Review Article

Medical and surgical approach to ocular surface reconstruction

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Abstract: Ocular surface disease (OSD) can have a severe impact on patients as it can lead to visual impairment and persistent discomfort. Ocular surface reconstruction (OSR) is an approach to the management of ocular diseases that cause structural damage to the ocular surface. OSR encompasses both medical and surgical treatment options. In this review, we discuss the medical and surgical strategies used in OSR. Medical management often aims to treat tear insufficiency, inflammation, and keratinization. Surgical treatments may be employed for a variety of reasons, including failure of medical management. This may include improving the oculo-palpebral structures in order to improve lid positioning and tear film. Additional therapies focus on improving tear production, such as through salivary gland transplantation. In situations where the ocular surface is so severely damaged that there is loss of limbal stem cells, limbal stem cell transplant (LSCT) may be indicated. Other surgeries such as amniotic membrane transplant (AMT) and conjunctival flaps (CFs) can help promote corneal healing. Finally, in severe situations where the cornea is beyond salvage, corneal transplantation, such as a penetrating keratoplasty (PKP), can be considered. OSR often requires a combination of medical and surgical approaches targeted to each specific patient's presentation in order to achieve optimal outcomes.

Keywords: Ocular surface reconstruction (OSR); ocular surface disease (OSD); amniotic membrane transplant (AMT); limbal stem cell transplant (LSCT); eyelid reconstruction

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Introduction

Ocular surface reconstruction (OSR) encompasses numerous approaches to treatment of ocular surface disease (OSD). The principles behind OSR were developed due to the need to manage conditions such as Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), ocular cicatricial pemphigoid (OCP), and chemical burns (1). In these conditions, acute and/or chronic ocular surface inflammation results in severe OSD (1). Furthermore, OSD is often associated with structural abnormalities such as limbal stem cell deficiency (LSCD), symblepharon formation, forniceal shortening, ocular surface keratinization, and corneal scarring—all of which may necessitate surgical correction to restore ocular anatomy and visual function. In this chapter, we describe medical and surgical interventions to repair the ocular surface (1).

Candidacy

Candidates for OSR often have ocular surface inflammation that needs pre-operative optimization, and all have anatomic abnormalities of the ocular surface requiring correction. In general, medical optimization should occur first. An exception to this rule is with certain acute inflammatory conditions, such as SJS, as discussed below, in which case patients should receive an amniotic membrane (AM) graft within the first 7 days of symptom

onset for severe disease (2).

Pre-operative medical management

Medical management of OSD is an important first step before considering surgical methods, and targeted medical treatment may also help improve the long-term success of any future surgery. Reducing inflammation throughout the ocular surface—but particularly in the limbal microenvironment—is critical. Medical management can be used to improve the tear film, promote health of the ocular surface epithelium, and improve patient comfort while they await surgical intervention.

Tear insufficiency

OSD is often characterized by signs and symptoms of dry eye disease (DED). Artificial tears can help promote ocular surface healing by replenishing the aqueous and/or lipid components of the tear film (3). Patients with significant ocular surface inflammation and/or anatomical sequelae should be advised to use preservative-free formulations to prevent toxicity from preservatives such as benzalkonium chloride (4). A low-dose topical steroid such as fluorometholone 0.1% or loteprednol 0.5% may be considered, with precautions taken regarding intraocular pressure elevation, cataract formation/progression, and secondary infection; to avoid preservatives, preservative-free steroid formulations may be considered, which may need to be obtained via a compounding pharmacy.

Warm compresses, eyelid hygiene, and medications such as oral doxycycline or azithromycin, or topical azithromycin, may also help improve symptoms in patients with meibomian gland dysfunction and resulting evaporative dry eye (5). In cases of aqueous tear deficiency and/or excess drainage, punctal occlusion can be achieved with punctal plugs or surgical closure of the puncta.

Autologous serum (AS) eyedrops can provide additional benefits. Derived from one's own blood serum, AS eye drops are rich in proteins and growth factors like epithelial growth factor (EGF) and neural growth factor (NGF), which may enhance wound healing. A recent report suggested that early, aggressive treatment of early contact lens-induced limbal stem cell disease with AS can result in disease reversal (6). However, AS may be contraindicated in cases of systemic inflammation and anemia. Instead, patients may receive allogeneic serum eye drops derived from the blood of a compatible donor (e.g., type AB universal serum donor), after appropriate blood screening and informed consent (7). In addition, it is possible to produce eye drops harvested from umbilical cord serum, which may provide further benefits due to elevated concentrations of EGF and NGF (8).

In patients with severe aqueous tear deficiency (e.g., Sjögren's syndrome), oral pilocarpine may be considered; it acts as muscarinic acetylcholine receptor agonist that may improve exocrine secretion of the lacrimal gland. In a placebo-controlled crossover study, after 10 weeks on 20 mg daily oral pilocarpine, patients with Sjögren's syndrome showed improved tear film quality, although over two-thirds of patients reported excessive sweating as a side effect (9). In patients with filamentary keratitis, topical N-acetylcysteine (NAC) may reduce the presence of filaments, as well as enhance corneal wound healing and reduce tear viscosity, although it may be difficult to source (10). In a randomized, controlled, double-blind study, instillation of NAC improved the mean tear film thickness within 10 minutes and this effect lasted for 24 hours (11).

For patients with severe DED in the setting of neurotrophic keratopathy and a persistent epithelial defect, topical NGF (cenegermin) may be considered (12,13). Typical dosing for cenegermin ophthalmic solution 0.002% (20 mcg/mL) is six times a day for 8 weeks. The nasal spray formulation of varenicline acts as a nicotinic acetylcholine receptor agonist that triggers tear production. Given its non-ophthalmic route of administration, varenicline nasal spray may be a means of reducing the risk of toxic keratoconjunctivitis for patients who may otherwise be on multiple topical agents.

Inflammation

Severe ocular surface inflammation may inhibit wound healing and can often be reduced with topical anti-inflammatory agents. Topical corticosteroids are effective at reducing inflammation and improving symptoms of OSD secondary to a wide variety of etiologies. However, long-term use of topical corticosteroids requires close monitoring (8). Among topical steroids, fluorometholone 0.1% may be considered due to its reduced ocular penetration. However, since fluorometholone contains preservatives, compounded steroid drops such as preservative-free dexamethasone 0.1% or methylprednisolone 1% may be considered as alternatives.

Topical cyclosporine may be considered as a means of reducing ocular surface inflammation without the

complications associated with steroids, although with lower efficacy. It is available commercially in 0.05% and 0.09% concentrations; higher concentrations may be obtained from a compounding pharmacy. Lifitegrast, approved by the Food and Drug Administration (FDA) in 2016 for DED, may also be considered (14). Topical tacrolimus, which is much more potent than cyclosporine, may be a suitable alternative, although an ophthalmologic formulation is not approved in the U.S. and therefore may also need to be obtained via a compounding pharmacy (8). Off-label use of a dermatologic formulation of tacrolimus ointment (0.03% or 0.1%) for ocular surface inflammation has been described.

In eyes with severe, chronic ocular surface inflammation, systemic immunosuppression may be required to achieve sufficient control in preparation for surgery (15). This is particularly important to consider in conditions causing a cicatrizing conjunctivitis such as SJS, mucous membrane pemphigoid (MMP)/OCP, and graft-versus-host disease (GVHD). Immunosuppressive doses of systemic steroids (oral prednisone or IV methylprednisolone) may be considered initially, with a transition to steroid-sparing agents such as mycophenolate mofetil (MMF) or methotrexate for long-term management (16). Additional systemic steroid dosing is advisable intraoperatively and in the post-operative period.

Keratinization

Lid margin keratinization (LMK) can be a chronic consequence of conditions such as SJS, OCP, chemical burns, and vitamin A deficiency. Due to the lid margin epitheliopathy, the ocular surface sustains progressive damage. The exact pathophysiology of LMK is unclear, as some propose it is due to keratinization of epithelium at the posterior lid margin of adjacent anterior eyelid epidermis, hyperkeratinization of epithelium from meibomian glands, or *de novo* metaplasia of the conjunctival epithelium (17). Keratinization can sometimes be managed medically with vitamin A ointment, which softens the built-up keratin, as well as manual sweeping with a cotton-tipped applicator at each clinic visit. Other management considerations include a specialty contact lens (see below) or a mucous membrane graft (MMG) (when the palpebral conjunctiva is involved).

Bioartificial devices

Scleral contact lenses (SCLs) can be used in patients with a variety of conditions, including severe keratoconjunctivitis sicca, LSCD, neurotrophic keratopathy, exposure keratopathy, LMK, and cicatrizing conjunctivitis. Scleral lenses are rigid, gas-permeable, large-diameter lenses that vault over the cornea. By maintaining a fluid interface between the ocular surface and posterior aspect of the contact lens, these lenses facilitate corneal healing and further protect the ocular surface from keratinization and cicatricial entropion (18). They have been shown to improve punctate staining and filamentary keratitis, and can also help to heal persistent epithelial defects. Furthermore, three-dimensional (3D)-printed custom lenses can be made to fit corneas with severely abnormal corneal or cornea-limbal contours, as may be seen with severe OSD (19).

Prosthetic Replacement of the Ocular Surface Ecosystem (PROSE) is a type of SCL that was developed in Boston. The device is typically well-tolerated by patients, and studies have shown significant improvements in visual acuity in over 80% of eyes among patients with LSCD and OSD who wear the device (20,21). Its use may be considered in patients with partial LSCD. The PROSE device is approved by the FDA for refractive management of an irregular corneal surface and for therapeutic use in eyes with severe OSD. Complications of SCL wear may include microbial keratitis and corneal hypoxia (20).

Post-operative medical management

Post-operative medical management includes continued lubrication, topical and systemic immunosuppression, and antibiotic prophylaxis. Further, post-operative management will be discussed as it relates to the specific surgical methods discussed below.

Surgical management

Eyelid reconstruction

There are a variety of eyelid malposition that may lead to complications of OSD including corneal ulceration and perforation. These include (I) eyelid paralysis; (II) cicatricial eyelid ectropion; (III) eyelid entropion; and (IV) trichiasis. Eyelid paralysis and cicatricial eyelid ectropion often lead to lagophthalmos (incomplete closure of eyelids when blinking) and exposure keratopathy, whereas entropion and trichiasis lead to rubbing of eyelashes and keratinized skin on the cornea (22). There are many approaches to manage eyelid malposition depending on the condition and attention must be paid to each patient's unique presentation

Table 1 Surgical considerations to correct eyelid abnormalities during ocular surface reconstruction

Abnormality	Surgical technique considerations
Eyelid paralysis	(I) Temporal tarsorrhaphy (temporary or permanent)
	(II) Platinum or gold weight placement
Cicatricial eyelid ectropion	(I) Lateral tarsal technique described in the "Cicatricial eyelid ectropion" section
	(II) Frost technique
Eyelid entropion	Depends on the cause and location of entropion. See the "Eyelid entropion" section
	(I) Correct horizontal laxity
	(II) Stabilization of the lower eyelid retractors
	(III) Partial excision of the orbicularis muscle close to the eyelid margin
Trichiasis	(I) Eyelash ablation (radiofrequency ablation, electrolysis, cryotherapy, or laser)
	(II) Lamellar split
	(III) Eyelash excision

to try and restore normal anatomy as best possible. Generally, all eyelid surgeries are performed before limbal or corneal surgeries.

Eyelid paralysis

Lagophthalmos and exposure keratopathy due to paralysis are most often due to facial nerve palsy and weakness of the orbicularis, this results in the inability of the upper eyelid to close and paralytic ectropion of the lower eyelid. Nocturnal lagophthalmos is especially damaging as the normal Bell's reflex that occurs during active blinking is not present while sleeping. Initial treatments include aggressive lubrication with artificial tears and ointment along with taping the eye closed at night (23). A temporary lateral tarsorrhaphy may be placed to allow for adequate ocular coverage while the nerve recovers. In instances where the facial nerve palsy will not recover, surgical correction is recommended to protect the ocular surface.

To help with upper eyelid closure, a platinum or gold weight may be placed either anterior to the tarsal plate, or just above it. This can be achieved through an eyelid crease incision. This allows the upper eyelid to close better without causing significant ptosis. The lower eyelid paralytic ectropion is addressed by a lateral tarsal strip procedure in which the lateral canthus is severed from the orbital rim with a lateral cantholysis (24). A small wedge of tarsus is then excised and then the tarsus is re-anchored to the lateral orbital rim, usually with a 4-0 or 5-0 absorbable suture (i.e., Vicryl). In more severe cases with a decreased Bell's reflex, a small permanent lateral tarsorrhaphy, or a lower eyelid retractor release can also be performed.

Permanent tarsorrhaphy involves splitting the lamella of the upper and lower lid over an area of 3–4 mm, and debriding the eyelid margin. The tarsus of the upper and lower eyelid is then sutured together in this area in a horizontal mattress fashion, followed by the anterior lamella, often using 6-0 absorbable sutures (25). A retractor release is performed while the inferior fornix is exposed after a lateral cantholysis. An incision is performed across the lower eyelid conjunctiva within the inferior fornix making sure to cut posterior to the inferior retractor layer to release it. This layer can be further released by recessing it away from the conjunctiva. The conjunctiva can then be closed if needed with a running or interrupted fast-absorbing suture (i.e., 6-0 plain gut) (*Table 1*).

Cicatricial eyelid ectropion

Lower eyelid ectropion due to age-related horizontal laxity of the eyelid can be corrected with the lateral tarsal technique described above. However, significant cicatrization of the eyelid skin may not allow the eyelid to move into the correct position. This can be caused by conditions such as burns, eyelid trauma, and after orbital fracture repair. In these cases, placement of a full-thickness skin graft is often required. For the lower eyelid, the surgical technique involves making a sub-ciliary incision across the length of the eyelid and then dissecting through the orbicularis down to the retractor layer. A lateral tarsal strip procedure is then performed (if there is laxity) to tighten and re-anchor the eyelid to lateral orbital rim. The

lower eyelid is then put on stretch by using an anchoring the upper part of the sub-ciliary incision to the brow using a double-armed 4-0 silk suture, going through the upper eyelid (Frost technique). The resultant gap in the skin is then filled with a full-thickness skin graft that can be taken from the either the post-auricular or supraclavicular region. In the case of upper eyelid cicatrization, a similar technique can be used, with the initial incision being in the upper eyelid crease, and without need to address the lateral canthus as in the lower eyelid (*Table 1*).

Eyelid entropion

Eyelid entropion is the inward turning of the eyelid, resulting in contact between the eyelashes and corneal surface. Entropion most commonly occurs due to increased laxity of the eyelid with age. In contrast to involutional ectropion where the eyelid turns outwards, involutional entropion occurs when the tone of the orbicularis overrides the stability of the eyelid retractors (the Levator and Muller muscle in the upper eyelid and the capsulopalpebral fascia in the lower eyelid) and causes the eyelid to turn inwards. Entropion may also occur secondary to conjunctival symblepharon, which is the abnormal fusion between the bulbar and palpebral conjunctiva. Symblepharon can be due to SJS, OCP, trauma, chemical or thermal burns, and trachoma. In these cases, abnormal adhesions are formed as there is loss of epithelial cells (ECs) from the bulbar and palpebral conjunctiva due to a dysfunctional healing process. Rare congenital cases may occur as well, such as in cryptophthalmos found in Fraser syndrome (26).

Involutional entropion most commonly occurs in the lower eyelid, resulting in eyelashes along the entire length of the eyelid to rub on the cornea. Topical treatment with antibiotic and lubricating ointment can allow it to be observed for a while, but it should be surgically corrected to avoid worsening of the ocular surface. Surgical treatment can include correction horizontal laxity, stabilization of the lower eyelid retractors, and partial excision of the orbicularis muscle close to the eyelid margin. Horizontal laxity is addressed using a standard lateral tarsal strip technique, but the retractor layer can be approached either from the conjunctival side with an inferior fornix incision, or through a sub-ciliary incision. Regardless of the approach, the goal is to suture the dehisced capsule-palpebral fascia back to the tarsal plate using a fast-absorbing suture (5-0 plain gut or 6-0 chromic gut). The sub-ciliary approach is more versatile as the orbicularis muscle can be addressed at the same time by excising the part of it just under the eyelashes, weakening the inward vector. This approach is especially useful for congenital entropion, where the main pathology is a robust orbicularis, not retractor layer dehiscence or horizontal laxity (27).

Involutional upper eyelid entropion is less common, but can occur in older patients where the balance between the inward and outward vectors of the upper eyelid breaks down. It can sometimes be observed, as the eyelashes may not be touching the cornea, but if corneal trauma from lashes is significant, then surgical intervention may be needed. Anterior lamellar rotation sutures (i.e., 6-0 Vicryl) can be placed through an upper eyelid crease incision to help rotate the skin and orbicularis tissue closest to the eyelid margin away from the cornea by suturing it to a point higher up on the tarsus. In more severe cases, the entire anterior lamella can be split away from the tarsus (including the eyelashes), a technique also used to correct trichiasis. This is achieved with a 15 Bard Parker blade cutting through the grey line across the entire length of the upper eyelid. The released anterior lamella is then sutured higher up on to the tarsal plate. A labial MMG may also be used to cover the raw eyelid margin, and can be sutured in with fast-absorbing sutures.

Surgical correction of cicatricial entropion must be performed by addressing symblepharon formation and loss of conjunctival fornices. A symblepharolysis is performed first, and in both the upper and lower eyelids, the eyelid must be released completely. This may require release of the retractor layers. Once the eyelid is released, the gap in the conjunctiva can be filled with a labial MMG to reconstruct the fornix, and a silicone stent may be used to help maintain forniceal depth. Variations of this include using a buccal mucosa graft or nasal turbinate mucosal graft in cases of mucin deficiency (28). Mitomycin C (MMC) or 5-fluorouracil can be applied as well to the sub-conjunctival forniceal area to decrease the risk of recurrent forniceal shrinkage (29) (*Table 1*).

Trichiasis

Trichiasis a disorder where the eyelashes are misdirected towards the globe and rub against the conjunctiva and cornea, causing damage to the ocular surface. Trichiasis is often due to acquired conditions involving inflammation or scarring of the eyelash follicles. Chronic blepharitis, skin inflammation (atopic diseases or eczema), or conjunctival inflammation (SJS) all can lead to trichiasis. Treatment first involves addressing the underlying condition. Non-surgical

methods to improve symptoms such as lubrication, bandage contact lens (BCL), or mechanical epilation can be used, but are often give only temporary relief.

Eyelash ablation can be used when a small area of the eyelid is involved, or multiple areas with a few trichiatic eyelashes. This can be done via radiofrequency ablation, electrolysis, cryotherapy, or laser. Radiofrequency ablation is used to ablate each eyelash follicle individually and remove the eyelash. Electrolysis is conducted by applying an electric current using an electrolysis needle inserted into the eyelash. Cryotherapy involves cooling the eyelid margin to reach −20 to −30 ℃. In laser treatment, an argon laser is used (50–200 μm spot size and power of 0.2 to 1.5 W for a duration of 200 microseconds) to destroy the eyelash follicle (30).

A surgical approach to trichiasis is considered for broad areas of trichiasis. A lamellar split, described in the entropion section, involves separating the anterior and posterior lamella of the affected area and shifting the eyelashes away from the eyelid margin (30). An excision of the eyelashes can be performed as well, or a labial MMG can be placed. Wedge resection can be used for surgical treatment of trichiasis affecting less than 1/3 of the width of the eyelid margin. A pentagon-shaped region of the eyelid is excised. A lateral cantholysis can be performed if there is significant horizontal tension and allows for easier approximation during closure (31).

Post-surgical considerations

After eyelid reconstruction surgery, patients should be monitored for signs of bleeding, pain, and infection. Patients are usually given topical antibiotic/steroid ointments such as tobramycin/dexamethasone or neomycin/polymyxin B/dexamethasone 2 to 4 times daily over the surgical incisions for the first 1–2 weeks. Pain medication may include tylenol alone, or a very limited supply of opioid medication for more extensive surgeries (*Table 1*).

Amniotic membrane transplant (AMT)

The amnion is the innermost layer of the placental sac and can be harvested for transplantation (32). AM was first introduced to clinical medicine as a substrate for skin transplantation (33), and has since been adapted for multiple medical purposes including for restoring mucous membranes. Its use in ophthalmology is usually to restore damaged tissue, prevent further degeneration from external factors, and promote re-cellularization (34), It has multiple biological properties and lacks immunogenicity, thus reducing the risk of an immune response (32). Additionally, amnion has been shown to improve pain and deliver anti-microbial benefits (35,36). In patients with neurotrophic ulcers of the cornea, nearly 70% of patients healed by AMT by 18.8 months (37).

It was first described for ocular use in the 1940's as a conjunctival substitute (38) after fibrotic tissue removal. It initially fell out of favor due to bloodborne virus infection and supply issues. However, by the 1990's AMT regained popularity as preservation, harvesting, and distribution methods were perfected. It can be preserved via cryopreservation, freeze-drying/lyophilization, dehydration/low temperature vacuum evaporation (32).

Patient selection

The strongest use case for AMT is in cases of acute SJS. Outcomes are significantly improved if AMT is performed within 7 days of symptom onset in these patients (2). AMT can be used in conjunctival limbal epithelial transplant (CLET), simple limbal epithelial transplant (SLET), cultivated oral mucosal epithelial transplantation (COMET), and simple oral mucosal epithelial transplantation (SOMET). It can also be helpful in bleb revisions, and in removal of ocular surface lesions where there is inadequate conjunctiva available (39). AMT can also be used as an alternative to mucosal membrane transplantation in lid revision, orbital linings, or symblepharolysis, in the absence of available conjunctival tissue (29,40,41). AMT is also helpful to cover the cornea and limbus at the end of ocular surface and/or corneal surgery, including penetrating keratoplasty (PKP), and especially in cases of neurotrophic keratopathy.

AMT has been well documented in pterygium excision, although its efficacy is lower than that of conjunctiva. Its use in the healing phase of injury is discussed below as it relates to LSCD. However, in the acute phase, AMT can also be transplanted epithelial side down within the first 7 days of chemical injury (42). While this can increase the rate of epithelial healing, it does not have an effect on secondary long-term visual outcomes, symblepharon formation, corneal clarity, or neovascularization. In the setting of burns, the use of AMT is largely dependent on the severity of the burn, but generally, AMT reduces inflammation and pain if applied within the first week of injury.

Surgical methods

Ocular AMT may be carried out using various transplantation methods, including inlay (regenerative), onlay (protective), and a combined approach (*Table 2*).

Inlay transplantation (graft)

The inlay transplantation involves the amnion being grafted into the damaged ocular surface after the defective tissue has been removed from the site. The amnion replaces the lost tissue can integrate into corneal stroma due to the formation of hemidesmosomes and desmosomes (43). It is placed with the epithelial side up as the graft can act as a substrate for epithelial regeneration. A rim of epithelium is removed from the periphery of the stromal defect so that there is no overlapping epithelium, which reduces the chance of proliferation under the graft and helps the inlay graft epithelium to grow. Residual membrane, often visible as white lines, may be visible after the tissue is incorporated into the cornea.

Onlay transplantation (patch)

Patch amnion transplantation is the addition of the tissue epithelial side down over the superficial wound. It serves as a temporary biological dressing thereby acting as a physical barrier against the environment and preventing symblepharon formation, ankyloblepharon, and other physical harm. The proteins secreted by the membrane limit scarring and fibrosis, and it is not intended to be integrated into the cornea.

Combination transplantation (sandwich)

This method uses both the inlay and the onlay methods to provide structural integrity and protection. Both allow for the delivery of anti-inflammatory properties.

Surgical technique

A 10-0 nylon running or interrupted suture can be placed with amnion epithelium side up over the cornea, with consideration of a second amnion was placed epithelium side down, in cases of corneal epithelial defects with thinning. Alternatively, wet or dry (dehydrated) AMT can be placed with or without tissue adhesive over the cornea, and covered with a BCL. Epithelial defects associated with neurotrophic keratopathy or infectious keratitis have the highest closure rates, typically seen within the first 3 months after AMT. The highest rates of healing are often seen following the "sandwich method" but this group also has the poorest visual outcomes (44). A thicker version of AMT has also been described for use in cases of OSR, including for tissue melt/ulceration.

AMT can also be used in conjunction with or without limbal stem cell transplant (LSCT) for treatment of LSCD. In order to prevent conjunctival EC migration over the cornea, one can use sector sequential conjunctival epitheliectomy (32). Another method involves amnion assisted conjunctival epithelial redirection, which utilizes the amnion patch to redirect the conjunctival cells and allow corneal ECs to regenerate. A 360° peritomy can also be performed with donor conjunctivokerato limbal grafts sutured at the 6 and 12 o'clock position with the inlay amnion graft placed under the outer edge of the recessed conjunctiva and the limbal explant. The outer AMT graft is held with fibrin glue and covers the cornea and adjacent sclera (32).

In those with advanced OCP, AMT can be placed over the cornea, bulbar and tarsal conjunctiva and anchored with an 8-0 Vicryl sutures to the conjunctival edges and deep fornixes with double armed 6-0 silk suture (45). One study has shown that forniceal depth improves up to 28 weeks following surgery (45).

Another use of AMT is in the treatment of severe DED. Suture-less AMT (such as PROKERA®) can lead to symptomatic improvement, both subjectively and objectively, when worn for 5 days (46,47). Cost is an important consideration in DED and should be weighed against long-term efficacy. Similar outcomes are seen in cicatrizing conjunctivitis including SJS, TEN, and GVHD. Ma *et al.* (47) demonstrated a method of amnion application in SJS/TEN by using a 10 cm × 5 cm rectangle of amnion with a custom-made forniceal ring to provide full coverage of the mucosal surface and eyelid margin. The amnion is secured by two nylon sutures or cyanoacrylate glue across the ocular surface (48). Shanbhag *et al.* have reported the use of a sutureless technique for bedside application of AMT in patients with SJS/TEN where a custom symblepharon ring is used to secure the AM over the ocular surface and cyanoacrylate glue is used to adhere the AMT to the eyelid margins (48).

SLET

SLET was first described in 2012 by Dr. Sangwan. It is a single-stage method in which a small autologous limbal graft is harvested. In the donor eye, a small conjunctival flap (CF) is created 1–2 mm away from the limbus. At the

Table 2 Ocular surgical considerations for OSR

Procedure	Patient selection	Surgical considerations	Pertinent post-operative complications
AMT	(I) SJS	(I) Inlay transplantation	(I) Infection
	(II) Use for CLET, SLET, COMET, or SOMET	(II) Onlay transplantation	(II) Hematoma
	(III) Bleb revisions	(III) Combination transplantation	(III) Granuloma
	(IV) If inadequate conjunctiva available		
	(V) Lid revision, orbital linings or symblepharolysis		
	(VI) Cover cornea at the end of ocular surface surgery		
	(VII) Chemical injury		
LSCT	(I) Chemical or thermal burn	(I) CLAU	(I) Graft rejection
	(II) Extensive conjunctivalization	(II) Lr-CLAL	(II) Infection
	Note: not recommended for the active phase of inflammation or before eyelid abnormalities are addressed	(III) KLAL	
Salivary gland transplant	(I) Severe dry eyes	(I) SMG transplant	(I) Infection
		(II) MSG transplant	(II) Vascular thrombosis
			(III) Duct obstruction
MMG	(I) Posterior migration of MCJ with LMK	See the "MMG"-"Surgical technique" section	(I) Bleeding
			(II) Graft necrosis
			(III) Graft displacement
			(IV) Ectropion
			(V) Entropion
			(VI) Keratinization at posterior edge
			(VII) Chalazion
			(VIII) Infection
			(IX) Paresthesia at donor site
CF	(I) Phthisical eyes being prepared for prosthetic shell	(I) Gunderson flap	(I) Retraction
	(II) Herpetic keratitis	(II) Racquet flap (single pedicle flap) with or without lamellar corneal patch or scleral patch graft	(II) Buttonholes
	(III) Bullous keratopathy		(III) Erosions
	(IV) Neuroparalytic keratopathy		(IV) Epithelial inclusion cysts
	(V) Traumatic relapsing keratopathy		(V) Corneal perforation
	(VI) Chronic infectious keratitis		(VI) Ptosis
	(VII) Corneal melting		(VII) Infection
	(VIII) Peripheral marginal ulceration		
	(IX) Painful corneas with little resolution with normal healing		
PKP	(I) Trauma	See the "Corneal transplantation (including PKP)"-"Surgical technique" section	(I) Graft failure/rejection
	(II) Chemical injuries		(II) Infection
	(III) Infectious keratitis		(III) Astigmatism
	(IV) Corneal scarring		

OSR, ocular surface reconstruction; AMT, amniotic membrane transplant; SJS, Stevens-Johnson syndrome; CLET, conjunctival limbal epithelial transplant; SLET, simple limbal epithelial transplant; COMET, cultivated oral mucosal epithelial transplantation; SOMET, simple oral mucosal epithelial transplantation; LSCT, limbal stem cell transplant; CLAU, conjunctival limbal autograft; lr-CLAL, living relative conjunctival limbal allograft; KLAL, keratolimbal allograft; SMG, submandibular gland; MSG, minor salivary gland; MMG, mucous membrane graft; MCJ, mucocutaneous junction; LMK, lid margin keratinization; CF, conjunctival flap; PKP, penetrating keratoplasty.

limbus, a 1 mm section is cut into the cornea and excised. In the recipient eye, a 360° peritomy is created, and the pannus is removed. Human AM is fixed into place with sutures or fibrin sealant, the small limbus pieces are arranged around the visual axis epithelial side up in a circular fashion, and the explants are glued in place with fibrin sealant. A large contact lens and antibiotic/steroid drops are placed in at the end of this procedure (49). Allogeneic SLET has also been described.

COMET

COMET was first described by Nakamura and colleagues in 2004 as a surgical method to introduce oral ECs instead of limbal stem cells onto the ocular surface. Oral mucosal tissue is collected via a small oral mucosal biopsy (measuring 2–3 mm^2) and is treated with antibiotics. The mucosal EC are isolated and subsequently seeded onto human AM (which has been previously deprived of its native EC and is positioned epithelial side up in culture plates). The EC-AM complex is cultured with MMC-inactivated fibroblasts. Surgical steps involve removal of the conjunctivalized epithelium over the cornea and surrounding subconjunctival tissues, treatment of the exposed tissues with MMC (this step was included in Nakamura's initial description but may be modified due to concern for MMC toxicity on ocular surface), with placement of the AM over the cornea, and closure with 10-0 nylon sutures at the limbus. A soft CL is placed, and topical antibiotics and steroids are administered (50).

Advantages of COMET include preservation of limbal stem cells in fellow eye, as well as avoiding the risk of rejection. A potential limitation and crucial consideration for COMET is the availability of viable oral mucosa, particularly as patients with SJS or OCP may also have concurrent oral mucosal involvement that causes oral EC damage.

SOMET

SOMET is similar to SLET in that it involves harvesting tissue from the patient (in this case from oral mucosa) and placing the allograft pieces onto the corneal surface without the steps of tissue culturing involved in COMET. Oral mucosal epithelium is harvested, cut into small pieces, then placed on the receiving eye. The original surgical technique by Inamochi was performed on rabbit eyes and involved placing oral mucosal epithelial grafts on top of denuded corneal stroma, followed by placement of SCL and a tarsorrhaphy—no glue, sutures, or AM were utilized (51,52). Subsequent surgical descriptions and procedures have utilized SOMET in conjunction with AMT, placing the oral mucosal graft either as a single piece or as smaller pieces. Preparation of the recipient eye and securing of grafts vary according to surgeon technique as well as nature of patient ocular surface status and disease (51,52).

Post-surgical considerations

Antimetabolites such as MMC (18) have been described for concurrent use with AMT when mucosal membranes are unavailable or limited., although MMC has fallen out of favor as it can lead to tissue melt and secondary infection. In these patients with significant cicatrization, immunosuppressive systemic therapy and topical steroids are the mainstay of medical management.

There is an implicit risk of infection after AMT. Adequate donor screening, testing, and handling are implemented to minimize this risk. Hematomas can also occur post-operatively and need to be drained if they cause discomfort or dislodge the transplant. Granulomas can also form around the sutured membrane. A study is now evaluating if AMT can be formulated as an eye drop to promote surface reconstruction and reduce signs and symptoms of OSD (53).

LSCT

The transition zone between the cornea and conjunctiva is the limbus, which houses the radial fibrovascular ridges called palisades of Vogt where corneal epithelial stem cells reside. LSCD can lead to corneal scarring and loss of transparency. LSCT describes a way to replace these damaged/missing stem cells with the goal of restoring the ocular surface.

LSCT may be an autologous (cells from the fellow eye) or allogenic (cells from living relative or cadaver) procedure to restore corneal epithelial stem cells. Initially, OSR was used synonymously with stem cell or limbal transplantation. Cases varied, and anterior segment surgeons felt the need to standardize the way OSR is described. Autologous LSCT was first reported in 1989 by Kenyon and Tseng (54) using conjunctival limbal autograft (CLAU) (*Table 2*).

Patient selection

Autologous LSCT is the treatment of choice for unilateral disease, such as in chemical/thermal injury. Standard

procedure is to transplant two segments of conjunctival limbal tissue at the 12 and 6 o'clock positions, since this protects from conjunctival invasion (1). This produces excellent results, with functional vision and re-epithelialization in 80–90% of patients (1).

For bilateral disease, cadaveric donors are may be used restore corneal epithelial phenotype in 50% to 70% of cases (1,55). Living relatives can also provide limbal allograft tissues [conjunctival limbal allograft (CLAL) or keratolimbal allograft (KLAL)]. This method is considered for patients with extensive conjunctivalization. LSCT is not recommended during active phases of inflammation, and all eyelid abnormalities should first be addressed before LSCT is performed (55).

Surgical technique

The nomenclature for LSCT is based on the source of donor tissue, carrier tissue used, and whether conjunctival or limbal tissue is transplanted. A CLAU uses tissue from the fellow eye; a living relative CLAL (lr-CLAL) uses tissue from a living relative; and a KLAL uses tissue from cadaveric donors (56). SLET, as described above, utilizes donor stem cells directly on AM placed on the ocular surface of the recipient, altogether bypassing the need for laboratory cell expansion. COMET, also described above, is a technique that introduces oral EC instead of limbal stem cells onto the ocular surface as part of an AMT procedure. The main advantage is avoiding risk rejection (with autologous SLET) and preservation of limbal stem cells in fellow eye (with COMET). These techniques may be combined with subsequent PKP to further improve visual outcomes, once the limbal stem cell are restored (57).

CLAU

To harvest tissue, one begins with 4-5mm of conjunctival tissue, moving anteriorly to remove a partial-thickness section of limbal epithelium of about one-third thickness. Preparation of the recipient eye begins with a 360° peritomy and securing the transplanting block at the 6 and 12 o'clock positions. Naturally, potential complications include loss of stem cells in the donor eye. This method carries no risk of rejection.

Lr-CLAL

Donors may be excluded if they have a history of contact lens usage and glaucoma who may eventually require trabeculectomy. Serologic testing of potential donors for syphilis, hepatitis B and C, and human immunodeficiency virus infection should be performed to avoid risk of transmission to the recipient. There is a risk of rejection and patients require systemic immunosuppression.

Lr-CLAL may result in better outcomes for patients with partial stem cell deficiency. In the most severe cases of OSD, if the patient has extensive conjunctival disease and total LSCD, the "Cincinnati procedure" may be pursued, in which KLAL and lr-CLAL are combined. The Cincinnati procedure begins with recipient eye preparation as for standard KLAL. Conjunctival tissue is placed superiorly and inferiorly and keratolimbal tissue is used to fill in the gaps nasally and temporally. Systemic immunosuppression is required, and these patients may be at higher risk for immunologic rejection because two different types of antigenic tissues are used (56,58).

KLAL

First, the central donor cornea is removed with a 7.50-mm trephine. Lamellar dissection is performed to remove the posterior two-thirds of the stroma along with Descemet's membrane and endothelium. A 360° peritomy is performed on the host eye, and a superficial keratectomy is performed to peel off pannus and conjunctivalized tissue, creating as smooth a surface as possible. AM can be transplanted at this time and can reduce inflammation and scarring (56). The limbal graft is secured to the eye using 10-0 nylon sutures, trying to match the donor's and recipient's limbus. Patients often receive triple immunosuppressive therapy—oral prednisone, cyclosporine, and azathioprine or, more recently, prednisone, tacrolimus, and MMF (56).

Newer techniques use *ex vivo* cultivated limbal ECs for transplantation. In this technique, generally 2 mm × 2 mm of donor cells is grown in the laboratory on fibroblast culture medium or graft tissue/AM in order to expand the donor cell population in an attempt to increase success rates and decrease epithelialization time (59).

Post-surgical considerations

Preservative-free topical antibiotics, topical immunosuppressants, and frequent preservative-free artificial tears are often used after surgery. Steroids are rapidly tapered in autologous limbal transplantation (60). Allograft transplants pose a high risk of rejection even in human leukocyte antigen (HLA) matched recipients. Therefore, graft survival depends on systemic immunosuppression for a prolonged, if not indefinite, period (61). Epithelial loss is closely monitored

post-operatively. Conjunctival epithelium can cross the explant at these sites and gain access to the corneal surface, and if observed, mechanical debridement of conjunctival cells should be promptly carried out (60).

Graft rejection is also a fear, and patients should be monitored closely. Signs of rejection include sectoral limbal injection, edema and infiltration of the graft, punctate keratopathy, and epithelial irregularities and defects, and surface keratinization (60). Patients with blink-related microtrauma, conjunctival inflammation, increased intraocular pressure, aqueous tear-deficient dry eye, lagophthalmos, and pathogenic symblepharon, may be at higher risk of rejection. All of these complications should be addressed at follow-up visits should they arise.

Salivary gland transplant

Patient selection

Due to their exocrine secretions, salivary glands can be used to provide substitute lubrication in cases of severe dry eye. Current methods include transplantation of either the submandibular gland (SMG) or minor salivary gland (MSG). Tissue sources are typically autologous, and thus these approaches are not suitable for patients with salivary gland dysfunction (e.g., Sjogren's syndrome). According to recommendations from the Tear Film and Ocular Surface Society (31), salivary gland transplantation should be pursued as a last-resort method when all other efforts have failed (*Table 2*).

Surgical technique

First described by Murube-del-Castillo in 1986 (62), SMG transplantation is a complex surgery that often requires coordination with oral and maxillofacial surgeons. The SMG is harvested from the submandibular triangle and implanted near the temporal region. A tunnel is prepared to the upper lateral conjunctival fornix, and the distal end of the end of Wharton duct is sutured to the upper lateral conjunctival fold (63). Graft viability can be checked by palpation. Schirmer's test can be a great method of monitoring microvascular circulation of the graft.

Initially described by Murube (64), MSG transplantation is considerably less invasive than SMG transplantation. Some prefer to have patients start antiseptic mouth wash 3–4 days preoperatively. Donor tissue is harvested from the inferior lip approximately 2 mm × 2 mm, using a full-thickness incision along the mucosa, and the salivary gland is harvested taking care to dissect as many lobules as possible. The harvested tissue is then soaked in polyvidone solution for a few minutes, then sutured using 7.0–8.0 long-acting absorbable sutures. A BCL can be used to protect the corneal epithelium and care is taken to avoid everting the lid and damaging the graft within the first post-operative month (65).

Post-operative considerations

The labial wounds do not necessarily require suturing and typically heal in 2–4 weeks. Patients should apply topical antibiotics and lubricants 4 to 8 times daily for about 2 weeks post-operatively, and some ophthalmologist prefer to have patients take tapering dose of topical and/or systemic steroids. Some perform a temporary tarsorrhaphy to further protect the corneal surface. In a series of six eyes of patients suffering from chemical injury and SJS, four eyes showed full epithelization and the remaining two eyes showed partial epithelization post-operatively (65).

In the long term, transplantation alleviates symptoms of xeropthalmia in 90% of cases and improves best-corrected visual acuity in 56% of cases. Surgical failures include vascular thrombosis and duct obstruction. In 60% of cases, patients experience epiphora post-operatively, which can be managed surgically through reduction of the graft and medically with topical atropine gel and botulinum toxin injection (66,67).

MMG

MMG can aid in OSR by providing a smooth lid margin to prevent further damage. Ideally the source of mucosal sites arises from non-keratinized epithelium substitutes for conjunctival epithelium at the lid margin. Oral mucosa, lip (labial) mucosa, is preferred due to ease of access and limited complications. Other possible sources for tissue include the buccal, nasal, rectal, or vaginal mucosa. Membrane grafting may be the only treatment to directly target the pathology and restore abnormal anatomy of the posterior lid margin (*Table 2*).

Patient selection

This surgical procedure replaces keratinized lid margin and surrounding scarred tissue with normal and healthy mucosa. Careful history must be obtained especially

regarding steroid status, as proceeding with surgery prior to immunosuppression could be detrimental. If fluorescein staining corresponds to the area of LMK, then the pathology is deemed lid-related keratopathy. Ideally, MMG would be best suited for an eye that has posterior migration of mucocutaneous junction (MCJ) with LMK with early lid-related keratopathy and some ocular surface wetness. MMG can halt keratopathy and prevent further ocular surface damage. When selecting a donor site, it is critical to avoid sites with ulceration and avoid oral mucosa in patients using smokeless tobacco as these areas may have higher rates of dysplastic changes.

Surgical technique

MMG should be performed under general anesthesia or under local peribulbar anesthesia if general anesthesia is contraindicated. First the labial mucosa is prepared. To do this, two stay sutures are passed 3–4 mm behind the MCJ at the lip margin. Then local anesthetic can be administered. The lids are prepared by using two stay sutures to evert the lid. The keratinized lid is then dissected by an anterior horizontal incision at the gray line. The incision is extended along the lid margin sparing the medial and lateral ends and creating a rectangular area including the keratinized lid margin and 4mm of tarsal conjunctiva. All incisions are superficial with intention of cleaving the epithelium without tarsal damage. The epithelium is incised and dissected taking care to ensure there are no residual patches of normal/keratinized epithelium on the tarsal-conjunctival bed as this can promote graft necrosis. To harvest the labial mucosa, tissue should be at least 1–2 mm from the MCJ and 3 mm from the frenulum. The graft should be in a biconvex manner and the dissection is carried out between lamina propria of the oral mucosa and the underlying connective tissue. The graft is thinned before transplantation to promote revascularization, and trimmed of excess tissue, muscle, and fat. Once cut to size, the tissue is then sutured to the recipient, making sue to have a gap of about 0.5 mm between the posterior margin and mucosal graft to prevent the graft from overriding the tarsal conjunctiva. Fibrin glue can be injected to the underside of the graft or massaging the MMG to the tarsus to promote adherence of the graft.

Post-surgical considerations

Patient can use steroid-antibiotics ointment twice a day until the sutures (5–7 days) are removed or the BCL is removed (if placed). Oral steroids can also be used for the first 3–4 weeks in tapering doses. Post-operative complications include bleeding, graft necrosis, graft displacement, ectropion, entropion, chalazion, keratinization at the posterior edge of the graft, paresthesia at the donor site, and infection (68) (*Table 2*).

CF

CFs represent another method to maintain the ocular surface. In 1958, Gundersen reintroduced the procedure to repair the cornea (69,70). The purpose of the flap is to restore the corneal surface and prevent corneal ulceration and secondary infection. The flap covers the corneal tissue, preventing tears, proteolytic enzymes and proinflammatory mediators from reaching the corneal ulcer and causing stromal lysis. It also supplies the corneal with vascular tissue to help recover corneal integrity and offer metabolic support to promote corneal healing. The flap can also improve pain, especially in bullous keratopathy, where the CF forms a complete surface of exposed corneal nerve endings.

Patient selection

This procedure was originally indicated for phthisical eyes being prepared for prosthetic shell, herpetic keratitis, bullous keratopathy, neuroparalytic keratopathy, traumatic relapsing keratopathy, chronic infectious keratitis, corneal melting, and peripheral marginal ulceration. CFs are especially useful if patients have painful corneas and little resolution by normal healing.

Gunderson flaps are primarily used in patients with reduced visual potential and to preserve the eye. To ensure proper outcomes, some considerations include, CF size, flap movement without traction, flap blood supply, avoiding cautery and epithelial entrapment, debridement. Conjunctival autographs can also be used.

Surgical technique

Several types of CF surgeries exist. The total CF described by Gunderson is a thin, bipedicle bridge flap. It involves 360° peritomy and debridement of the entire corneal epithelium, which is then mobilized at the superior fornix to cover the ocular surface (69,70). Disadvantages of this approach include, difficulty monitoring corneal disease and measuring intraocular pressure, fornix shortening, ptosis, corneal opacification, and vascularization. The

bipedicle bridge flap ("bucket handle") is used for small central or paracentral lesions. It involves a 180° peritomy and separation of the conjunctiva from tenon's capsule. An incision parallel to the limbus and mobilization of the corneal over the ulcer completes this procedure.

The racquet flap, or single pedicle flap, is used for perilimbal lesions. The advancement flap is used for perilimbal lesions typically in conjunction with lamellar corneal patch or scleral patch graft. It involves creating a peritomy and pulling the adjacent conjunctiva over the peripheral corneal lesion. CF can also be combined with other surgeries such as a deep lamellar keratectomy to aid in infection healing and alleviate pain (71). Adding cryotherapy, to the flap surgery can also aid in ocular surface recovery reduce inflammation (72). Fibrin glue can be used to secure the flap into place, reduce surgical time, aid in faster ocular surface recovery, and minimize post-operative pain and scarring (73).

Post-surgical considerations

Post-operative complications include CF retraction, buttonholes, erosions, epithelial inclusion cysts, corneal perforation, and ptosis. If the flap was used for a chronic infection, there is a risk of persistence of the infection under the flap or perforation under the flap (74,75). These compilations need to be balanced when discussing surgical options with patients. If PKP or lamellar keratoplasty is to be performed to this eye, the CF may be removed. A CF procedure tends to destroy or displace most limbal stem cells, a limbal autograft or allograft after removal of the flap may be necessary in order to provide a permanent source of normal ECs before an optical corneal transplant is attempted.

Corneal transplantation (including PKP)

Patient selection

Corneal transplantation is an important surgical treatment for OSD; here, we will focus primarily on PKP. PKP has a variety of indications in OSD including after trauma, chemical injuries, infectious keratitis, and corneal degenerations/dystrophies leading to ocular surface issues. However, 10-year survival of the graft is greatest in patients with keratoconus (95%), with survival rates decreasing precipitously in higher risk cases such as trauma (33%) and chemical burns (19%) (76). Moreover, repeated attempts at PKP may also result in poor prognosis (77). Importantly, in patients with LSCD, a PKP is not an appropriate treatment as the graft will certainly fail without healthy limbal stem cells. It can be considered for patients at the same time as or after LSCT. As shown in one study, patients with total LSCD who underwent PKP approximately 19 months following LSCT showed 72% graft survival at 32 months (78) (*Table 2*).

Surgical technique

PKP can be done either under general or MAC/peri or retro-bulbar block depending on surgeons preference and discussions with patients. Prior to surgery, the corneal trephine and door punch is determined. Typically, the size should encompass the entire corneal pathology. Initially, the donor tissue is prepared prior to entering the eye. Using a paracentesis blade the anterior chamber is filled with viscoelastic. After which the host cornea is trephined. The cornea is then sutured in place with continuous or interrupted sutures. Typically, sutures are placed 180° away from the other suture, starting first with 12, 3, 6, and 9 o'clock positions. Each suture should have equal tension and approximately 16 sutures are typically placed. Prior the placing the final two sutures, the viscoelastic is removed from the anterior chamber. The wounds are hydrated at the end of the surgery, and subconjunctival steroids and antibiotics are often injected. PKP can be combined with a variety of other surgeries including cataract surgery, glaucoma surgery or retinal surgery. It is important to consider that the state of the ocular surface at the time of PKP is critical in the likelihood of graft survival (79). It can also be performed alongside other OSR surgeries such as LSCT and AMT.

Post-surgical considerations

High-risk cases of PKP may require immunosuppression for several months following the procedure through the use of both systemic and topical drugs, including corticosteroids as well as cyclosporine A and MMF (77).

Up to one in five patients report experiencing greater than 5 diopters of astigmatic error post-operatively. Such patients are often unable to achieve corrected vision through glasses alone and may require rigid gas permeable or SCLs (80).

Conclusions

OSD can have a devastating impact on patients, as it

disrupts corneal stability leading to visual impairment and physical discomfort. In severe cases, restoring ocular surface homeostasis requires careful medical and surgical planning. As described in this chapter, there are a variety of methods that can be implemented including medical treatments and surgical techniques. Medical treatment focuses on optimizing the ocular surface by targeting inflammatory pathways, improving tear film, and/or preventing and treating infections. Medical therapies are often used to prepare the ocular surface for surgical treatment and may be continued in the post-operative period. Surgical approaches to OSR focus on targeting the root cause of OSD. This can be done by improving the oculo-palpebral structures in order to improve lid positioning and tear film. Additional therapies focus on improving tear production, such as through salivary gland transplantation. In situations where the ocular surface is so severely damaged that there is loss of limbal stem cells, LSCT can be considered. Other surgeries such as AMT and CFs can help promote corneal healing. Finally, in severe situations where the cornea that is beyond salvage, corneal transplantation may be considered. It is important to consider that OSR often requires a combination of medical and surgical approaches, and each treatment must be catered to the individual presentation.

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