DFU pertaining to cleaning and sterilization should be followed.
- Ophthalmic viscosurgical device solution, which can dry and harden within minutes, should not be allowed to dry on the instruments.
- Instruments should be wiped with a dampened lint-free cloth and flushed and/or immersed in sterile water in the operating room (OR) immediately following use, in strict accordance with manufacturer’s DFU for each instrument. Sterile water baths used for cleaning or soaking soiled instruments should be kept in areas removed from the operative field and removed from sites that maintain instruments needed to complete the surgical procedure.
- The DFU for some reused cannulated instrument specify the solution, volumes, and frequency for flushing of each lumen. Flushing should be completed as specified in the OR or in the decontamination area.
• Whether they are used, instruments opened for a procedure should be transported from the OR in a closed container to the decontamination area, where cleaning should be completed immediately.
• Disposable cannulas and tubing should be used whenever possible, and they should be discarded after each use. These devices are sold without DFU for cleaning, and thorough cleaning is difficult to achieve and to validate.
• Devices labeled for single use only should not be reused; single-use devices do not include instructions for reuse or reprocessing. The FDA actively regulates third-party and hospital reproprocessors of single-use devices according to FDA guidance.
• To avoid contamination with bioburden and cleaning chemicals, intraocular instruments should be cleaned separately from nonophthalmologic surgical instruments.
• The importance of enzymatic detergents for the cleaning of soiled intraocular instruments has not been established. Inappropriate use and incomplete rinsing of enzymatic detergents have been associated with outbreaks of TASS. If the DFU does not prohibit the use of a detergent and if a detergent is used
• Care should be taken to ensure instructions for proper dilution, outdate, and disposal are followed.
• The cleaning solution should be mixed with measured amounts of water and detergent (i.e., not mixed with estimated volumes), according to the detergent’s DFU.
• Following cleaning with detergents, with or without the use of an ultrasonic cleaner, instruments should be thoroughly rinsed with copious volumes of water to ensure removal of all detergent. If rinse volumes are specified by the detergent manufacturer’s DFU or by the equipment manufacturer’s DFU, they should be considered minimum volumes. Use of tap water for rinsing and for removal of detergent should be compatible with the manufacturer’s DFU for the detergent and for the equipment. The final rinse should be with sterile distilled or sterile deionized water.
• If an ultrasonic cleaner is used
• Ensure that gross soil has been removed prior to placement in the ultrasonic cleaner.
• Check the manufacturer’s DFU of instruments to identify instruments that should not be subjected to ultrasonic cleaning.
• An ultrasonic unit designated for cleaning of medical instruments should be used.
• Validation of functioning, degassing, and preventive maintenance should be performed as recommended in the ultrasonic cleaner’s DFU.
• Ultrasonic machines must be emptied, cleaned, disinfected, rinsed, and dried at least daily and preferably after each use. Unless specified otherwise by the manufacturer, cleaning should be performed with an EPA-registered, facility-approved disinfectant and followed by sterile or tap water rinse sufficient to fully remove the cleaning agent. If not contraindicated by the ultrasonic cleaner’s manufacturer, final rinse with 70% to 90% ethyl or isopropyl alcohol is recommended when feasible and unassociated with risk for fire. The machine should be dried completely with a lint free cloth.
• Refilling should occur immediately prior to use.
• Manual cleaning processes
• Brushes should be designed for cleaning medical instruments.
Cleaning tools such as syringes and brushes should be discarded after each use. If brushes are reused, they should be designed for reuse and they should be cleaned and high-level disinfected or sterilized, preferably after each use, or at least once daily.

Cleaning solutions should be discarded after each use.

When flushing is used as part of a cleaning technique, the effluent should be discharged into a sink or separate basin so the fluid is not reused. Discharge of the effluent should be completed to minimize splash and aerosolization.

\[\text{Rinsing}\]

Follow the manufacturer’s DFU for selecting the appropriate type of rinse water for equipment.

Unless otherwise specified by the manufacturer’s DFU, sterile distilled or sterile deionized water should be used for the final rinse of instruments.

Rinsing should provide flow of water through and/or over instruments, with effluent discarded as it is used, so only debris-free water is used for rinsing.

Agitation in a basin of water should not be used as a final rinse.

Following thorough rinsing, instruments with lumens should be dried with forced or compressed air.

Compressed air should be filtered and free of oil and water.

Instruments with lumens should be fully dried.

Specific instruments: phacoemulsifier handpiece, irrigator/aspirator, irrigator/aspirator tips, and inserters

Flush phacoemulsifier handpiece with balanced saline solution prior to removing from the operative field.

Wipe each instrument with a lint-free cloth and place immediately in a bath of sterile water. Remove from the operative field and remove from sites that maintain instruments needed for completion of the surgical procedure, in strict accordance with the manufacturer’s DFU for each piece of equipment.

Clean and flush each item in accordance with the manufacturer’s DFU and verify removal of all debris inclusive of OVD.

Inspect irrigator/aspirator tips, preferably under magnification, before sterilization.

If reusable woven materials are used for draping the sterile field, to absorb condensate in steam sterilized instrument trays or to wipe instruments, they should be laundered and rinsed thoroughly between each use to eliminate surgical compounds, debris, and cleaning agents.

Inadequate rinsing of high pH detergents used in institutional laundering can leave chemical residues that could be transferred to intraocular instruments. Laundry procedures should be reviewed and monitored to ensure delivery of residue-free, reused woven materials; otherwise disposable, chemical, and lint-free materials should be used.

All woven materials used in intraocular surgery or instrument management should be lint free.

Cleanliness and integrity of instruments should be verified.

Instruments should be visually inspected for debris and damage, preferably under magnification, immediately after cleaning and before packaging for sterilization to ensure removal of visible debris.

Additional or repeated cleaning and rinsing steps may be required on a case-by-case basis to ensure removal of all debris and OVD.
Surgeons should examine instruments under the microscope prior to each use and reject any instrument that shows signs of residual debris or defects.

Sterilization
- The method for sterilizing intraocular surgical instruments should be in accordance with the DFU of the instruments and with the DFU of the sterilizer manufacturer.
- Steam sterilization should be completed in accordance with published guidelines.
- Glutaraldehyde is not recommended for sterilizing intraocular instruments because of the toxicity of glutaraldehyde residues resulting from inadequate rinsing or contamination during post-sterilization handling. Other low temperature methods of sterilization should not be used unless the ophthalmic instrument manufacturer and the sterilizer manufacturer have validated the method for the specific instruments with respect to efficacy of sterilization, potential ocular toxicity (e.g., from oxidation of metals), and instrument functionality.
- Verification of sterilizer function should be completed at least weekly, preferably daily, in accordance with the sterilizer manufacturer’s instructions for use and with published guidelines, and documented in the facility log.
- Measures should be taken to ensure that preventive maintenance, cleaning, and inspection of sterilizers are performed on a scheduled basis, according to the sterilizer manufacturer’s written instructions. All preventive maintenance should be documented.
- Maintenance of boilers, of the water filtration systems, and of the quality of water supplying the steam-sterilizing system should be verified at least yearly.

Healthcare organizations may find consultation with companies specializing in boiler maintenance and water quality helpful.

Administrative controls should be implemented.

Policies and procedures regarding cleaning and sterilizing intraocular surgical instruments should be written, reviewed periodically (at least annually), and kept readily available within the practice setting.

A sufficient number of instrument sets, phacoemulsifier handpieces, irrigator/aspirators, and inserters should be purchased to allow adequate time for cleaning and sterilization between procedures.

Personnel involved in handling and cleaning and/or sterilizing intraocular surgical instruments should:

- Be educated about TASS and its causes at hire and updated regularly thereafter.
- ii. Receive initial education, training, and validation of competency in the cleaning, inspection, preparation, packaging, sterilization, storage, and distribution of all intraocular surgical instruments. Education, training and validation of competency should be updated at least annually and prior to introduction of any new devices or procedures.

Prognosis
Prognosis is generally divided into 3 groups depending on the severity of TASS:

- Mild presentation of TASS: Rapid clearing of the corneal edema with no long-term corneal or trabecular damage and normal or near normal visual acuity.
- Moderate presentation of TASS: A persistent corneal edema that will take several weeks to clear, intraocular pressure
that is difficult to control, and a moderate effect on visual acuity.

- Severe presentation of TASS: a marked corneal edema that does not clear, iris and trabecular meshwork damage with resultant glaucoma, and possible cystoid macular edema. Visual outcome is usually poor despite medical or surgical intervention. A potential sequel manifestation of TASS is Urrets-Zavalia syndrome (UZS).

Despite the above descriptions, predicting the outcome for patients remains difficult because of the multiple etiologies and associations linked to TASS.

**Conclusion**

TASS, if occurs, can be fatal to the eye. Therefore, it is best to prevent the syndrome using all possible precautions. If TASS develops despite these preventive steps, additional surgeries should be stopped. A complete check of all surgical equipment and personnel involved is necessary before any new surgeries can be performed. In general, corneal edema due to TASS may not be resolved with topical steroid or hypertonic NaCl treatments. The prognosis in this situation is very bad. A penetrating keratoplasty is the only choice of treatment. In summary, the overall operative conditions, including sterilization and reuse of surgical equipment, requires special attention as well as continuous and thorough management.

**Table 1: Differentiating Toxic Anterior Segment Syndrome and Infectious Endophthalmitis**

<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
<th>TASS</th>
<th>Infectious Endophthalmitis</th>
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</thead>
<tbody>
<tr>
<td>Onset</td>
<td>12-24 hours usually</td>
<td>2-7 days usually</td>
</tr>
<tr>
<td>Pain</td>
<td>Usually none but can be mild to moderate</td>
<td>Usually severe</td>
</tr>
<tr>
<td>Corneal edema</td>
<td>Limbus to limbus</td>
<td>Specific to area of trauma</td>
</tr>
<tr>
<td>Intraocular pressure</td>
<td>May increase suddenly</td>
<td>Usually not elevated</td>
</tr>
<tr>
<td>Anterior chamber inflammation</td>
<td>Moderate-to-severe anterior chamber reaction with increased white blood cells and +fibrin. Hypopyon may be noted.</td>
<td>Moderate-to-severe anterior chamber reaction. Fibrin is variable. Hypopyon often present (75% of the time).</td>
</tr>
<tr>
<td>Vitritis</td>
<td>Very rare</td>
<td>Always present</td>
</tr>
<tr>
<td>Pupil</td>
<td>Fixed and dilated</td>
<td>Reactive</td>
</tr>
<tr>
<td>Lid swelling</td>
<td>Usually not evident</td>
<td>Often present</td>
</tr>
<tr>
<td>Visual acuity</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Response to steroids</td>
<td>Dramatic improvement</td>
<td>Equivocal</td>
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References