

Botulinum Toxin and Dermal Fillers for Facial Aging

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Faculty

Mark Rose, BS, MA, LP, is a licensed psychologist in the State of Minnesota with a private consulting practice and a medical research analyst with a biomedical communications firm. Earlier healthcare technology assessment work led to medical device and pharmaceutical sector experience in new product development involving cancer ablative devices and pain therapeutics. Along with substantial experience in addiction research, Mr. Rose has contributed to the authorship of numerous papers on CNS, oncology, and other medical disorders. He is the lead author of papers published in peer-reviewed addiction, psychiatry, and pain medicine journals and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to law firms that represent disability claimants or criminal defendants on cases related to chronic pain, psychiatric/substance use disorders, and acute pharmacologic/toxicologic effects. Mr. Rose is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine and is a member of several professional organizations.

Faculty Disclosure

Contributing faculty, Mark Rose, BS, MA, LP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planners

John M. Leonard, MD

Jane C. Norman, RN, MSN, CNE, PhD

Director of Development and Academic Affairs

Sarah Campbell

Division Planners/Director Disclosure

The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for physicians, nurses, and other healthcare professionals who may administer or care for patients who have undergone aesthetic procedures.

Accreditations & Approvals



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Course Objective

This course is designed to provide clinicians with the knowledge necessary to provide minimally invasive aesthetic procedures and to care for patients who have undergone these procedures.

Learning Objectives

Upon completion of this course, you should be able to:

1. Outline the background of aesthetic medicine and botulinum toxin/filler use.
2. Describe the process of usual facial aging.
3. Discuss the mechanism of action and clinical use of botulinum toxin for the treatment of facial aging.
4. Compare and contrast the classes of dermal filling agents available.
5. Analyze components that affect the appropriate selection of dermal filling agent.
6. Describe key aspects of individualized assessment of patients seeking aesthetic treatments for facial aging.
7. Outline the minimally invasive approach to the treatment of facial aging.
8. Evaluate patient-related factors affecting suitability for various aesthetic treatments.
9. Identify acute and potentially severe side effects of botulinum toxin/filler use.
10. Discuss the role of biofilm infections in delayed reactions to dermal fillers.



Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Visibly apparent aging and loss of youthful appearance are frequent concerns of patients seeking cosmetic treatment. Botulinum toxin and dermal (soft tissue) fillers are minimally invasive (i.e., injection-delivered) therapies that, along with knowledge advances, have revolutionized cosmetic treatment of aging features.

The clinical features of aging are the result of bone resorption; ligament laxity; redistribution, volume loss, and descent of facial soft tissue; and formation of lines and folds in inelastic, sagging skin. This complexity is not amenable to single-modality treatment; current practice combines botulinum toxin and fillers as the core approach, with other therapies added. Filling isolated lines or creases is de-emphasized.

In carefully selected patients with strict adherence to safety standards, desired results can be achieved with a low risk to safety. With increasing consumer demand, injector backgrounds and settings have expanded beyond oversight. Rises in catastrophic complications are largely unknown, as the “risk-free” perception of botulinum toxin and fillers continues. Clinicians and patients may be unaware of the range of U.S. Food and Drug Administration (FDA)-approved minimally invasive options, advances in the understanding and addressing facial aging with these therapies, and the potential of serious complications with incorrect use. These areas are the focus of this course.

Beyond the scope of this course are cosmetic surgery (e.g., rhinoplasty, face-lift), reconstructive or rehabilitative surgery, cosmetic concerns of systemic origin (e.g., lipoatrophy from antiretroviral therapy), and nonfacial cosmetic concerns. Laser, energy, and topical therapies are noninvasive interventions for sun-damaged, aged skin and acne scars, but they will not be the focus of this course. Cosmetic medicine is a point of convergence for diverse psychological, social, cultural, and racial factors, all of which should

be considered for each patient. The properties of products discussed in this course are unique. This requires reference by commercial brand, but should not be construed as endorsement of any commercial product.

TERMINOLOGY

Plastic surgery includes subfields of reconstructive or rehabilitative surgery for congenital malformations or acquired disfigurements, and cosmetic surgery for correction, restoration, or enhancement of appearance [1]. “Aesthetic medicine” was coined to replace “cosmetic medicine/surgery,” but the terms remain interchangeable [2].

The cosmetic medicine literature describes features with terms (e.g., defect, defective, deformity, deformation) that carry different meanings outside of this highly specialized professional audience. It is not the intent of this course to imply that normal aging of the face or skin is in any way a defect aside from the patient’s perception or desires in terms of appearance. Beauty is a standard that varies by culture, time, age, and personal experiences, and there is no one standard for any facial feature or individual.

Therapeutic goals are variously described as volumizing, re-volumizing, rejuvenation, restoration, harmonization, resurfacing, correction, and others, with little consistency. This course will not attempt to modify terminology used in the published literature, except to improve logical consistency.

BACKGROUND

Until the 1990s, facial aging was attributed to gravitational effects that required surgical lifting and tightening to defy soft-tissue descent. Facial aging as a multi-tissue process of descent, volume loss, and resorption was first described in 1965 but remained obscure, and the focus on superficial tissue descent and correction persisted [3; 4; 5; 6].

Botulinum toxin and dermal fillers were introduced to correct cosmetic defects without the need for surgery. Earlier use to spot-correct isolated wrinkles and creases led to temporary but limited benefits, with no advantage over surgical facelift for persons with moderate or advanced aging features [4; 5; 6; 7].

Studies identified soft tissue volume loss and hard tissue resorption as causal to facial aging. This prompted filler injection into deep tissue for revolumizing; new fillers designed for specific tissue placement; use of lower-dose botulinum toxin to improve outcomes; advances in lasers and energy devices for resurfacing or tightening with minimal recovery time; and evidence of synergistic efficacy and superior cosmetic outcomes with combined therapies [6; 7; 8]. These advances brought a paradigm shift from “wrinkle-chasing,” with isolated clinical benefit, to recognition of facial aging as a complex interaction of extrinsic and intrinsic factors across multiple tissue planes requiring a three-dimensional, multilayered treatment approach [9; 10]. Surgical facelift requires patients to wait until visible aging is sufficient to warrant surgery, often with sudden, sometimes unnatural, changes in appearance. Minimally invasive therapy offers a more gradual, natural-looking harmonization preferred by many patients [7].

Botulinum toxin and dermal filler injection techniques are constantly evolving; what was considered state-of-the-art 5 to 10 years ago no longer represents a practice standard [11]. Every year, the American Society of Plastic Surgeons (ASPS) and the American Society for Dermatologic Surgery (ASDS) separately publish the number of procedures performed by their board-certified members. In 2019, ASPS members performed 18.1 million cosmetic procedures—16.3 million nonsurgical (82% female)—at a total cost of \$16.7 billion. Among patients who received cosmetic procedures, 70% were Caucasian, 11% were Hispanic, 9% were African American, 7% were Asian, and 3% were other [12]. The 7.7 million botulinum toxin and 2.7 million dermal filler procedures reported by ASPS in 2019 represent an increase of 878% and 312%, respectively,

compared with 2000 [12]. ASDS members in 2019 performed an additional 2.3 million botulinum toxin (88% female) and 1.6 million filler (90% female) procedures, a 60% and 78% increase from 2012, respectively [13].

Between 2012 and 2017, there was a 50% increase in cosmetic procedure requests by persons younger than 30 years of age (90% female), and in 2016, more than 229,000 cosmetic procedures were performed in patients 18 years of age or younger [14; 15]. The annual figures by ASPS/ASDS are considered the benchmark for cosmetic procedures, trends, and demand, but they significantly under-represent the actual number of minimally invasive procedures performed outside of their membership [16; 17; 18; 19; 20].

INCREASING CONCERNS

As cosmetic treatment methods have evolved, provider backgrounds expanded from specialists in plastic surgery (traditional) to dermatology, ophthalmology, and otolaryngology, then to dentists and registered nurses, followed by licensed aestheticians, unsanctioned medical personnel (e.g., medical assistants), and lay practitioners [17]. As such, the experience and qualifications of injectors is increasingly questionable and unpredictable. A large and growing proportion is performed in medical spas, spas, hair salons, other commercial settings, and at “Botox and filler parties” in private homes by non-healthcare professionals, sometimes without written informed consent [16; 17].

There is an increasing number of filler complications from intravascular injection, an immediate, severe event that can result in blindness, tissue necrosis, or stroke, and from bacterial biofilm infection, when filler injection seeds skin-surface bacteria into tissue with the filler product [19]. Biofilm infections may become disfiguring, are often antibiotic-resistant, and are potentially a methicillin-resistant *Staphylococcus aureus* (MRSA) infection [21]. The increasingly unregulated state of botulinum toxin and filler injection practice, the absence of a universal adverse event reporting mechanism, and potentially power-

ful financial incentives to conceal complications have prompted calls for greater regulation of providers and practice and for relabeling of filler injections as “dermal implants” to accurately reflect the risks inherent in placing an inanimate object into human tissue [16; 17; 18; 22; 23].

The face ages in a unique but relatively consistent manner, creating a distinct but recognizable “aged” appearance. As people age, many are left with the feeling that their physical appearance is no longer an accurate representation of their mental state. Some opt to pursue cosmetic procedures for “matching their outsides with their insides” [24]. In skilled hands with diligent execution of precautions, the results attainable without surgery can be impressive, with a good safety margin. Improper patient selection, preparation, or technique invites problems ranging from patient dissatisfaction and poor cosmetic outcomes to increased risks of serious and potentially catastrophic complications of intravascular injection or delayed bacterial infections. The idea that botulinum toxin and fillers are risk-free cosmetic treatments is thoroughly dispelled.

THE PROCESSES OF FACIAL AGING

In the face, the process of aging that culminates in cosmetic concerns is complex. Changes of the facial skeleton, soft tissue, retaining ligaments, fat compartments, and the skin contribute to the features of facial aging in varying degrees, influenced by intrinsic (e.g., genetic) and extrinsic (e.g., sun exposure) factors [25]. To understand facial aging and appropriate interventions requires multidimensional knowledge of the normal anatomy and physiology of facial tissue layers, age-related changes in histology and morphology in each plane, and their multilevel interactions to form cosmetic features of aging.

Perceptual models used in cosmetic medicine can assist in conceptualizing these changes. Each model views facial aging from a different perspective. Presented in sequence, the models break down the

complex, dynamic, multidimensional process into its dimensional components. The predominant models are [4; 26; 27; 28; 29; 30; 31; 32]:

- The two-dimensional (2-D) model: Organizes the surface anatomy and superficial cosmetic defects into horizontal zones that anchor morphologic features to familiar anatomic boundaries
- The three-dimensional (3-D) model: Delineates facial anatomy into its underlying tissue layers to describe normal and age-related changes in structure/function at each facial tissue level
- The integrative model: “Zooms out” from the 3-D model to describe how tissue-level changes interact to form the visible features of facial aging
- The aesthetic zones/units model: Describes cosmetic defects of facial aging as changes in underlying and surrounding tissue within anatomically compartmentalized units

All four models will be used later in this course to describe the cosmetic features of facial aging and recommended minimally invasive interventions.

THE TWO-DIMENSIONAL MODEL

To describe the anatomic locations of common cosmetic concerns widely referenced in this course (*Table 1*), the face is divided into three horizontal zones with defined anatomic boundaries [4; 30; 31; 32]:

- The upper face: Forehead, glabella (smooth area between eyebrows), periocular (lateral to the eyes) areas, and temples
- The midface: Between the glabella and tip of nose, lateral to the zygoma (cheekbone). The malar area is highly relevant, as the malar is the cheekbone prominence. The submalar is the bony area underneath the cheekbone.
- The lower face: The perioral area (lips), mandible, chin, and neck

FACIAL AGING FEATURES		
Zone	Cosmetic feature	Description
Upper face	Glabellar rhytides	Vertical lines between the eyebrows
	Horizontal forehead rhytides	Horizontal creases on the forehead, exacerbated during brow elevation
	Lateral canthal rhytides (“crow’s feet”)	Multiple periocular lines and wrinkles that radiate lateral to the eye, more prominent when smiling
	Brow ptosis (drooping)	Tissue descent that can mimic angry or scowling expressions
	Temporal fossa wasting	Concavity of the temple area
Midface	Nasojugal fold (tear trough depression)	Depression between the rim of the orbital bone and the nasal sidewall
	“Bunny lines”	Wrinkles on the dorsal and lateral nose during contraction of the upper nasalis muscle
	Nasolabial folds ^a	Creases extending from the lateral nasal alae to the lateral mouth
Lower face	Perioral lip rhytides (“whistler’s wrinkles”)	Vertical wrinkles extending from the lip border
	Mouth frown	A downward turn of the corners of the mouth
	Melomental folds (“marionette lines”)	Facial lines extending from the corners of the mouth to the mandible (jaw)
	Mental crease	A horizontal groove present on the chin
	<i>Peau d’orange</i> chin	Multiple dimples on the chin during contraction of the mentalis muscle
	Masseteric hypertrophy	Square appearance to the jawline
	Gingival (gummy) smile	Significant upper gum display during smiling ^b
Neck ^c	Platysmal bands	Vertical linear bands present on the anterior neck
	Horizontal neck lines	Horizontal bands present on the upper neck
^a Sometimes assigned to the lower face. ^b Not necessarily age-related. ^c The neck is usually included in the lower face for three horizontal zones.		
Source: [10; 33; 34]		Table 1

THE 3-D MODEL: NORMAL ANATOMY OF FACIAL TISSUE

The two-dimensional model is a good descriptive framework for cosmetic concerns but does not describe the aging processes of underlying facial tissue that inform their minimally invasive correction. This area is addressed by the three-dimensional model.

The Skin

The skin consists of the epidermis and dermis, mutually dependent layers that rest on the superficial fat layer [35].

Epidermis

The epidermis is the most superficial layer, composed of stratified squamous cells or keratinocytes (90%) and melanocytes (approximately 8%). The epidermis is directly exposed to the environment and its damaging effects. To replace damaged cells, new cells must constantly form and migrate to the surface over two to four weeks [35; 36].

Melanocytes produce melanin, which gives pigment to the skin and absorbs ultraviolet (UV) light to prevent DNA damage. Absolute numbers of melanocytes are constant across races. The amount of melanin produced, size of melanosomes, and extent

of aggregation account for differences in pigmentation. Epidermal melanocyte density declines with aging [35; 36; 37].

Dermis

The superficial papillary dermis (20% of the dermis) is loose connective tissue with capillaries, reticular fibers, and some collagen. Small projections (dermal papillae) into the epidermis maintain adhesion between the layers and nourish the epidermis [35; 36].

The deeper reticular dermis is dense connective tissue, and the deepest level borders the superficial fat layer. Collagen makes up most of the dermis (75% is collagen type I), providing strength and structure to the skin. Elastin fibers, synthesized by fibroblasts and keratinocytes, give elasticity and resilience. Fibroblasts, the major cell type of the dermis, produce procollagen and elastin fibers [35].

Filling the spaces between collagen and elastin fibers is an extracellular matrix of glycosaminoglycans (hyaluronic acid), chondroitin sulfates, and glycoproteins (carbohydrates or amino sugars linked to a protein) [35; 36; 38].

The Superficial Fat Layer

The superficial fat layer, consisting of adipose tissue and collagen network, contributes to thermoregulation, shock absorption, wound healing, and immune function. The adipocytes can transform into myofibroblasts to influence local collagen synthesis [39]. Fibrous partitions separate the superficial fat into perioral (around the lips), nasolabial, cheek, and periorbital (around the eye sockets) compartments [40].

In the midface, the malar fat is composed of superficial fat compartments that lie above the superficial fascia. From medial to lateral, they are [25; 41]:

- The nasolabial fat
- The superficial medial cheek, middle cheek, and lateral temporal cheek fat
- The inferior infraorbital fat, where under-eye “bags” appear, above the superficial medial cheek

Superficial Musculo-Aponeurotic System

The soft tissue is complex, because active movement over and around the orbital and oral cavities requires a muscle layer within soft tissues that connects with the overlying skin [42]. The superficial musculo-aponeurotic system is an organized fibrous network comprised of the platysma muscle, parotid fascia, and fibromuscular layer covering the cheek. The superficial musculo-aponeurotic system divides the deep and superficial fat, connects the facial muscles to the dermis in a moveable continuous plane, and functions to transmit, distribute, and amplify the activity of all facial muscles [43; 44].

Muscles and Ligaments

Muscles of facial expression and muscles that facilitate chewing, smiling, speaking, and blinking alter the tension in adjacent skin, unlike other muscles that attach to bones or tendons. Muscles of facial expression significantly impact facial aesthetics, as repeated contraction can form dynamic rhytids and static lines [44; 45; 46; 47].

The Deep Fat Layer

The deep fat layer is separated from superficial fat by the superficial musculo-aponeurotic system in the midface, platysma in the neck, and superficial temporal fascia in the temples, forming deep fat pads with fibrous ligament partitions [39; 40]. Deep fat compartments in the midface are [25; 41]:

- The deep cheek fat, which divides into medial (deep and medial to nasolabial fat) and lateral (deep to superficial medial cheek fat) parts. The deep medial cheek extends medially almost to the lateral incisor tooth.
- Medial portion of the buccal fat pad, just lateral to the deep lateral cheek
- The medial and lateral suborbicularis oculi fat, deep to the orbicularis oculi muscle of the lower eyelid

The Deep Fascia

The deep fascia layers are interconnected and secured to the facial skeleton in specific areas by a network of retaining ligaments, perpendicular to the layers and connect all layers to the deep fascia. The deep fascia provides the attachment for ligament origins and is formed by the periosteum on the facial skeleton and by deep muscle fascia where the skeleton is overlain by the masticatory structures [42].

The Facial Skeleton

The facial skeleton forms the scaffold on which soft tissues are draped and has a substantial effect on appearance. The primary bones of the facial skeleton by horizontal zone are [31; 46; 48]:

- Upper face: The frontal bone (forehead), bordered below by the glabella (smooth area between eyebrows) and frontonasal groove, and laterally by the supra-orbital (above-eye) ridges.
- Midface: Medial and middle thirds of the midface skeleton formed by the maxilla (houses roof of the mouth, extends upward to orbital floor). The lateral third is formed by the zygoma (cheekbone) body and arch.
- Lower face: The mandible (jaw bone) is the primary bone.

The 3-D Model: Age-Related Alteration

Age-related physiologic processes lead to morphologic changes of the facial skeleton, soft tissue, retaining ligaments, fat compartments, and skin. The three-dimensional alterations of facial aging require accurate evaluation to provide patients the optimal aesthetic strategy [25; 30; 42].

The Facial Skeleton

From prominent bone formation in youth, age-related changes in the relative dynamics of bone expansion and bone loss lead to predominant bone resorption in the aging craniofacial skeleton, an important contributor to facial aging [42; 49].

Skeletal resorption and atrophy is uneven, and bone reduction is greatest in facial areas where prominent aging stigmata appear [4; 25; 31; 42; 50]. The maxilla has the greatest resorption; substantial reduction in its anterior projection largely contributes to aged appearance. The periorbital bones and anterior and inferior mandible (prejowl area) resorb extensively; the chin becomes shorter. The posterior and superior mandible undergo bone formation, increasing the mandible angle from 97° in younger skulls to 135° in older skulls. Maxilla and mandible resorption appreciably reduces the facial height. The mid-face recedes, but the forehead continuously expands.

Local changes in soft tissue and mechanical needs can also induce bone remodeling [50]. Mechano-transduction transforms mechanical energy into electro-chemical signaling to tissues or cells. Through this process, chronic facial muscle tension or over-use contributes to skeletal changes by impacting molecular signaling pathways, which alters bone remodeling patterns [51].

Reduction of anterior projection in the aging facial skeleton occurs immediately beneath the periosteum attached to the bone surface. The periosteum recedes with the bone; ligament origins recede with the periosteum [42].

Facial Fat

Superficial and deep facial fat is highly compartmentalized. Aging significantly alters the volume, structure, and position of facial fat compartments. Typically, deep fat atrophies and superficial fat may be unchanged or hypertrophy. Assessment of the fat depletion pattern is crucial for volumetric restoration. With attention to ligament involvement, the pattern is fairly predictable [8; 25; 30; 41; 42; 50; 53]. It occurs first in the periorbital and malar fat. The most extensive loss of deep fat occurs in the lateral and medial orbital fat and medial cheek fat. Likewise, the most extensive loss of superficial fat occurs with lateral temporal and preauricular fat.

Ligaments

Ligaments confine the fat areas; retaining ligaments anchor and stabilize the skin and facial fascia. With aging, medial ligaments of the center face keep their strength with strong fixation points, but lateral ligaments weaken and lose ability to prevent movement of fat compartments (though they may retain the borders). With loss of lateral fat volume and ligament support, the malar fat moves inferomedially and the superficial nasolabial and superior/inferior jowl fat move medially.

Superficial Musculo-Aponeurotic System and Muscles

The ligaments also transmit the effect of skeleton resorption by strongly connecting the skeleton with the superficial musculo-aponeurotic system. Glabella and masseter muscles can become hypo- or hypertonic. Chronic muscle use in facial expressions can aggravate some features of aging. Atrophy is prominent in masticatory muscles.

Epidermis and Dermis

Aging substantially alters the skin. Dermal collagen content declines by roughly 1% every year starting at around 40 years of age in women and 50 years of age in men. The remaining collagen fibers become disorganized, compact, and fragmented. Elastic fibers decrease in number and diameter. Epidermal thinning, collagen loss, and dermal elastosis contribute to fine rhytids of the aging face. Loss of muscle tone, skin elasticity, and thickness leads to sagging [41; 49].

These dermal changes trigger a cascade of secondary events that greatly influence surrounding tissues. Wrinkles and furrows, a main focus of patients seeking cosmetic treatment for aging, develop from a slow, progressive alteration of all facial structures [49]. UV radiation from sun exposure substantially contributes to skin changes in aging.

THE INTEGRATIVE AND AESTHETIC UNITS PERSPECTIVES

The two- and three-dimensional models describe age-related changes within facial tissue layers. However, the integrative and aesthetic units models describe how these changes interact and combine into the cosmetic features of facial aging [4; 25; 30; 41; 42; 52].

As noted, bone resorption is extensive in orbital and periorbital, malar, submalar, and mandibular areas. Soft tissue loss occurs in periorbital, forehead, glabellar, temporal, malar, perioral, mandibular, and mental areas. Retaining ligaments of fat compartments weaken; facial fat and soft tissue descent forms malar bags, folds, and sagging in nasolabial, jowl, and submental areas.

Increased orbit size and posterior maxillary resorption promote inferior displacement of the malar fat, accentuation of nasolabial folds, a blunted midface, and loss of support for periorbital tissues that contributes to perioral lines. Infraorbital volume loss exposes the inferior border of the orbicularis oculi muscle that helps form a malar crescent over the zygomatic eminence (lateral) and the nasojugal fold (medial); formerly concealed infraorbital fat pads ("palpebral bags") emerge.

Periorbital and perioral skin wrinkling from repeated muscle action progress from dynamic rhytids to static rhytids as the skin changes become permanent. Volume loss, distributional changes, and sagging disrupt the defining arcs and convexities of youth and contribute to the distinct morphology of the aging face.

Youthful Appearance and Aging

Loss of youthful features and development of aging features are frequent cosmetic concerns of patients. Expert plastic surgeons and cosmetic dermatologists are broadly uniform in characterizing youthful features and age-related changes. The following section specifically describes female features; male features will be discussed later in the course [4; 29; 32; 49; 54; 55; 56; 57; 58].

The youthful face has a diffuse, balanced distribution of superficial and deep fat, conferring a smooth, three-dimensional topography delineated by a series of arcs and convexities, without clear distinction between temple, eyelid, and malar areas. On frontal view, the primary arc of the jawline, convexities of the temples, and multiple smaller secondary arcs of the lips are evident. In profile, the definitive features of youth are the lateral cheek projection, extending as an unbroken convex line from the lower eyelid to the cheek (the “ogee” curve).

Youthful features converge on the malar area. Prominent malar eminences are a hallmark of beauty in many cultures, and malar area convexity (roundness) is a defining feature of a youthful face. With aging, the malar fat position over the zygoma and orbital rim diminishes and descends. Ptotic cheek fat, and descent of malar soft tissue, produces sunken cheeks and shadows, leaving behind a cheek concavity accentuated by depletion of malar fullness.

From the front, the jawline appears scalloped; the temporal, buccal, and suborbital areas hollow; and the lips straight and angular. In profile, the primary arc of the cheek is broken, the mandibular arc replaced by a jowl line, and the forehead and brow lose their anterior projection.

Youthful features and age-related changes have agreement, but the extent of cosmetic correction is debated. A multinational panel of cosmetic medicine experts recommended an age-appropriate approach as the criterion standard, with a conservative approach preferable [52].

The Facial Aesthetic Units Perspective

The aesthetic units perspective informs how some visibly apparent aging features develop and directs cosmetic intervention. The surface and subsurface structural changes in skin thickness, composition of subcutaneous tissue, contour of the facial skeleton, and location and integrity of retaining ligaments contribute to variability of bony landmarks, formation of lines and wrinkles, variable skin pigmentation, and overall discontinuity of the facial region, termed “facial aesthetic units” [28].

In younger persons, facial aesthetic units flow together, appearing as a smoothly contoured, single dynamic structure without perceptible division. With aging, the redistribution of facial fat, loss of tissue volume, and retention of ligament borders induce a demarcation of the underlying facial structures. The compartmentalized aesthetic units become distinct as changes within and between distinct aesthetic units collectively contribute to an overall aged facial appearance [4; 28].

A strong correlation was found between observer judgment of age and visually obvious separation of facial aesthetic units, suggesting it may serve as a psychophysical cue fundamental to perception of facial aging. This finding also aligns with current practice. Facial rejuvenation can include creation of more homogeneous skin tones, texture, and facial symmetry, and smooth contours between anatomical regions by blending the transition of facial aesthetic units for a harmonious and youthful facial appearance [28].

BOTULINUM TOXIN

DISCOVERY AND DEVELOPMENT

Botulinum toxin is derived from neurotoxins produced by *Clostridium botulinum*, the gram-positive bacillus that causes botulism. Subsequent to the 1897 discovery of *C. botulinum* as etiologic agent of botulism, seven botulinum toxin serotypes (A, B, C1, D, E, F, and G) with differing pharmacologic properties have been identified. Only serotypes A and B are used clinically, with type A (botulinum toxin-A) the most widely used for both medical and aesthetic indications [59].

During the late 1960s and early 1970s, the clinical value of botulinum toxin became evident in the treatment of strabismus. This was followed by demonstrated benefit in blepharospasm, hemifacial spasm, cervical dystonia, and other disorders of muscle hyperactivity and spasticity. From the first report of botulinum toxin-A injection for a cosmetic indication (glabellar frown lines) in 1992, its use has expanded to become the most requested procedure in aesthetic medicine. One commercial brand of

BOTULINUM TOXIN PRODUCTS AND FORMULATIONS			
Name, Serotype	Commercial Product	FDA-Approved Indications	Comments
ONA type-A	Botox Botox Cosmetic Vistabel Vistabex Vacuum-dried powder (50 or 100 U/vial)	Glabellar, lateral canthal, and forehead lines	The original, most-studied formulation. Widely used off-label for treating other lines and facial contouring.
ABO type-A	Dysport (300 or 500 U/vial)	Glabellar lines	First marketed in Europe
INCO type-A	Bocouture or Xeomin (as lyophilized powder in 50 or 100 U)	Glabellar lines	Newer formulation. Free of complexing proteins. May reduce risks of sensitization and antibody formation.
PRA type-A	Jeuveau (4 U [0.1 mL] IM in each of five sites)	Glabellar lines	Newer formulation. Similar in efficacy to ONA.
RIMA type-B	Myobloc, in liquid (5,000 U/mL)	No cosmetic indications	Less studied than type-A. Used in off-label facial lines. Distributed in the United States and Canada.
ABO = abobotulinumtoxinA, INCO = incobotulinumtoxinA, ONA = onabotulinumtoxinA, PRA = prabotulinumtoxinA, RIMA = rimabotulinumtoxinB, U = units.			
Source: [59]			Table 2

botulinum toxin-A, Botox, has become popularized as the generic reference for all cosmetic botulinum toxin [60; 61].

Botulinum toxin-A is the primary form used for cosmetic treatment. While less extensively studied for cosmetic indications, botulinum toxin-B also appears to be effective [59].

MECHANISM OF ACTION

Botulinum toxins block the release of acetylcholine from motor neurons at the neuromuscular junction. By inhibiting acetylcholine neurotransmission between peripheral nerve endings and muscle fibers, botulinum toxin weakens or paralyzes skeletal muscle and, in aesthetic medicine, weakens muscular contraction [10].

Botulinum toxin blocks presynaptic acetylcholine release, causing reduced or diminished muscle contraction. This results in temporary improvement in the appearance of the areas affected by lines and wrinkles, for facial contouring and improving the skin [62]. The inhibitory effect is temporary; recovery of muscular function is often evident by three months, but the cosmetic effect may persist longer [10; 33].

AVAILABLE PRODUCTS AND FORMULATIONS

Four botulinum toxin formulations are approved by the FDA for aesthetic use (**Table 2**). The FDA recommends using specific names (e.g., ONA or ABO, Botox or Dysport), instead of serotypes (e.g., botulinum toxin-A), to prevent confusion between products [59]. Discussion in this course is limited to the four serotype A botulinum toxin products approved for cosmetic use; the off-label use of RIMA will not be explored. Unless a specific product is described, botulinum toxin is used to broadly reference the use of FDA-approved botulinum toxin-A formulations.

ONA, ABO, PRA, and INCO must be reconstituted before using, with sterile, non-preserved saline recommended by their respective makers. In practice, many clinicians reconstitute these products in saline containing benzyl alcohol to reduce injection-site pain [63]. Compelling evidence now suggests that reconstitution using preserved saline dramatically improves patient comfort without compromising efficacy [18].

The formulations (i.e., ONA, INCO, PRA, and ABO) are not interchangeable. The products differ in units, chemical properties, biologic activities, weight, and manufacturing process. Production process and conditions such as pH, temperature, formulation, and concentration are crucial; alterations in any can increase the likelihood of formation of inactivated toxoid proteins, which in turn may be immunogenic [62].

Dose conversions are not standardized. Dosing is not interchangeable, and the products and procedures should be selected and prescribed according to individual needs and aims of treatment [62].

CLINICAL USE OF BOTULINUM TOXIN

With aging, decreased skin elasticity and repeated muscle contraction cause hyper-functional facial lines, particularly in the glabellar and periorbital regions. Depressor muscles overpower the levators to result in ptosis of the brow and mid-cheek groove, and patients develop horizontal forehead rhytides, glabellar frown lines, or lateral canthal “crow’s feet,” indications for botulinum toxin use [64].

Botulinum toxin is also extensively used off-label for brow shaping, eyebrow lifting, opening the aperture of the eye, decreasing mouth frown, defining the jaw line, increasing lip show, decreasing gummy smile, reducing “bar-code” lines around the mouth, eliminating “golf ball” chin, reducing platysma bands, and softening a squared, masculine jaw [65].

Patients treated with botulinum toxin for aesthetic purposes can expect their results to last at least three months, but effects can persist four to five months depending on the area treated, dose, and formulation used. The results may last longer for some patients, especially after repeated treatment [62].

Long-term outcome data support practice trends in decreased dosing and increased botulinum toxin injection intervals. Patients treated for glabellar lines over an average of nine years reported high levels of satisfaction sustained by repeated treatment and greater reductions in their perceived age with increasingly longer treatment durations [6].

While botulinum toxin monotherapy of dynamic rhytides is effective, current practice favors botulinum toxin combined with fillers, lasers, and/or light- or energy-based devices for synergistic effects and superior and more durable improvements [10; 33; 59].

Dilution of FDA-approved botulinum toxin for off-label intradermal injection is used for reducing surface wrinkling by weakening superficial facial muscle activity but sparing deeper muscle function. This approach is also used for reducing upper face rhytides without affecting brow muscles [64; 66].

Safe and effective use of botulinum toxin requires the understanding of anatomy, movement of muscles in isolation and in relation to other muscles, the concept of compensatory strengthening, and observant evaluation of the patient at rest (static) and with normal and exaggerated animation (dynamic). Every patient is unique, and inter-patient differences can be vast [65].

Patient Selection

To help determine botulinum toxin suitability, assess facial muscle function and tone in static and dynamic states looking for signs of stronger contraction (e.g., greater dynamic movement, deeper lines, larger apparent mass during use) [67]. Observing dynamic movement of the skin can help identify areas of stronger or weaker muscle contraction, why certain wrinkles are formed, and which muscles are creating them. The findings assign patients to one of the following categories [67]:

- **Kinetic:** Regular muscle contraction and wrinkles during active expression, but not at rest. Botulinum toxin very likely effective.
- **Hyperkinetic:** More excessive muscle contraction. May require more frequent, higher-dose botulinum toxin to achieve the desired effect.
- **Hypertonic:** Inability to relax specific muscles, visible wrinkles at rest. Some benefits may be possible with botulinum toxin, but adding filler injections may be necessary.

- Deep static lines with loss of skin elasticity:
Unsuitable for botulinum toxin injection.

Side Effects and Safety

Compared with dermal fillers, prevention of botulinum toxin adverse effects is more straight-forward [18; 33; 59; 62]. Common acute side effects include transient swelling, bruising, and headache. Ice or cooling is commonly used for post-injection comfort and to prevent bruising. Temperature seems to influence botulinum toxin uptake, suggesting that cooling the area might undermine efficacy.

Poor treatment response can result from insufficient or incorrect dosing, anatomical variation, or errors in drug handling during preparation, storage, or administration. Diffusion of toxin to untargeted areas from improper injection placement can result in excessive muscle weakness, cosmetic disfigurement, and/or functional deficits that persist for months.

Contraindications

Injection-site infection, known hypersensitivity to any product component, and allergy to cow milk proteins for ABO only are all contraindications to botulinum toxin treatment [59]. Perioral botulinum toxin injections in professional speaker, vocalist, or musician patients require discussion of the potential functional impact from weakened or impaired muscle tone, a possible contraindication.



EVIDENCE-BASED
PRACTICE
RECOMMENDATION

The Australasian College of Dermatologists strongly recommends that botulinum toxin-A treatment be avoided during pregnancy and breastfeeding owing to the lack of adequate data on the developmental risk to a human fetus from the use of these agents in pregnant women and evidence of reproductive toxicity in animal studies.

(<https://onlinelibrary.wiley.com/doi/full/10.1111/ajd.13273>. Last accessed March 26, 2021.)

Level of Evidence: Expert Opinion/Consensus Statement

SOFT TISSUE (DERMAL) FILLERS

A variety of injectable soft tissue (dermal) filling agents are available for correction of prominent skin lines, fat atrophy, volume lost, and other contour changes of facial soft tissue (**Table 3**) [68]. Fillers are classed on different variables that inform appropriate selection and potential complications: biodegradability, longevity in the tissue, and histologic reaction [69; 70; 71].

The FDA designates fillers as either absorbable/temporary (e.g., hyaluronic acid, calcium hydroxyapatite [CaHA], poly-L-lactic acid [PLLA]) or non-absorbable/permanent (e.g., polymethylmethacrylate [PMMA]) based on the agent's biodegradability. If an agent absorbs within 18 months, it is considered temporary; if it does not absorb within 24 months, it is considered permanent. Some agents combine absorbable material for immediate effect and carrier until a nonabsorbable material induces fibroblast stimulatory effects (in more than 18 months). These agents are considered semipermanent. Agents with minimal tissue response are considered volumizers, while those that induce a strong tissue reaction are considered stimulators.

Temporary fillers use FDA-approved biodegradable materials absorbed by the body over time. Permanent fillers persist indefinitely in tissue. Some FDA-approved fillers, such as collagen-based products or avian-derived hyaluronic acid (Hylaform), remain available but are largely replaced by hyaluronic acid fillers with superior clinical properties and/or negligible allergenic potential [68; 73; 74].

Most acute side effects and potential serious adverse effects of FDA-approved dermal fillers are common across fillers. All filler agents are contraindicated in patients with known hypersensitivity to any product component specific to the product. There are a variety of other contraindications to the use of various dermal fillers (**Table 4**).

With all fillers, treatment should undercorrect the defect and avoid overcorrection. All treatment sites should be massaged immediately after injection to facilitate an even distribution.

FDA-APPROVED DERMAL FILLERS AND CLINICAL USE	
Product, Year Approved	Approved Indications
Hyaluronic acid: Galderma Labs	
Restylane ^a , 2003	Correction of moderate-to-severe facial rhytides and/or folds Lip augmentation
Restylane-L, 2012	
Restylane Silk, 2014	Lip augmentation Correction of perioral rhytides
Restylane Lyft, 2015	Correction of moderate-to-severe deep facial rhytides and folds
Restylane Defyne, 2016	Correction of moderate-to-severe facial rhytides and folds with age-related volume loss
Restylane Refyne, 2016	Correction of moderate-to-severe facial rhytides and folds
Hyaluronic acid: Allergan	
Juvéderm XC, 2006	Correction of moderate-to-severe facial rhytides and folds
Juvéderm Ultra XC, 2006	
Juvéderm Ultra Plus XC, 2006	
Juvéderm Ultra Plus XC, 2015	Lip augmentation Correction of perioral rhytides
Juvéderm Voluma XC, 2013	Correction of age-related volume deficit in the midface Cheek augmentation
Juvéderm Volbella XC, 2016	Lip augmentation Correction of perioral rhytides
Juvéderm Vollure XC, 2017	Injection into the mid-to-deep dermis for correction of moderate-to-severe facial wrinkles and folds (e.g., nasolabial folds)
Hyaluronic acid: Merz Aesthetics	
Belotero Balance, 2011	Correction of facial rhytides and folds, especially around the nose and mouth
Hyaluronic acid: Teoxane S.A.	
RHA 2 and RHA 3, 2017	Injection into the mid-to-deep dermis for correction of moderate-to-severe dynamic facial wrinkles and folds (e.g., nasolabial folds)
RHA 4, 2017	Injection in deep dermis to superficial subcutaneous tissue for correction of moderate-to-severe dynamic facial wrinkles and folds (e.g., nasolabial folds)
Hyaluronic acid: Prollenium Medical Technologies, Inc.	
Revanesse Versa, 2018	Injection in mid to deep dermis for correction of moderate-to-severe facial wrinkles and folds (e.g., nasolabial folds)
Calcium hydroxylapatite (CaHA): Merz Aesthetics	
Radiesse ^a , 2006	Correction of moderate-to-severe facial rhytides and folds
Radiesse(+), 2015	
Poly-L-lactic acid (PLLA): Galderma Labs	
Sculptra Aesthetic, 2009	Correction of shallow-to-deep nasolabial fold contour deficiencies and other facial rhytides
Polymethylmethacrylate (PMMA): Suneva Medical	
Bellafill, 2006	Correction of volume deficits around the mouth (e.g., nasolabial folds)
Bellafill, 2015	Correction of acne scars
^a Does not contain lidocaine.	
Source: [72; 73]	

Table 3

Table 3

CONTRAINDICATIONS TO DERMAL FILLERS	
Contraindication	Specific Conditions
Relative and absolute contraindications	
Allergic history	Multiple severe allergies Anaphylaxis Heightened immune responses to common inhaled and food allergens (atopy) Allergy to latex, hyaluronic acid products, streptococcal/other gram-positive bacterial proteins, or lidocaine Desensitization therapy during filler treatment
Scar-related	History of hypertrophic scarring or keloid formation Scars at intended treatment site
Bleeding-related	Current anticoagulant or antiplatelet therapy History of bleeding, clotting (hemophilia), or connective tissue disorders
Active autoimmune disease	Systemic lupus erythematosus Rheumatoid arthritis Hashimoto thyroiditis
Patient-related factors	Unattainable expectations Pregnancy Lactation
Contraindications unless fully resolved with treatment	
Inflammatory skin diseases	Atopic dermatitis Seborrheic dermatitis Acne Rosacea Psoriasis
Skin infection or any unhealed facial wound	Impetigo Folliculitis <i>Propionibacterium acnes</i> Viral warts Perioral HPV Molluscum contagiosa Streptococci or staphylococci bacterial infections <i>Candida</i> (yeast) infections
Local infection	ENT, oral cavity, or dental infections or abscess
Remote infection	Intestinal tract, urinary tract, or bladder infection
Inflammatory processes	Pimples Hives Rashes Cysts
ENT = ear, nose, or throat, HPV = human papillomavirus.	
Source: [19; 75]	

Table 4

HYALURONIC ACID

Hyaluronic acid is a glycosaminoglycan disaccharide and natural constituent of the dermal extracellular matrix, cartilage, and connective tissue. Hyaluronic acid is highly hydrophilic, enabling dermal hyaluronic acid to hydrate and cushion the skin and fill

empty spaces within the extracellular matrix. Dermal hyaluronic acid content declines with skin aging, which reduces water-binding capacity and elasticity, induces volume loss, and promotes the development of rhytids and other aging features [72; 73; 76; 77].

Unmodified hyaluronic acid readily dissolves in water to form a viscous gel, but injected into the dermis, it is quickly degraded by hyaluronidase and free radicals in the skin [76]. Most FDA-approved hyaluronic acid fillers use nonanimal stabilized hyaluronic acid synthesized from *Streptococcus equi* bacteria. Liquid nonanimal stabilized hyaluronic acid, as with native hyaluronic acid, is rapidly broken down [72; 77]. To increase stability and longevity, manufacturers use crosslinking agents to bind hyaluronic acid polymer chains to each other, resulting in a gel that resists enzymatic and free radical breakdown. Most fillers use 1,4-butanediol diglycidyl ether (BDDE) as a cross-linker [76; 77]. The hyaluronic acid modification process, proprietary to each maker, allows a portfolio of hyaluronic acid filler consistencies with varied rheologic properties (e.g., viscosity, gel hardness, lifting ability, tissue integration) that determine optimal tissue placement depth and product longevity [19; 78; 79].

Hyaluronic acid can bind 1,000 times its volume in water. This water-binding and space-filling effect underlies the volumizing efficacy of hyaluronic acid fillers [76]. Efficacy has been observed to persist beyond a time frame explained by space-filling effects alone. This led to research of other mechanisms, which identified induction of adipogenesis, neocollagenesis through mechanical tension on fibroblasts, and periosteal stem cell activation followed by new tissue formation with periosteal filler placement [52; 80; 81].

Hyaluronic acid fillers combined with botulinum toxin act synergistically to produce superior, more durable effects than either monotherapy. For example, the longevity of effects is improved when treating sites of dynamic wrinkles, such as glabellar lines. Reduced filler deformation due to botulinum-toxin induced local muscle relaxation at least partially accounts for this effect [68].

CALCIUM HYDROXYLAPATITE

Calcium hydroxylapatite (CaHA) is a mineral commonly found in human teeth and bones that functions as a scaffold for collagen ingrowth. CaHA filler contains CaHA microspheres as biodegradable particles suspended in an aqueous carboxymethyl-cellulose gel carrier. Once injected, the carrier gel gradually resorbs; the microspheres stimulate a fibroblastic response resulting in active physiologic remodeling of the extracellular matrix and long-term collagen deposition around the implant that promotes volumizing. The microspheres eventually degrade into calcium and phosphate ions and are excreted. The effects last around 18 months [10; 73; 79].

Radiesse (formerly Radiance) is the only FDA-approved CaHA filler, indicated for correcting moderate-to-severe soft-tissue defects, facial folds, and wrinkles, including nasolabial folds [72]. The viscoelastic filler is well suited for supraperiosteal and deep fat placement. When injected more superficially, it should be diluted 1:1 or 1:2 [10; 68]. Radiesse(+), formulated with 0.3% lidocaine, was approved in 2015 to reduce pain without needing to premix before injection [82].

Radiesse is contraindicated in patients with a history of anaphylaxis or multiple severe allergies [68]. Radiesse injection of the lips risks forming nodules and should be avoided. Radiesse is visible on x-ray and may obscure underlying features [73].

POLY-L-LACTIC ACID

Poly-L-lactic acid (PLLA) is a biodegradable, biocompatible, synthetic polymer used for decades in resorbable sutures, orthopedic plates, and urologic stents. First approved in 1999 as a dermal filler in Europe, PLLA received FDA approval in 2004 for the treatment of HIV-associated lipoatrophy (Sculptra) and in 2009 for aesthetic treatment in immunocompetent patients (Sculptra Aesthetic) [49; 72; 73].

PLLA induces a subclinical inflammatory response that stimulates fibroblast proliferation, neocollagenesis, and type I collagen formation, leading to a progressive increase in dermal volume [68; 72]. Each PLLA injection produces a gradual treatment effect with limited correction. Three injection sessions at six-week intervals are generally required, but improvements after the final injection can last up to two years. Patients should be counseled that final results can take months to achieve [83; 84].

Treatment should aim to undercorrect, because the results progressively improve over time. Injections should be spaced at least three weeks apart because transient post-injection edema can mimic a full correction [68].

Injections should be placed into the deep dermis or subcutaneous fat. The lip and periorbital region should be avoided due to risk for nodule formation. Subcutaneous papules are a common adverse effect [68].

POLYMETHYLMETHACRYLATE MICROSPHERES

Polymethylmethacrylate (PMMA) is a non-biodegradable, biocompatible, synthetic polymer used in medical devices such as bone cement and intraocular lenses. As a soft tissue filler, PMMA microspheres are tiny, round, smooth particles suspended in a gel-like solution containing lidocaine and bovine collagen [73].

The collagen gel gives an initial volume but is resorbed over one to three months. The microspheres stimulate a local inflammatory reaction, followed by deposition of granulation tissue that encapsulate the microspheres and mature into connective tissue. By three months post-injection, the microspheres are surrounded by newly formed collagen, accounting for the observed volume-filling effect [74; 79; 84]. Tissue encapsulation of PMMA microspheres makes the results irreversible.

The PMMA filler Bellafill is the only FDA-approved permanent filler. Treatment of nasolabial folds and facial acne scars are the only approved cosmetic indications, but Bellafill is used off-label to volumize other mid- and lower-face contour defects [74; 85].

The bovine collagen carries potential immunogenic issues. Clearance for Bellafill injection requires non-reactive response to skin-testing for bovine collagen hypersensitivity one month pre-procedure [74; 79].

Good PMMA candidates are patients with well-defined lines and furrows and minimal excess skin [74; 85]. PMMA use is not recommended in areas of thin skin (e.g., lower eyelid, neck), the lips, and in patients with generally thin, loose skin [74].

Bellafill is intended for deep tissue placement. A series of conservative injections can be required for optimal results, with touch-up injections performed one to three months after initial treatment [74]. Optimal results require 3 to 12 months for sufficient new collagen synthesis, and additional improvement beyond 12 months may occur [86].

FILLER SELECTION

Hyaluronic Acid Fillers

Unlike CaHA (Radiesse), PLLA (Sculptra), and PMMA (Bellafill) fillers, availability of numerous hyaluronic acid products requires judicious product selection based on rheologic properties. Each facial area and anatomic plane subjects filler to biomechanical stressors of compression, stretching, and lateral shearing from skin tension, muscle activity, and fat volume of varying intensity and frequency [78; 87].

Rheology studies the flow and deformation of filler material subjected to biomechanical stressors to understand their clinical properties and behavior. Manufacturers crosslink and modify hyaluronic acid products (e.g., Hylacross, Vycross) using methods that determine gel rheology. The rheologic properties leverage the distinct tissue distribution patterns and clinical behaviors of hyaluronic acid products [76; 77].

The clinical behavior of Radiesse is influenced by the same rheologic factors as hyaluronic acid fillers. Rheologic properties are unique to each hyaluronic acid and CaHA product, between filler families. The major rheologic properties are [9; 29; 52; 76; 78; 88; 89; 90]:

- Shearing: Force pushing one part of a body in one direction and another part in the opposite direction
- Elasticity: Ability to resist deformation by external forces
- Viscosity: Ability to resist shearing forces
- Cohesivity: Ability to resist vertical compression and stretching
- Hydrophilicity (water-binding ability): Capacity to attract water and expand
- Particle size: Contributes to overall lifting and filling power
- Particle concentration and crosslinking: Influences durability by resisting enzymatic degradation.

Clinically, the elasticity of filler reflects the gel's firmness. The level of viscosity will determine the pattern and extent of tissue integration. High-viscosity agents resist tissue spread and shearing. Low-viscosity agents are ideal for superficial placement to treat shallow folds and lines and are best used where spread and softness is more important than volume (e.g., the lips) [52; 76; 77; 78]. Conversely, high-elasticity and high-viscosity gels are best suited for deep placement to treat deep folds and restore volume loss by creating volume and lift in the mid- and lower face.

Cohesivity is spreading related to tissue depth and ability to hold form or shape under stress by overlying/underlying muscle and skin compression. Cohesivity increases with degree of cross-linking and hyaluronic acid concentration. Low-cohesivity gels are easier to mold and spread evenly in the skin, making them suited for correcting small rhytides. High-cohesivity gels are suited for revolumizing large areas of volume loss.

Restylane Lyft is an example of a high-elasticity, large-particle gel with greater filling power and resistance to degradation in deep-tissue volumizing. Juvéderm products use elasticity from highest to lowest in gels intended for deep (Voluma), midlevel (Vollure), and superficial (Volbella) tissue placement.

Calcium Hydroxylapatite

With a high lift capacity and results that last more than one year, Radiesse works well to fill volume loss in the midface and is placed in a manner similar to injection of hyaluronic acid products [84]. The use of Radiesse for melomental folds ("marionette lines") has been reported extensively, with effective and durable results [58].

Of note, Radiesse may be more likely than other fillers to result in intra-arterial complications, skin necrosis, and blindness. The increased propensity to cause vascular compromise could be related to particle size, with larger particles resulting in more proximal vessel obstruction. Certain particles may also stimulate the clotting cascade, ultimately resulting in skin necrosis [16]. This seems to elevate precautions in using this product near vascular danger zones.

Poly-L-Lactic Acid (Sculptra)

PLLA volumizes soft tissue in a gradual, progressive, and predictable manner, providing natural-looking restoration of facial volume [91]. Although it is categorized as biodegradable by the FDA, the duration of action is 12 to 24 months and, with repeat treatment, several years. As noted, PLLA is more accurately classed as a semipermanent dermal filler [84; 92].

PLLA should be avoided in perioral and periocular areas; in the neck where thin skin requires superficial injection; and in mandibular ligament/platysma muscles [49; 58]. Superficial injection in the dermis is also inappropriate. PLAA injection is recommended for the suprapariosteal in the temples, lateral brow, zygomatic area, maxillary area, mandibular area, and mental area [93]. It may also be used in the subcutaneous fat in the mid-cheek

regions and preauricular area. More specifically, recommended PLLA injection sites are [49; 58; 93]:

- Temporal fossa: Supraperiosteal at the temporal muscle origin
- Lateral brow: Supraperiosteal at the tail of the brow
- Medial malar region: Supraperiosteal on the zygomatic bone, maxilla, and pyriform fossa
- Submalar/mid-cheek: Deep subcutaneous plane where bony background is absent
- Lateral third of the mandible/mandibular angle and lower lateral cheek: Superficial subcutaneous fat above the parotid gland and masseter muscle
- Mandible/chin: Supraperiosteal over the menton and prejowl sulcus

Sculptra may provide global volume restoration in lean patients who are too depleted for space-occupying fillers, an alternative to deep volumizing hyaluronic acid fillers that could be too expensive and difficult to use as scaffolding [94].

Polymethylmethacrylate (Bellafill)

Used as a deep tissue filler for mid- and lower-face volume loss, Bellafill seems comparable to other filler types in efficacy [84]. This shifts the basis for Bellafill selection to patient preference and appropriateness [34; 74].

Persistent effects, possibly with a single treatment (or with minor touch-ups), can make Bellafill attractive, but treatment with permanent fillers requires careful screening. Patients who have histories of unsubstantiated dissatisfaction with cosmetic results, are unsure of their desired outcome, or are new to fillers are poor candidates for Bellafill [34; 74].

Other Considerations in Filler Selection

Clinician experience influences the choice of filler. Improper use can result in an unacceptably high risk for adverse effects, and clinicians not trained in using specific fillers should refrain from their use [34; 74]. Complications or unfavorable cosmetic results with permanent fillers may require surgical intervention and may be impossible to completely reverse.

The desired duration of effect should be considered. Fillers that eventually degrade in tissue (e.g., hyaluronic acid) offer the advantage of reversibility but require multiple subsequent treatments to maintain the desired effect. Adverse effects of products may not become apparent until post-market, making it prudent to select products with an established safety/adverse event profile from clinical use [95].

DEOXYCHOLIC ACID

Deoxycholic acid (Kybella) is FDA-approved for treatment of moderate-to-severe submental fullness/convexity ("double chin"). Injection into the subcutaneous fat below the chin area causes focal adipolysis and necrosis. This induces macrophages to clear cell membrane fragments, recruit fibroblasts, and stimulate neocollagenesis. Once destroyed, adipocytes cannot store or accumulate fat. Submental appearance is improved through subcutaneous fat reduction and tissue tightening [96; 97].

Kybella is an alternative to liposuction for achieving an aesthetically pleasing jawline by submental fat reduction, but comparisons in clinical trials are lacking. Kybella is given in 0.2-mL injections, spaced 1 cm apart, until all sites in the planned treatment area are injected. Up to 50 injections, or 10 mL, are allowed per session. Several sessions spaced at least four weeks apart are usually required. In phase 3 clinical trials, the drug was effective and safe, although a significant number of patients experienced pain, transient bruising, edema, and numbness [98; 99].

In the phase 3 trials, patients were injected with a mean 186 mg of drug as treatment. Cosmetic surgeons reported charging a mean \$691 per 20-mg vial of deoxycholic acid, which would have cost the average study participant \$6,426.35. In contrast, the average patient cost for submental liposuction is \$2,976.56. While Kybella is cost-effective only for patients with mild-to-moderate submental lipos who require fewer injections and treatments, the avoidance of surgery for some patients may outweigh the greater expense [99].

With 65,800 procedures performed in 2019, Kybella uptake into cosmetic practice seems limited following its 2015 FDA approval [12].

INDIVIDUALIZED ASSESSMENT AND TREATMENT PLANNING

KEY ASSESSMENT ELEMENTS

Optimal assessment of facial aging begins with a thorough patient history and examination that assesses anatomical structure and age-related changes to the bone, fat, muscle, and skin. Specifically, this should include [10; 49]:

- Skeletal changes
- Degree and location of volume loss
- Muscle anatomy and movement
- Appearance of lines and wrinkles
- Skin quality
- General facial appearance, symmetry, or any imbalance in facial proportions

The use of photonumeric scales are recommended for the objective assessment of facial aging features. Photonumeric scales have the advantage of providing a consistent visual frame of reference that minimizes variability in perception and subjectivity [100].

With these scales, assessment of the upper, mid, and lower face is performed, with specific aging features rated using a 0–4 scale (0: absent; 4: advanced) [101; 102; 103]. The score helps inform the appropriate level of intervention [10]:

- Early intervention: Individuals with minimal evidence of facial aging (Levels 0–1)
- Restoration: Individuals with moderate to advanced signs of aging (Levels 2–4)

The assessment lays the foundation for a detailed, individualized treatment plan that balances clinical experience with patient desires and expectations [10]. In this initial period, it is important to discuss treatment goals and ensure the patient understands the progressive nature of the aging process. Costs

should also be reviewed, and in patients with limited financial means, treatment should focus on areas that will have the greatest impact. When the individualized treatment plan is formulated, the extent and sequence of procedures and/or treatments should be discussed. Clinicians should ensure the patient understands the maintenance involved in any type of facial restoration and that overtreatment and unnatural results (and likewise undertreatment and suboptimal results) will be avoided.

ETHNIC CONSIDERATIONS

Fundamental to individualized patient assessment is careful consideration of racial/ethnic and gender variation in facial aging features. In this course, the terms used to reference ancestry are Caucasian (European, North African, southwest Asian/Middle Eastern), African (sub-Saharan Africa), Latino/Hispanic (Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture), East Asian (China, Korea, Japan), Southeast Asian (Thailand, Singapore, Indonesia), and South Asian (the Indian subcontinent) [104].

People of all races have distinct ethnic features, yet cultural standards of beauty share remarkable similarity around the world, such as balance, proportion, and symmetry of facial features, and clear, unblemished, and youthful skin [105; 106].

The aging process may manifest differently among various ethnic/racial group; aging promotes and accentuates intrinsic differences of facial morphology and structure. This leads to variations in aged features, such as “Caucasian corners” of lips that develop into marionette lines [94; 105].

Relative to other ethnic/racial groups, the earlier onset and more extensive facial aging common in Caucasian patients reflects the interaction of morphologic features and skin quality. Bony remodeling, facial fat and soft tissue volume loss, deflation, and descent give rise to the same common signs of aging in all ethnic groups, making restoration of volume and correction of related sequelae fundamental strategies for every patient [52; 105].

FITZPATRICK SKIN PHOTOTYPES			
Phototype	Unexposed Skin Color	Sun Exposure Response ^a	Examples
I	Pale white	Always burns, never tans	Red hair with freckles
II	White	Burns easily, minimal tan	Fair-haired Caucasian, Northeast Asian
III	Olive to light brown	Burns minimally, gradually tans	Mediterranean Caucasian, East Asians
IV	Moderate brown	Burns minimally, tans well	Some Southwest Asian (Middle East) Caucasian, South Asian, Hispanic
V	Dark brown	Rarely burns, tans profusely	Darker Hispanic, some African
VI	Deeply pigmented dark brown to black	Never burns, tans deeply	Darker African, Indigenous Australian
^a After one hour on sun-shielded, untanned skin.			
Source: [107; 108; 109]			Table 5

Skin Phototype

A powerful determinant of skin aging is the amount of melanin pigment in skin, which determines skin color or phototype. The Fitzpatrick Scale is a classification system that assigns individuals to one of six distinct phototypes based on skin complexion and response to UV radiation exposure (**Table 5**) [35; 107]. Phototype is more tied to the equatorial proximity of one's ancestors than to specific ethnicity.

Variations in Aging Features

In phototypes IV–VI, the thicker, more compact dermis and higher melanin content delays the onset of skin aging, skin laxity, and sagging. In these individuals, aged skin presents with muscular or expressive lines instead of early fine wrinkling [10].

Craniofacial measurements of diverse racial/ethnic groups were originally compiled for reconstructive surgeons, who required normative data in treating congenital or post-traumatic facial disfigurements. These data inform cosmetic practice in diverse patients who age differently [111; 112]. Unless otherwise stated, Caucasian facial characteristics are the point of reference for ethnic/racial variations discussed in the following sections [104]. This is the literature standard and should be taken as a guide rather than a determinate of beauty or value.

African

Compared with Caucasians, persons of African descent have skin that maintains its structural integrity and youthful appearance. This bestows lower rates of facial rhytides, brow ptosis, lip aging, lip volume loss, and perioral rhytides formation [104; 112].

Facial aging tends to show more prominently in the periorbital region and midface. Patients with African ancestry can exhibit pronounced sagging of the malar fat pads, soft-tissue laxity, and jowl formation of the midface. Unlike the laxity and descent of Caucasian skin, the thickness and weight of skin contribute to jowling in these patients [104].

Aging Black patients often have fewer issues requiring soft-tissue augmentation but may seek to restore the youthful fullness of their lips. Typically the upper lip alone is treated, as the lower lip usually maintains its volume [112].

Latino/Hispanic

This heterogeneous group encompasses individuals with any combination of Caucasian, Native American, and/or African-American features. For patients with predominately Native American characteristics, approaches for East Asians are recommended; when Caucasian characteristics predominate, approaches appropriate for this group are used [112].

Patients of Mexican or Central or South American origin tend to have rounder faces with heavy eyelids, a prominent malar eminence and midface area, broader nose, abbreviated nasal length, and a recessed chin. With aging, the mid-cheek area becomes thicker and heavier, with fat pad accumulation and more prominent nasolabial folds, along with eyebrow and eyelid drooping and lower lid fat accumulation [104].

East Asian

East Asians tend to have a wider face with wider bitemporal and bizygomatic width, shorter in vertical height, lower structural projection of the midface, and lack of brow, nasal, and chin projection. Aging is likely to present as central face retrusion; flattening of the anteromedial midface; recessed piriform fossa; and a flatter forehead. A flatter facial skeletal framework promotes greater soft-tissue descent of the midface, malar fat pad ptosis, and tear trough formation [52; 105].

These features account for the prevalence of fillers of the medial midface, nose, chin, and forehead of younger Asian patients. In older patients, these regions are a priority, along with correcting age-related disharmonies. Volumizing is limited to the medial maxilla area to enhance central projection and to avoid further widening the midface. Lip augmentation is usually not needed, especially in patients of Southeast Asian origin who present greater lip fullness and may more likely desire lip reduction to balance the lower third of the face [52; 104; 112].

South Asian

South-Asian populations differ from Caucasian and East Asians, with smaller width of the malar prominences, smaller mandibular width and height, a much shorter lower third of the face compared with the middle and upper thirds, and smaller facial skeletal width compared with Caucasians. The downward medial descent of soft tissue is more aggressive due to higher volumes of facial fat pad over a smaller bone framework [56].

Bony changes and loss of lateral temple and cheek fat are best approached by volumizing the anterior mid-cheek and nasolabial fat pads, avoiding the deep medial midface fat pads. Nasolabial and medial midface correction should be very conservative, with emphasis on deep fat volumizer placement in lateral zones [56].

A concern of some patients is of repeated filler treatment producing an overtreated appearance and unsatisfying outcome. To address this concern, avoid volumizing the medial midface where soft tissue descent aggregates, compensating for this pattern by focusing on lateral midface volumizing [56].

GENDER CONSIDERATIONS

Men represent a small but growing proportion of cosmetic patients and distinctly differ from women in facial anatomy, physiology, and aging. Knowledge of sexual dimorphism (phenotypic differences between sexes) of the entire facial form, including the skeletal structure, musculature, vasculature, soft tissue, and skin is vital for aesthetic outcomes. Female facial characteristics remain the frame of reference for male variations [50; 110; 113; 114; 117].

Sexual dimorphism of skull characteristics is foundational to gender differences in facial features (**Table 6**). The facial vasculature of men is greater in density. Men have increased facial muscle mass, including the mimetic muscles, greater facial muscle movement, and greater upward vertical movement capacity in facial expressions (e.g., smiling, puckering of lips). Unlike the more curvilinear cheekbone in women, the male midface is more angled due to strong muscle insertions. Facial movement contributes to rhytid formation. Men have greater severity and distribution of facial rhytides; the perioral area is the only exception.

Facial subcutaneous fat exhibits sexual dimorphism. The subcutaneous fat is 1.5 times thicker in the medial malar fat compartment of women, but the distribution is uniform in men. Men have less soft tissue in the cheek area overall, and the subcutaneous fat layer is thinner in men regardless of age.

SEXUAL DIMORPHISM OF THE SKULL		
Area of the Face	Female	Male
Forehead	More straight	More oblique
Glabella	Curved and subtle	Frontonasal suture is more prominent
Supraorbital rim	Less conspicuous	More striking
Midface	Subtle angles	Irregular surface and little anterior projection
Zygoma	More prominent and curvilinear	Less prominent
Mandible	Lighter, with subtle angles	Larger, stronger, with clear-cut angles
Chin	Smaller and rounded shape	Larger and square-shaped
Source: [50]		Table 6

The loss of subcutaneous fat, thicker skin, and more prominent facial musculature results in deeper expression lines and contributes to the greater severity of male rhytides. The prominent volume loss makes men appear older than their age, relative to women. Aging also causes a more significant downward shift of the lower eyelid in men.

Treatment Considerations

Understanding sexual dimorphism is crucial to prevent unwanted feminization of male features, a primary concern of male patients seeking aesthetic treatment [52; 114; 115; 116]. In addition, cosmetic intervention that produces an exaggeration, rather than restoration, of typical male features can result in an aggressive or threatening appearance [117]. Of course, some men do wish to attain a more feminine or masculine appearance, but this is beyond the scope of this course, which focuses on cosmetic procedures to address unwanted facial changes associated with aging.

General approaches to minimally invasive correction of cosmetic concerns in older men vary by the area of the face [52; 113; 114; 115; 116].

Upper Face

Overfilling the temple should be avoided, because temporal hollowing is aesthetically appealing in many men. With botulinum toxin for rhytides, the lateral frontalis muscle is injected to prevent lateral brow arching and to maintain the flat male brow position. The frontalis may require more injections due to the larger forehead area. In a brow already

lower with age, inferior frontalis injection requires caution to avoid ptosis (when brow position falls below the orbital rim) [52; 113; 114; 115; 116].

Midface

In the subcutaneous medial cheek fat compartment, uniform injection of filler replaces volume loss while maintaining a flatter and more angular cheek contour. The structural support may also improve the tear trough and palpebral malar groove. Fillers should be injected laterally along the zygomatic arch, avoiding a feminizing convexity from overvolumizing the anterior and medial cheeks [52; 113; 114; 115; 116].

Lower Face

Filler injections can restore or enhance the projection of the chin; increasing its forward projection helps tighten the jawline area, and increasing its lateral borders helps to square a recessed chin and add definition to the jawline. To restore volume or enhance shape, the suprapariosteal temporal-buccal fat pad is injected, which will project the jaw laterally and strengthen the jawline if a more square jaw is desired [52; 113; 114; 115; 116].

AGE CONSIDERATIONS

Aesthetic medicine professionals are confronted by increasing demand for cosmetic treatments by young patients. Treating this age group can be difficult to justify, but standard physiologic aging and individual concerns can guide age-appropriate cosmetic counseling, prevention, and intervention [118].

In patients younger than 20 years of age, minimally invasive cosmetic procedures are generally inappropriate. Emphasis is placed on prevention counseling (e.g., protection against sun damage) and addressing age-independent congenital characteristics or acquired disharmonies (e.g., acne scars) [52; 118]. Cumulative exposures to UV radiation, smoking, and pollution can initiate early collagen decline, leading to noticeable fine lines and wrinkles in some patients in their 20s. Appropriate treatment includes noninvasive modalities or botulinum toxin, which is FDA-approved for rhytides in patients 18 years of age and older [118; 119].

The typical age of patients who seek cosmetic procedures is between 30 and 50 years. When clinically indicated, fillers and toxin can demonstrably benefit older and younger patients. Patients between 30 and 50 years of age often achieve the most benefit from botulinum toxin treatment; a greater proportion of rhytides in older patients may be due to loss of skin elasticity, which is not alleviated by botulinum toxin [33]. There is no upper limit for age beyond which benefits cease, assuming that dose and injection sites are tailored to muscle mass and function [52].

THE MINIMALLY INVASIVE TREATMENT APPROACH

In the recommended practice of minimally invasive therapy for aging features, discussion begins with an overview of evidence that informs practice and the sequence of treatment delivery. Next, for each horizontal zone, the clinical features of aging are briefly reviewed and corresponding interventions are described.

The practice standard for facial aging is volume replacement, tissue tightening, and skin rejuvenation (resurfacing). Therapies for skin resurfacing include lasers/light (e.g., intense pulsed light, fractional laser), energy (e.g., microfocused ultrasound with visualization, radiofrequency) and topical (e.g., microdermabrasion, chemical peels) modalities.

These mostly noninvasive therapies are mentioned by necessity as recommended components of multimodal treatment, but specifics of their use are beyond the scope of this course.

RECOMMENDED THERAPY COMBINATIONS

Improved understanding of facial aging and mechanisms of therapies inform their combination and sequence of use. With superior outcomes repeatedly demonstrated with combination therapy over monotherapy, this approach is now recommended for most patients [6; 10; 33; 34; 52; 120].

Botulinum Toxin Plus Hyaluronic Acid Fillers

Botulinum toxin and hyaluronic acid fillers act synergistically for superior improvements and duration [34; 52; 79; 87; 120]. Recognition that hyperdynamic muscle activity leads to both soft tissue volume loss and rhytides has prompted botulinum toxin injection one to two weeks before fillers. Botulinum toxin increases filler efficacy by diminishing the dynamic muscle component of the target, and improves longevity by preventing filler breakdown from repetitive muscle activity. Fillers can extend botulinum toxin efficacy to six months.

Botulinum toxin is less effective in deep lines and creases (e.g., glabellar or forehead rhytides), and repetitive muscle contraction degrades filler efficacy to soften the appearance. Botulinum toxin/fillers overcome the respective monotherapy limitations to produce superior extent and duration of improvement, without increased bothersome or significant side effects. Outcomes are optimized by treating aesthetic units.

Botulinum Toxin/Hyaluronic Acid Fillers Plus Lasers/Light Therapies

Combined with energy-based therapies, the efficacy of botulinum toxin/fillers is superior to monotherapy, without increased spread of botulinum toxin, filler migration, or other untoward effects [10; 94]. Botulinum toxin before laser resurfacing improves post-laser healing, collagen remodeling, and aesthetic results, while post-laser botulinum toxin reduces wrinkle recurrence, prolonging resurfacing efficacy.

Botulinum toxin added to intense pulsed-light treatment of photoaging increases overall aesthetic benefits. Microfocused ultrasound and radiofrequency stimulate fibroblast proliferation and new collagen for efficacy in cutaneous sagging, wrinkling, and marionette lines. Outcomes are usually more satisfactory combined with hyaluronic acid fillers.

RECOMMENDED THERAPY SEQUENCE

Ideally, all treatments should be spaced apart at least two weeks, with botulinum toxin given two weeks before filler injections in areas of static lines, dynamic rhytides, or deep folds. However, patients may prefer same-day botulinum toxin and filler injection for convenience. This is thought to be safe, with botulinum toxin injection before fillers to avoid toxin spread beyond the treated area [8; 10; 11; 29; 30; 52; 71]. In the four weeks before and after filler injection, lasers, intense pulsed light, chemical peels, microdermabrasion, and over-the-counter or prescription wrinkle treatments should be avoided. It is also important to avoid concurrent botulinum toxin with laser resurfacing or microfocused ultrasound; increased blood flow and edema may promote toxin diffusion and side effect risks.

The midface is treated first. Patients with nasolabial fold complaints may require education that correcting midface volume naturally and effectively treats overall aging features. The filler injection sequence is lateral, then middle, then medial fat compartments; in some cases, a sequence from deep to superficial tissue planes is suitable. New filler injection over previous fillers (“layering”) is discouraged due to greater risk of potentially serious complications [8; 10; 11; 29; 30; 52; 71].

PATIENT-TAILORED TREATMENT

While minimally invasive procedures can improve facial texture and volumize, reduce, contour, lift, or reinforce soft tissue, optimal safety and aesthetic outcomes require individualized treatment planning based on assessment of skin changes, tissue quality, extent and pattern of muscle contraction, and soft/hard tissue volume loss [2; 52]. These

principles become obscured when rigid adherence to algorithms or cutaneous landmarks (which shift with age) supersedes a patient-tailored approach [52].

Declining tissue quality and skin laxity are indications for combining fillers with lasers or energy-based devices. In older patients, fewer injection sites and smaller toxin doses at each site may be indicated if muscle mass or function is reduced [52].

THE TRI-VECTOR TECHNIQUE

Patients present with varying levels of lipoatrophy regardless of age, and the tri-vector technique adapts practice standards into an easily patient-tailored framework [121]. In each horizontal zone, this approach initiates filler injections in lateral compartments, working from lateral to medial.

In this approach, step one is supra-periosteal filler injections. In the upper face, injections are made in the temporal fossa to address forehead atrophy, brow ptosis, and temporal volume loss. Filler in the midface addresses volume loss of preauricular (in front of ear) lateral cheek and mid-cheek fat, tear trough, and infra-nasal lines/folds; in the jawline, injections can address mandibular angle changes and maxilla and mandibular fat volume loss (also marionette lines).

The second step consists of deep dermis filler injections at three ligament support sites to provide fibrous fixation points and restrain facial skin against gravitational changes. These sites are:

- McGregor patch (posterior to zygomaticus minor muscle)
- Pyriform aperture (superior part of nasolabial fold)
- Modiolus (lateral to inferior part of nasolabial fold)

The final step in this approach is patient-specific. It may include filler injection in dermal or superficial fat layers to contour the face, soften any sharp angles (especially in jawline area), or address focal superficial lipoatrophy sites [121].

THE UPPER FACE

In each horizontal facial zone, there are compartmentalized anatomic regions that undergo changes and/or loss of volume and tissue integrity with age. Differences in underlying bony structure, weight, and soft-tissue quality influence inter-patient variations in specific aging changes [29; 49].

The youthful upper face is characterized by a subtle convexity of the temple, forehead, and lateral brow and upper eyelid fullness [29]. The aged forehead skin, with loss of bone and fat support, is pulled by repetitive activity of depressor muscles and mimetic musculature to form horizontal rhytides. With temporal and forehead volume loss, glabellar rhytides deepen and lateral canthal rhytides (crow's feet) develop at rest and at smile [10].

The eyebrows, a powerful and versatile facial feature, greatly contribute to the perception of facial attractiveness, and fundamentally inform sexual dimorphism, facial recognition, and nonverbal communication [122]. Low medial brows, even without furrowed wrinkles, signal hostility and anger [65]. Brow ptosis develops as periorbital bone remodeling and temporal deep fat loss erode the support and fullness of the upper lid, causing the brow to descend to the superior orbital rim [4; 29]. Fixed glabellar frown lines, transverse forehead furrows, temporal hollowing, skeletonized supraorbital rim, brow ptosis, and redundant upper eyelid skin combine to form an aged appearance to the upper face [4; 29].

The forehead, glabella, and temples are treated as one aesthetic unit, with botulinum toxin for muscle modulation, fillers to improve temporal hollowing and contours of the forehead, and microfocused ultrasound to lift the ptotic brow and tighten the skin [10; 11]. This “aesthetic unit” principle is underscored by inter-relationships of the brow elevator (frontalis) and depressor (corrugator, procerus, orbicularis oculi) muscles. With antagonistic function, botulinum toxin injection in one muscle causes unopposed strength in another [11; 79].

Botulinum Toxin Treatment

Lines, furrows, and creases develop over time from hyperactive, repetitive use and contraction of various muscles. Botulinum toxin injection into culpable muscles can smooth vertical glabellar rhytides (glabellar complex muscles), horizontal forehead rhytides (frontalis muscle), and periorbital lateral canthal rhytides (lateral orbicularis oculi muscle) [33].

Horizontal Forehead Rhytides

The frontalis, the sole elevator muscle in the upper face, contracts to raise the eyebrows and upper eyelid to express surprise or fright. Frontalis contraction eventually forms horizontal forehead rhytides [33; 67].

Horizontal forehead rhytides require simultaneous botulinum toxin injections of the frontalis and brow depressors. With frontalis muscle injection alone, unopposed activity of depressor muscles will induce a lowered, angry-looking brow ptosis. Frontalis injections are 2–3 cm above the brows; closer brow placement risks inhibition of facial expression and brow ptosis [11; 33].

Glabellar Rhytides

Treatment of glabellar frown lines is an integral part of harmonizing the brow shape and eyebrow position. Glabellar lines are caused by contraction of the corrugator and orbicularis oculi muscles (move the brow medially) and the procerus and depressor supercilii muscles (pull the brow inferiorly). Botulinum toxin injection of corrugator and procerus muscles weakens the brow depressors to improve glabellar rhytides. Injections are made above the supraorbital rim to avoid upper eyelid ptosis. Men typically require higher doses due to greater muscle mass in this area [33].

Lateral Canthal Rhytides

Contraction of the lateral orbicularis oculi muscle produces lines (crow's feet) that radiate from the lateral canthus. These lines initially appear on smiling or squinting (dynamic) but can become static (at rest) due of aging, photodamage, and skin remodeling.

Crow's feet are treated with multiple botulinum toxin injections into the lateral orbicularis oculi muscle, lateral to the orbital rim with the facial musculature at rest [11; 33; 79].

Brow Lift

Brow ptosis, a common feature of aging, can produce facial features at rest that mimic angry or scowling expressions. Brow shape and height are controlled by the opposing action of brow elevator (frontalis) and depressor muscles [33]. Botulinum toxin is injected as in treating glabellar lines (above), the lateral orbicularis oculi, and in the lateral corrugators 1–2 cm above the orbital rim to avoid the Mephisto or Spock eyebrow (quizzical look). Injections limited to the superolateral orbicularis oculi muscle (tail of the eyebrow) can give a lateral eyebrow elevation [10; 11; 33; 79].

Hypertrophic Orbicularis Oculi

Botulinum toxin injection can widen the ocular aperture by weakening the orbicularis oculi muscle complex, producing a wider, rounder eye during smiling and at rest [33].

Dermal Fillers

Given the substantial variability in anatomy and aging of the upper face, reversible (hyaluronic acid) fillers may be preferred; clinicians with experience and a level of comfort may consider stimulatory (PLLA) fillers [10; 11].

Fillers for temple and upper brow volume loss require elevated elasticity and viscosity for periosteal placement, to give structural and lifting support to overlying tissues with low risk of displacement (e.g., Restylane Lyft, Radiesse, Juvéderm Voluma-XC, Juvéderm Ultra Plus XC) [29]. Fillers for volumizing the upper lid, forehead, and crow's feet should have lower elasticity and viscosity for superficial placement (e.g., Restylane-L, Restylane-Silk, Belotero Balance, Juvéderm Ultra XC) [29].

The anatomic order of contouring influences the ultimate outcome of facial volumization. Augmenting the temple alone may provide lateral brow support and should be addressed before moving more caudally [29]. The upper face is a challenging area for fillers because of risk for serious complications [11].

Temple Volumization

Fillers for temporal volume loss and hollowing intend to eliminate concavity and achieve a uniform or slightly convex contour between the temporal fusion line and the zygomatic arch. Severe volume loss may require multiple treatment sessions [8; 11].

Brow and Upper Lid

Volume loss occurs in bone and more superficial tissues including subcutaneous fat and the retro-orbicularis oculi fat pad. To correct this deficit, the initial filler injection is directly onto periosteum 1 cm superior to the upper lateral orbital rim or just above the superior lateral brow hairline [29].

Eyebrow Shaping

The position and/or shape of the eyebrow often changes with aging. Fillers can enhance eyebrow contour and volume and may improve elevation of the eyebrow tail when botulinum toxin provides insufficient eyebrow lifting [11].

Forehead Contouring

Dynamic forehead lines are usually treated with botulinum toxin, but fillers can treat deep horizontal lines to create a smooth contour across the forehead. The filler is injected at least 2 cm above the eyebrow, with the needle tip on bone [11]. For tightening eyelid skin, radiofrequency is preferred because of its efficacy and built-in safety features [10].

THE MIDFACE

In facial aesthetics, the midface is a main determinant of perceptions of facial attractiveness, influenced by synergy of the eyes, nose, lips, and cheekbones (central facial triangle). It is also the focal point for restoration of a youthful topography. As such, the midface should be treated first [4; 10; 122].

Degenerative changes occur in nearly all anatomic components of the midface. The mid-cheek manifests the most complex soft tissue changes with aging, and volume loss of the deep mid-facial fat is a primary determinant of an aged appearance. Fat within each compartment changes independently over time, losing volume and shifting as the facial ligaments attenuate and the bony skeleton recedes [10; 31].

Loss of maxilla projection and skeletal support and inferior displacement of soft tissues contribute to the tear-trough deformity, malar mounds, and prominent nasolabial fold and groove. The cheeks lose projection to assume a sunken appearance. Prominent transitions between cheek fat pads and flattening of the malar prominence mark the deflated midface; the heart-shaped face of youth becomes distinctly pear shaped [10; 29; 31].

Accurate assessment of midface volume loss is the single most important factor for appropriate correction of facial volume; precise restoration may rejuvenate the upper and lower face [29]. To define these midface areas, draw one line from the lateral canthus to the lateral oral commissure and a second line from the tragus to the nasal ala. The lines intersect to form quadrants. Examine the upper-outer (zygomatico-malar region), upper-inner (anteromedial cheek), and lower-outer (submalar region) quadrants for volume loss and treat accordingly [84; 123; 124].

The medial suborbicularis oculi fat migrates inferiorly with aging. The medial part of the deep medial cheek fat extends almost to the lateral incisor tooth. Volumizing both medial fat pads is crucial for correcting cheek sagging—a major contributor to deep nasolabial folds [2; 40].

Fillers are used for volumization and contouring the upper cheek and lid-cheek junction, the submalar and preauricular areas. Botulinum toxin plays a limited role [125]. Recommendations for the midface advise treating the malar area first; volumizing the

malar and restoring its contours gives a lifting effect that may reduce or negate the need for filling other midface areas [30; 55]. Careful attention should be paid to restorative effects on the lower lid, nasolabial fold, nasal base, and upper lip during malar augmentation [29].

Malar Area

Fillers are injected to create vertical pillars over the bone to support and lift the malar area. The following injection sequence is lateral to medial, to achieve a tenting effect with less filler needed for medial injection [8; 30; 94]:

- In the lateral midface, the zygomatic (cheekbone) arch and prominence (crucial for optimal cheek restoration)
- Lateral compartment of the superficial cheek fat pad and the preauricular superficial fat compartment
- Middle compartment of the superficial cheek fat (medial sub-orbicularis oculi fat)

A variety of fillers can volumize the malar/lateral cheek region with good results (e.g., hyaluronic acid, CaHA, PLLA, PMMA) [84].

Lower Lid

Volume restoration of tear trough deformity with filler injection is a difficult technique in a danger zone for vascular complications and should only be performed by experts [84].

Deep Medial Cheek

Volumizing the deep medial cheek fat increases anterior projection, reduces the nasolabial fold, and recreates a youthful cheek within its natural boundaries [25; 40]. Juvéderm Voluma XC, Juvéderm Ultra Plus XC, Restylane Lyft, Radiesse, PLLA, and PMMA are all suited for deep midface volumizing [29; 84]. Patients with significant orbital fat herniation may benefit more from surgery; fillers alone may be inadequate to reduce the transition between protuberant fat pad and concave tear trough [84].

Nasal Tip and Upper Nasolabial Fold

Deep volumizing of the nasal sill can provide support to the aging nasal tip, a natural correction of the upper nasolabial fold, and a minor lift to the upper lip. Treatment requires periosteal placement of high-elasticity, large-particle fillers [29].

Botulinum toxin can correct “bunny lines”—horizontal rhytides that traverse the nasal bridge and the downward slope of the nose when the patient is smiling—and elevation of the nasal tip [10; 125]. In the midface, nasolabial folds are treated last [10].

Nasolabial Folds

Most fillers are indicated for treating nasolabial folds by the FDA, but unlike other midface areas, nasolabial folds hypertrophy with age. Thus, fillers are suggested to soften a prominent fold, not to volumize. First correct deficient malar volume, then soften residual nasolabial folds conservatively using moderate-elasticity and -viscosity filler (e.g., Restylane-L, Juvéderm Ultra XC) injections in the superficial fat just to the dermis [29].

Low-dose botulinum toxin into each lip elevator complex above the nasofacial groove can collapse the upper nasolabial fold but may vertically lengthen the upper lip, an aging-related feature. Botulinum toxin should not be directly injected into nasolabial folds, as this may result in an asymmetrical smile or lip ptosis [33].

After addressing volume loss, microfocused ultrasound treatment of the overlying superficial musculo-aponeurotic system and skin envelope addresses laxity and bridges the aesthetic unit compartments to create a smooth cheek contour [10; 126].

THE LOWER FACE AND NECK

During the aging process, bony and soft-tissue structures in the lower face undergo significant alterations [4; 10; 29; 58]. Malar and perioral fat volume loss, bone resorption, and ligament laxity cause increasingly lax skin to droop downward over a changing lower face structure. The general widening and loss of integrity of the lower face can appear as a relative increase in jowl volume with decreased jawline strength and perioral/lip volume.

Jowling is one of the most unwanted effects of aging and a primary concern of aging patients. The jowls become prominent with deflation of superficial fat exposing deeper fat pads, descent of deep fat pads, and increased septal laxity. Loss of volume in the prejowl sulcus, posterior jawline, and inferior preauricular region exacerbates the appearance of jowls.

Superficial and deep atrophy of the perioral area manifests as a lengthening and flattening of the upper lip complex, loss of vermillion and vermillion border volume, and formation of vertical perioral rhytides. The oral commissures turn down, and the mentalis region flattens or becomes ptotic. Protrusion of the central chin results from loss of lateral and inferior volume. These changes are superimposed on and intensified by mandibular bony changes that result in decreased vertical ramus height, a widening mandibular angle, and loss of anterior mandibular (mental) projection. Platysma muscle contraction from support of deeper neck and floor of mouth structures promotes vertical fibrous bands on the neck; laxity in overlying skin creates horizontal rhytides.

Botulinum toxin and filler combinations are especially effective in the lower face to address dynamic musculature, loss of volume and support, and skin laxity [10]. Some believe that fillers are more important than botulinum toxin and should be used first to provide structure and support before considering botulinum toxin for dynamic lines [127].

Jawline

Structural volumizing of the lower face should begin with correction of the jawline, using fillers with high elasticity (Restylane Lyft, Radiesse, Juvéderm Voluma XC, or Juvéderm Ultra Plus XC) [29]. Injector preference/experience will also determine filler choice [10].

Mandibular shrinkage and redistribution of fat leads to the emergence of jowls and loss of jawline definition. To smooth the jawline and camouflage the prejowl, the inferior mandibular border is injected in the supraperiosteal plane. Injection under the mandibular rim improves the prejowl concavity. The jowl is not directly injected, to avoid blood vessels [8; 58].

A technique referred to as the “Nefertiti lift” involves small amounts of botulinum toxin injected along the jaw and into the lateral, upper platysmal band to improve the appearance of pouches. With skin laxity, the addition of microfocused ultrasound helps lift the jowls for a tighter appearance [10].

In women, an overly squared jaw can be undesired. If sagging is not an issue, botulinum toxin injection of the masseter results in a softening of the determined, clenched appearance and a more feminine face [65].

Chin

Botulinum toxin injections just anterior to the bony mentum on each side of the midline weaken the mentalis muscle contraction responsible for mental crease, and injections into the mentalis muscle at the prominence of the chin can help reduce a *peau d’orange* chin [33; 65]. Fillers create definition and fill residual depressions. Injection is placed on the periosteum and deep subcutaneous tissue to create vertical pillars. Fillers with greater lift are preferred [8; 58].

The perioral region is considered one aesthetic unit, comprising the lips, oral commissures, and melomental folds (marionette lines). Botulinum toxin is commonly used for perioral rhytides but requires caution, as improper injection may result in a flaccid cheek, an incompetent mouth, an asymmetrical smile, or speech pathology [10; 79]. Perioral volumization may independently restore and support the lips by enhancing lip volume and should be preceded by direct mucosal lip volumizing in an aging face [29].

Moderate-elasticity fillers (e.g., Restylane-L, Restylane-L Silk, Juvéderm Ultra XC, Belotero Balance) are injected in the subcutaneous plane, first in the oral commissure until a subtle upturning is achieved, then in the upper and lower lip columns for volumizing support. This will improve the appearance of vertical lip rhytides and philtral columns [29].

Vertical perioral rhytides are common cosmetic concerns, induced or exacerbated by repetitive orbicularis oris muscle contraction. With fillers, a short-lived improvement and fairly rapid recurrence is likely caused by normal perioral animation. Low-dose botulinum toxin is injected adjacent to the vermillion border in the areas of rhytides, and lateral to the Cupid’s bow area of the lip. Avoid injecting the oral commissures (corners of the lip) and the midline area to reduce the risk of a drooping lateral lip [33].

Mouth frown results when the depressor anguli oris muscle pulls the corners of the mouth downward, in opposition to the action of zygomaticus major/minor muscles, producing a frowning expression. Botulinum toxin injection weakens the depressor anguli oris, allowing the zygomaticus to elevate the corners of the mouth, which return to a horizontal position. Botulinum toxin is injected into the insertion point of the mentalis muscle, because upward pull of the mentalis contributes to mouth frown [33].

Melomental folds (marionette lines) are exacerbated by contraction of the depressor anguli oris muscle. This is treated by botulinum toxin injection into the posterior margin of each depressor anguli oris immediately above the mandible [33].

THE NECK

Platysmal bands, often the first sign of aging of the neck, appear as two vertical, bulky cords from the lower border of the mandible to the suprasternal region. Formerly thought to result from skin laxity and loss of platysma muscle tone, these vertical muscular bands are now attributed to platysma muscle activity, treated by denervating the platysma muscle with botulinum toxin instead of tightening the skin [128]. Very-low-dose botulinum toxin is injected superficially into only specific platysmal bands, to avoid dysphagia [79]. Improvement of the overall appearance of the neck requires fillers for structural support of the chin and jawline and botulinum toxin for the masseter, platysmal bands, or horizontal neck lines [33; 127].

PATIENT SELECTION AND EVALUATION

As discussed, the careful assessment of patients forms the basis of individualized treatment planning. Because aesthetic procedures are elective, the benefits must clearly outweigh the risks. Healthcare providers have a responsibility to refuse requests in which the risk-benefit ratio is not in the patient's best interest, and to refer patients elsewhere for consideration of treatments the clinician cannot or prefers not to perform. Patients rely on the healthcare provider to act as a "learned intermediary" and to exercise fiduciary responsibility in advising the patient on the best course of action [95].

Patients should be carefully selected by thorough assessment of medical history, motivation, and expectations to identify contraindications. The increasing incidence of serious dermal filler complications has expanded the cutaneous and systemic contraindications to filler treatment, relevant to botulinum toxin because combined therapy is common.

Following screening, careful discussion addresses the specific cosmetic concerns and possible benefits and risks across a range of available options. A treatment plan is arrived at through shared decision-making; informed consent and documentation are made.

For those who are not proficient in English, it is important that the patient history and information regarding the risks associated with the use of botulinum toxin/dermal fillers be obtained in the patient's native language, if possible. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required.

SCREENING AND SELECTION

Screening and Assessment of Medical Contraindications

The patient may request a cosmetic therapy, but the aesthetic provider should ultimately "select" the patient. Most complications stem from inappropriate patient selection, inadequate antiseptic preparation, or improper treatment technique. Selecting appropriate patients, or perhaps more importantly, not treating inappropriate patients, is the first crucial step in avoiding complications [71].

A thorough history of skin conditions, allergies, systemic disease, current medication use, and previous cosmetic procedures is mandatory. Patients may not see important aspects of their history as relevant. To help ensure disclosure, assess skin-related and systemic conditions by linking to potential adverse effects [19; 71].

Some skin disorders and local or remote infections can promote injection seeding of infective agents that populate the filler site, or hematogenous spread to implanted fillers and later biofilm formation or transition from infection to hypersensitivity [19; 129; 130]. These conditions require careful screening. Fillers have risks of injection-site keloid formation or hyperpigmentation; patients with these conditions should avoid fillers [75].

Screening may identify conditions whereby filler therapy is contraindicated, deferred until resolution, or considered cautiously. Significant comorbidity, polypharmacy, or use of immunomodulatory drugs can greatly complicate adverse effect management if it becomes necessary [22].

Screening and Assessment of Psychological Contraindications

Understanding the motivations for cosmetic treatment is vital to minimizing inappropriate patient selection. Unrealistic expectations, which are contraindications to cosmetic treatment, are prevalent in some psychological conditions [19; 75]. Low self-esteem can lead to unrealistic goals and expectations.

High neuroticism and/or anxiety may influence expectations, and outcomes tend to be poorer [131]. The most important mental disorder consideration is body dysmorphic disorder.

Body dysmorphic disorder is a psychiatric disorder characterized by preoccupation with an imagined defect in appearance or distorted perception of one's body image. These patients may be unduly invested in the cosmetic procedure as the solution to other life problems. Unrealistic expectations are followed by dissatisfaction with results that do not correlate with objective outcomes [132; 133]. Dissatisfied patients with body dysmorphic disorder have been reported to retaliate against their cosmetic providers with lawsuits, threats of violence, physical assault, and in rare cases, homicide [134; 135].

Compulsive behaviors have been described in patients who, driven by the quest for physical perfection, demand and obtain multiple sequential cosmetic injections despite the increasing risk. Compulsive demand for cosmetic procedures falls on a spectrum of dysmorphophobic behaviors [136; 137]. Body dysmorphic disorder is also associated with "doctor-shopping" [131].

Whether the diagnostic threshold for body dysmorphic disorder is a contraindication to nonsurgical cosmetic procedures is unresolved, but many consider signs of body dysmorphic disorder a firm contraindication to cosmetic treatment [19; 131; 132; 138]. Appropriate onward referral may be required when psychopathology is apparent [131; 139].

PATIENT EVALUATION AND CONSENT

After the patient has been screened for medical and psychological contraindications to cosmetic treatment, the next step is to determine if treatment expectations can be met or managed with education and counseling. Following this, treatment options are explored and a plan is developed and documented.

Patient Motivation and Treatment Expectations

American healthcare consumers are both aging and youth-oriented [94]. A majority of the population is dissatisfied with their appearance, rates of cosmetic interventions continue to increase, and the expectations of many patients have risen proportionately [131].

Patient motivation for cosmetic therapy, benefits anticipated, and satisfaction with the outcome are closely inter-related. The expectations and motives for seeking treatment are complex and diverse. Patient dissatisfaction usually derives from failing to manage or meet expectations, underscoring the importance of identifying expectations at the first consultation and documenting this discussion [131]. The clinician should establish underlying motivations, differentiate patient wants from needs, and temper expectations within realistic goals [19].

Patient motivation is considered external when expecting physical changes to influence some aspect of their life (e.g., partner will love them more, career success). Unrealistic expectations with external motivation require discussion, as these patients are more likely to be dissatisfied with outcomes. In contrast, internally motivated patients (driven by a desire to look better for themselves) are good candidates [131; 138].

Other factors can influence expectations [94; 131]. Younger patients can be especially sensitive to peer group acceptance and social media images, but correction of an objectively undesired feature can also be therapeutic. Traditional and digital media promote unrealistic expectations of an idealized appearance, and along with marketing, this has led some patients to believe a youthful appearance can be maintained indefinitely, has a quick fix, or is guaranteed with a "miracle treatment." Partners, families, and friends can exert strong influences that can be helpful to separate from the patient's own expectations. Expectations tend to be higher among more educated patients.

Expectation Management

Patient expectations should be managed so they do not envisage an unrealistic outcome. The treatment of inadequately informed patients is fraught with potential problems and risks of dissatisfaction [71].

Patient education on the risks, potential benefits, and limitations of cosmetic procedures may modify expectations. Good information is associated with better outcomes, and hearing these details may lead the patient to prefer a different course of treatment than first proposed [131].

A 2016 guideline stresses the importance of giving prospective cosmetic patients time to reflect on what they learned during the initial consultation—a “cooling-off period” [140]. However, a 2015 consensus statement suggested initiating at least part of the treatment plan the same day to build patient confidence in aesthetic procedures and in the clinician [94]. It may be best to assess on a patient-by-patient basis which approach is appropriate.

The FACE-Q is a validated screening instrument that measures patient expectations of cosmetic treatment, such as appearance-related psychosocial distress and how they expect their appearance and quality of life to change after cosmetic treatment [141]. Use of the FACE-Q can help augment, but not replace, patient-clinician discussions of factors that influence expectations of cosmetic treatments [131].

An effective approach to expectation management is the mnemonic STEP [94]:

- Stress what can and cannot be done with minimally invasive aesthetic treatments.
- Target specific areas of patient concern.
- Envision what the effect of the aesthetic outcome would be like to the patient.
- Preframe the patient to the expected outcome.

Developing a Treatment Plan

The clinician should be both probing and empathetic. Patients may be ashamed they look older than their peers but too embarrassed to directly discuss it. Others may see their concerns as vain and frivolous. Many patients are unaware of the range and versatility of cosmetic procedures or believe their concerns are beyond remediation [94]. Keep the focus on cosmetic concerns rather than any preconceived treatment approach.

Educate the patient to focus on the underlying cause, not the superficial manifestation, of her/his cosmetic complaint. For example, sagging skin is often caused by volume loss, making volume augmentation the appropriate treatment [94].

Discuss realistic expectations for the results of specific treatments. For example, if a patient requests a specific treatment for prominent nasolabial folds with the goal of looking younger, explain that nasolabial folds can be treated directly, but would not produce a more youthful appearance—correcting the underlying volume loss could restore a youthful appearance, even with some residual folds [94].

Many patients have concerns about several facial areas. Asking: “If you could fix only one thing today, what would it be?” can help clarify their relative priorities to base a reasonable sequence of procedures [94].

Clarify expectations of time frame to determine what is realistic and feasible when patients require the desired effects before an important event, such as a wedding. Other patients may want progressive, rather than immediate, aesthetic improvement. Also understand the degree of patient risk tolerance in treatment selection [94].

Discuss the implications of botulinum toxin treatment of the orbicularis oris muscle. The reduction of fine motor control around the mouth may be detrimental to professional speakers, vocalists, or musicians [94].

Informed Consent and Documentation

The risk of malpractice claims is highest in cosmetic medicine. Most result from inadequate informed consent instead of procedural failures [16]. To fully inform decision-making and consent to treatment of patients, carefully discuss the possible benefits, disadvantages, and limitations over a broad range of options [7; 95].

Beyond an unnatural look, the three main patient concerns are pain, complications, and costs. It is essential to discuss treatment costs, obtain financial consent, and plan over the long term to obviate financial stress. Addressing these issues upfront is instrumental in establishing the trust that underpins true patient satisfaction [19].

Shared decision-making, an essential element of evidence-based medicine, explores available treatment options, possible benefits and harms of each option, and best match to the patient's characteristics and preferences [142]. Obtaining signed informed consent is crucial in creating awareness and acceptance of potential complications. An informed consent document confirms patient understanding of the potential adverse effects and expected treatment outcome. The document should outline common and uncommon but serious adverse events. Supplying written pre- and post-instructions during the initial consultation can help to establish realistic expectations and minimize dissatisfaction [19; 34].

Photographic documentation is essential for medico-legal purposes and appraisal of results. To ensure good quality pre- and post-treatment photographs, the patient should remove all makeup and jewelry and pull hair back or up using a hairband; a black/dark background is preferred. Multiple images at rest and during animation are recommended, including anterior, oblique, and lateral views with the head in a neutral, neck-extended, and neck-flexed position. Proper lighting, consistent angles, and a fixed camera distance are mandatory. A single-lens reflex camera and tripod are recommended instead of smartphones [19].

ADVERSE EFFECTS

As mentioned, there is increasing concern of serious adverse events involving dermal filler injections. Some experts noted that by 2010, the increasingly sophisticated training in nonsurgical cosmetic treatment was already neglecting adverse events and their management [22]. With the rapid growth in consumer demand for injection cosmetic therapies, the quality of training, skill, and credentialing of injectors and facilities are increasingly unclear. Along with inadequate regulation, the net effect is described as compromising not only patient safety but the reputation of the field [19; 20; 23].

With serious adverse events a focus of concern, there is an expansion of recommended measures to prevent, reduce, and manage adverse events before they become disastrous complications.

PREVENTION AND RISK REDUCTION

Several approaches are recommended before injection therapy to prevent or reduce complications by mitigating patient, clinician, or procedure risk factors.

Pretreatment Patient Management

Some complications may be prevented by careful pre-treatment patient management. Filler injection can reactivate latent herpes simplex virus (HSV) infection. Prophylactic antivirals (e.g., acyclovir, valaciclovir, famciclovir) are recommended with patient history of HSV in the intended injection area. Patients with a current outbreak of HSV should receive antivirals, with fillers deferred until resolution of herpes lesions [143; 144]. For two to four weeks before and after filler treatment, patients should be counseled to avoid [92; 143; 144]:

- Dental procedures, oral hygienist visits, tooth bleaching/whitening
- Immunizations/vaccinations
- Other medical procedures
- Any facial procedure inducing inflammation or skin barrier disruption

In addition, products with blood-thinning effects should be avoided the week before filler treatment. This includes food/beverages (e.g., red wine, dark chocolate, grapefruit) and certain supplements/over-the-counter medications (e.g., vitamin E, ginkgo biloba, fish oils, St. John's wort, nonsteroidal anti-inflammatory drugs [NSAIDs]). Prescribed anticoagulants (e.g., aspirin, warfarin, clopidogrel, apixaban, rivaroxaban, dabigatran) should also be withheld, but only when cleared by the prescribing physician [92; 143; 144].

A pretreatment checklist should be provided to the patient that includes these points and explains the importance of having any infective or inflammatory conditions treated before the procedure; the treatment should be rescheduled if the pretreatment checklist is incomplete. The patient should receive the checklist with sufficient time to plan relevant medical visits around the treatment date. Contact patients one week pretreatment to ensure they possess and understand the checklist and have no precluding factors [19].

Procedure- and Clinician-Related Factors

Knowing previous surgical (e.g., rhinoplasty) or nonsurgical cosmetic procedures and locations is vital to prevent complications. Fixation, scarring, or alteration of underlying vasculature and anatomy at procedure sites can facilitate intravascular filler injection. "Layering" new fillers over a previously injected semi/fully intact filler can provoke dormant biofilm or inflammatory response [19; 71; 145].

Vascular Complications

Vascular occlusion from injected filler material may lead to potentially catastrophic complications of tissue necrosis, blindness, or stroke. Even with advanced knowledge of facial anatomy, vascular injury cannot be avoided with 100% certainty. However, measures can be taken to help reduce risks and mitigate intravascular adverse events if they develop. A key step is understanding the danger zones for vascular occlusion, areas where arteries

have little or no collateral circulation, extensive anastomoses with the internal carotid artery, or are prone to external compression. Risk factors for vascular occlusion are summarized in **Table 7** [19; 146; 147]. **Table 8** outlines strategies to mitigate these potential complications.

Infection Risk

To minimize infection, stringent aseptic technique is mandatory [19; 151]. Prior to any intervention, it is vital to clean, degrease, and disinfect the patient's skin. Remove makeup and cleanse carefully with 2% chlorhexidine in 70% alcohol, avoiding ocular exposure. When treating the perioral area, consider antiseptic mouthwash containing chlorhexidine or povidone-iodine for sterilizing the oral cavity.

The clinician should remove all jewelry, wash hands with antiseptic cleanser, and use gloves for all injections. Once the syringe is held, sterility is lost and aseptic technique is crucial. Not touching any needle or cannula component that penetrates the skin may further reduce infective complications. Cleansing a broad area avoids infective risk from inadvertently resting a cannula on adjacent uncleaned skin. Frequently change needles/cannula when using multiple entry points.

Biopsy can play a crucial role in diagnosing and treating filler-related adverse events, but cosmetic patients strongly resist facial biopsy unless absolutely necessary. A medicolegal process is always justified [152].

After treatment is administered, it is important to assess the patient's response. Clinicians should routinely check perfusion in treated and watershed (e.g., glabella, nasal tip, upper lip) areas [19]. Consider that makeup can obscure skin tone and signs of vascular compromise. Patients should be furnished with written post-treatment instructions and contact numbers. A follow-up call to the patient should be made within 24 hours, and the clinician/clinic should be available by phone for 48 hours postprocedure [19].

RISK FACTORS FOR VASCULAR COMPLICATIONS DURING FILLER INJECTION	
Factor	Description
Injection site danger zones	Injections to the nose, nasolabial fold, forehead, and glabella are at increased risk for blindness. Injections to the glabellar region, nasal tip/alar triangle, and lips increase the risk for necrosis.
Injected volume	Bolus injections near danger zones increase risk of necrosis.
Filler type	Non-hyaluronic acid fillers cannot be dissolved. Necrosis is more common with denser or more permanent fillers.
Needle gauge	Sharp needles puncture arteries more easily. Aspiration before injecting is suggested, but unreliable. Blunt cannulas are less likely to puncture vessels.
Scarring	Scarring from prior cosmetic procedures or trauma can alter the local vascular pattern.
Source: [70; 145; 146; 147; 148; 149; 150]	

Table 7

RISK MITIGATION STRATEGIES FOR FILLER-RELATED VASCULAR COMPLICATIONS	
Step	Recommended Strategy
Knowledge	Know injection-site vascular anatomy, and be aware of inter-patient variations.
“Go easy”	Inject slowly, and apply the least amount of pressure necessary. Keep the needle moving. Restrict bolus injections to periosteal plane.
Monitor closely	Watch for blanching or any changes in skin color.
Be aware	In a vascular occlusion, epinephrine can mask skin blanching, and local anesthetic or lidocaine can mask pain.
Listen to your patient	Immediately stop injecting if resistance is encountered, or if patient reports pain, discomfort, or changes in vision.
Have a plan	Onsite protocols for immediate, early, and late adverse events should be easily accessible.
Discharge instructions	Describe in writing the signs/symptoms of vessel occlusion and where and why to seek medical attention.
Staff education	Educate clinic staff on accurate assessment and appropriate referral of patients who report filler adverse events.
Report the incident	Report vascular compromise adverse events to the FDA and filler manufacturer.
Source: [70; 145; 146; 147; 148; 149; 150]	

Table 8

All facilities should have easily accessible protocols for early and delayed-onset reactions [19]. Resuscitation measures (e.g., epinephrine, IV access, fluids) and an adequate supply of hyaluronidase should be kept on hand, with regular checks of expiration dates on emergency drugs. In addition, contact information for an ophthalmologist or oculoplastic surgeon experienced in treating retinal artery occlusion should be maintained.

Anesthesia/Analgesia

Pain control is crucial to ensuring a positive experience for patients [76]. Topical anesthetics or local nerve blocks are commonly used to reduce pain, although many fillers are also formulated with lidocaine. To reduce pain, use the smallest suitable needle, slow infiltration, and the least needle punctures necessary. Other measures to help reduce pain include ice application, skin vibration, patient distraction, and a relaxed, soothing treatment environment [34].

COMMON ACUTE SIDE EFFECTS

Pain, bruising, redness, itching, and swelling are common, self-limiting side effects following dermal filler injections. Persistence beyond seven days should be closely assessed [144].

Pain

Pain is relatively common and is more likely with multiple needle punctures. However, pain may also be a sign of impending vascular compromise, discussed in detail later in this course. Pain can be minimized by using slow needle introduction, ice anesthesia, and filler warmed to body temperature [70].

Erythema

Erythema (redness) usually resolves without treatment. Longer-lasting or persistent erythema suggests hypersensitivity reaction or infection and requires careful evaluation. Oral tetracycline, isotretinoin, topical tacrolimus, or medium-strength topical steroids are suggested for persistent erythema; long-term, high-potency topical steroids should be avoided. In severe cases, oral propranolol (20 mg) can make erythema less evident [70; 143].

Edema

Edema (swelling) in the first few days is normal with all fillers and can be managed by gentle pressure and ice packs [83]. Episodic swelling and edema following filler injection can occur after sun exposure, exercise, or saunas. It is important not to confuse normal edema with allergic reaction; manage with ice packs, topical steroids, and avoidance of vasodilating stimuli [70].

Ice is recommended and commonly applied on the injection site to prevent and manage pain and edema, but it has also been associated with infection. An Oregon plastic surgery clinic described an outbreak of facial *Mycobacterium chelonae* infection (presenting as swollen skin nodules with drainage or discoloration three to six weeks after inoculation) following filler injections. The infections required

three to four months of multiple oral or IV antimicrobial agents to resolve. The source was traced to clinic tap water, used for ice applied immediately pre- or post-injection [153]. As such, cold packs rather than ice may be safer options.



If ice is used to control pain following botulinum toxin or dermal filler injection, the Australasian College of Dermatologists recommends placing it inside either a sterile glove or a nonsterile glove, then wiping the glove with alcohol or chlorhexidine to sterilize it, as ice is not sterile. Alternatively, frozen gel packs may be used in the same way.

(<https://onlinelibrary.wiley.com/doi/full/10.1111/ajd.13273>. Last accessed March 26, 2021.)

Level of Evidence: Expert Opinion/Consensus Statement

Bruising

Bruising, hematoma, and ecchymosis can result from needle pricks and bleeding. This can be minimized by firm pressure on the needle insertion site and prevented by cessation of alcohol and supplements with anticoagulant effects one week before treatment. Intense pulsed light and vascular lasers have been used to treat persistent symptoms [70].

Lesions

Papulopustular lesions occur when filler injected too superficially in the papillary dermis occludes, or extrudes through, sebaceous or sweat gland openings and mimics bacterial infection or acneiform eruption. Post-injection massage can help in prevention, and topical astringents can help in their resolution [70].

Overcorrection can appear as bumps, nodules, or irregularities when too much material is injected. In these cases, hyaluronic acid products should be resolved using hyaluronidase. With non-hyaluronic acid fillers, puncture and drainage of excess product may suffice [70].

INFREQUENT ACUTE ADVERSE EVENTS

Dysesthesias and Paresthesia

Dysesthesias and paresthesia are symptoms of nerve injury following direct trauma, injection of filler into a nerve, or tissue compression by the product. Nerve damage is usually transient and reversible, infrequently permanent, with the infraorbital nerve the most common site [143].

Intracranial Penetration

For deep periosteal or supraperiosteal injections, the needle is advanced to the level of the bone and retracted slightly. Accidental intracranial penetration is a demonstrated risk, but the prevalence is unknown [70].

VASCULAR COMPROMISE

Vascular compromise is the result of vascular occlusion following inadvertent intravascular filler injection or vascular compression by adjacent filler material. Embolism occurs when filler material enters the vasculature, impeding blood flow. Vascular compromise can involve arterial or venous occlusion [70; 143; 150].

Areas at highest risk of embolism have minimal collateral circulation (the nose), terminal blood supply (the glabella), large vessels (the nasal artery), or large areas (forehead) supplied by a vessel with minimal collateral circulation (terminal supratrochlear artery) [154]. Embolization of filler material is a potentially catastrophic complication with possible sequela of tissue necrosis, blindness, or cerebrovascular accident. The literature is replete with examples of permanent blindness following hyaluronic acid, PLLA, or CaHA filler injections [122; 155]. Intravascular injection occurs more frequently than assumed. In a study of expert aesthetic physicians, 62% reported inducing one or more such events [156].

Tissue Necrosis

With embolism induced by intra-arterial injection, damage to endothelial cells leads to ischemic changes in the skin, tissue degradation, and necrosis [71].

Cells undergoing necrosis swell and then burst, releasing their contents to trigger a local inflammatory reaction, with swelling, pain, heat, and redness. Intra-arterial injection can lead to embolism, platelet aggregation, subsequent occlusion in a terminal branch, and delayed-onset necrosis [145].

Necrosis can follow vascular occlusion due to vessel compression by filler material or filler-induced tissue swelling, and onset can be delayed. Tissue necrosis can occur with all dermal filler types but is more likely with particulate fillers [83; 145]. With blood supply reliant on a single arterial branch, the glabella, nasal ala, and nasolabial folds are most vulnerable to necrosis [70; 83].

The cardinal features of vascular occlusion and necrosis are changes in skin color and pain [70; 71; 145; 150]. Skin blanching and severe pain are immediate with arterial occlusion. However, epinephrine use may mask blanching, and pain may not fully appear until local anesthetic or nerve block wears off. If not swiftly resolved, the affected skin will develop reticulated erythema, purpura, ulceration, and scarring.

With venous occlusion, red/bluish skin color changes appear immediately to hours later, with or without pain, progressing to blisters, pustules, and tissue necrosis within a few days.

Blindness

The most feared complication of filler injections is blindness following occlusion of the central retinal artery, the final branch of the ophthalmic artery. Comparing average diameters, injected hyaluronic acid filler particles (400 μm) easily move through the ophthalmic artery (2 mm) to block the central retinal artery (160 μm) [122; 154; 157].

The routes to occlusion and blindness vary by proximal branch of the ophthalmic artery inadvertently injected. When the force of injection exceeds intra-arterial pressure, the injectate can move proximally in the angular artery and then proximal of the origin of the central retinal artery. With pressure on the syringe released, the material moves distally into the

retinal artery. Central retinal artery occlusion follows injection into the glabellar region (through the supratrochlear artery into the supraorbital artery) or the nasolabial fold (in any anastomosis of the dorsal nasal artery from the ophthalmic artery) [154]. Blindness, visual field deficit, or blurring is instant, often with excruciating ocular pain [70; 83; 143].

Stroke

With greater pressure on the plunger or for a longer time, the filler may travel into the internal carotid artery and then enter cerebral circulation, producing a stroke [122; 150]. Unilateral blindness and left-sided hemiplegia immediately following glabellar area injections are reported. However, these effects are rare with dermal fillers and more likely with autologous fat injections [70]. Pulmonary embolism and panophthalmoplegia have also been reported with filler injections [19].

Management of Vascular Compromise

Intense pain is considered an initial sign of intravascular filler injection, but as noted, it may be obscured by lidocaine in fillers or by local anesthetic. Vigilance for skin color change is mandatory [19]. With any suspicion of vascular occlusion from inappropriate pain, skin blanching, or mottled discoloration, immediately stop injecting and aspirate any product when withdrawing the needle (if possible). It is vital to facilitate an immediate, aggressive response to remove the product and promote blood flow [19; 71].

Hyaluronidase Reversal

With hyaluronic acid fillers, hyaluronidase injection is the foundation of emergent therapy for most adverse events, a powerful advantage of these products, as no other dermal filler material has a reversing agent [19]. Hyaluronidase injection enzymatically dissolves the hyaluronic acid filler material [68].

Hyaluronidase is indispensable in resolving acute hyaluronic acid filler adverse events. All clinicians who provide hyaluronic acid filler injection should always have an adequate supply of hyaluronidase in the office for emergencies and regularly check the product expiration date [122].

Hyaluronidase is recommended in vascular compromise from all filler types to reduce edema and potentially decrease vessel-occluding pressure. When injected immediately, hyaluronidase degrades hyaluronan, a potent proinflammatory mediator associated with tissue necrosis [58; 71].



EVIDENCE-BASED
PRACTICE
RECOMMENDATION

Hyaluronidase has also been shown to diffuse into the lumen of blood vessels even when injected external to it. According to the Aesthetic Complications Expert Group, for potential cases of necrosis due to intravascular deposition of hyaluronic acid, it is not essential to inject directly into the vessel—injection into the surrounding area is also likely to result in dissolution of the product.

(<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6057733>. Last accessed March 26, 2021.)

Level of Evidence: Expert Opinion/Consensus Statement

High-dose hyaluronidase (500–1,000 IU) mixed with lidocaine is injected in the affected vessel, the surrounding path of the vessel, and its terminal branch; a large-bore cannula avoids bruising that obscures signs of improving skin color. Doses up to 1,500 U may be used if needed; the consequences of inadequate dosing are dire. Repeat hourly for three to four hours and daily for at least four days or as long as signs of ischemia persist [71; 146; 158; 159].

Injecting high-dose hyaluronidase diluted with lidocaine induces vasodilation and hyaluronic acid dispersion and, with saline, allows coverage of a larger area [71]. Vigorously massage the treated area during and after all hyaluronidase injections to optimize the results and aid mechanical breakdown [158].

Because anaphylaxis is a potential side effect of hyaluronidase and skin testing for hypersensitivity reaction is not an option in emergencies, risk mitigation requires full resuscitation equipment on site and training in its use [34; 95; 158].

Promote Blood Flow to the Affected Area

Apply warm compresses, and vigorously massage or tap the area. To limit platelet aggregation, clot formation, and further compromise, the patient should be administered two tablets (650 mg) of aspirin to chew and swallow, followed by 75 mg per day until necrosis resolves [19; 71; 145].

Some experts recommend nitroglycerin paste 2% to promote vasodilation [70; 145; 160; 161]. However, others caution against its use before the hyaluronic acid has dissolved with two or three days of treatment, as dilation of adjacent unobstructed vascular pathways may propagate the embolus toward the orbital area [19]. Low-molecular-weight heparin has also been used in the management of patients with filler-induced vascular occlusion [34].



For necrosis following dermal filler injection, nitroglycerin paste (rectal paste, used off label) can be applied under an occlusive dressing for several days. The Aesthetic Complications Expert Group recommends applying for 12 hours and then removing for 12 hours until clinical improvement is seen or until it is no longer tolerated.

(<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6057733>. Last accessed March 26, 2021.)

Level of Evidence: Expert Opinion/Consensus Statement

Additional Recommendations

Necrotic cells and tissue invite opportunistic infection. The measures needed to promote healing and prevent further complications depend on the extent of necrosis and range from appropriate dressing and wound care with topical and/or oral antibiotics to surgical debridement for removal of dead tissue. Susceptible patients may require antiherpetic medication with perioral-area necrosis [145].

Necrosis can be very painful, and pain management should be considered. While over-the-counter analgesics may be adequate in some cases, more severe pain can require opioids [145]. Because necrosis can cause significant scarring and distress to patients, practitioners should prepare for a possible malpractice claim filed by the patient [145].

Ophthalmic Events

An ophthalmic event is a medical emergency, with 60 to 90 minutes the absolute time window for saving vision. Blindness from central retinal artery occlusion is resolvable following hyaluronic acid filler injection only with rapid intervention by retrobulbar injection of hyaluronidase. Occlusion longer than 60 to 90 minutes is irreversible [19].

An ophthalmologist or oculoplastic surgeon should be contacted immediately and the patient transported to the clinic. The general emergency department is inappropriate [122].

To save vision, a needle is advanced in the inferotemporal quadrant of the orbit, inferior and lateral to the optic nerve, with hyaluronidase 2–4 cc (150–200 U/mL) injected into the inferolateral orbit [122]. Attempt rapid ocular pulsed massage. Having the patient hyperventilate in a paper bag may promote retinal vessel dilation. If possible, annotate the time of the vascular event and the visual acuity if lack of light perception or loss of vision occurs [19].

ALLERGIC/HYPERSENSITIVITY REACTIONS

Acute infections appear as acute inflammation or abscesses at the injection site. If left untreated, the initial reddening and hardening can result in fistula formation, discharge of pus and filler, and potentially permanent disfigurement [162].

Hypersensitivity/allergic reactions occur when injected filler material triggers an immune response. Etiology differs by post-injection onset: acute (minutes to hours) or delayed (within days) [19; 71; 143; 163].

Acute Hypersensitivity Reaction

Type I hypersensitivity reactions, mediated by immunoglobulin E (IgE), may present with angioedema or anaphylaxis. Check vital signs; anaphylactic shock is a medical emergency. Angioedema can also progress to airway obstruction. Any systemic manifestation should be considered impending anaphylaxis and treat as such. This involves immediately administering IV epinephrine; if insufficient to maintain perfusion, consider additional vasopressor agents (e.g., dopamine, norepinephrine, glucagon). H1-receptor antagonists (plus cimetidine) are recommended for histamine-induced hypotension.

Hospital admission should be considered for more severe cases, as late-phase reactions may occur more than 36 hours after onset. If possible, remove the dermal filler using hyaluronidase as needed.

Delayed Hypersensitivity Reaction

Type IV hypersensitivity reactions, mediated by T lymphocytes and not antibodies, usually present with induration, erythema, edema, or various types of skin lesions, including painful erythematous nodules. Management consists of cold compresses for localized angioedema and H1-receptor antagonists for histamine-induced hypotension and pruritus. H2-receptor antagonists, oral corticosteroids, and ibuprofen are additional measures.

DELAYED COMPLICATIONS: INFLAMMATION OR INFECTION?

Understanding of delayed dermal filler adverse events and pathogenesis has been a slowly evolving process, impeded by the inconsistent terminology describing these adverse events [148; 152]. Delayed filler adverse events have long been considered foreign body immune responses or type IV immunologic reactions to filler materials or contaminants from production, reinforced by negative bacterial culture tests of pus from nodules and the low-grade nature of most inflammations [69; 144; 150; 164]. Sporadic findings of bacterial infection in late-onset nodules were often ascribed to departures from anti-

septic standards in skin prep or handling of fillers [165; 166]. However, steroid or high-dose NSAID therapy to suppress a presumed inflammatory/immune response led to worsened inflammation and abscesses in some patients, who often required IV antibiotics or surgery [22; 162].

In 2009, molecular diagnostics with fluorescence *in situ* hybridization and advanced imaging established bacterial colonization of tissue and filler material as the causality of chronic inflammation and nodules [165; 167; 168]. In 2010, the role of biofilm in late filler complications gained attention, helping explain adverse reactions to steroid therapy. These dense bacterial colonies on surfaces secrete extracellular polymers, forming a protective matrix against host defenses and antibiotics. Knowledge of biofilm involvement improved the characterization of filler adverse events [152; 162].

A foreign body granuloma results when immune response, unable to enzymatically degrade a foreign body, forms lymphocytic inflammation and fibrosis entrapping the body, preventing its migration. Foreign body granulomas are histologically distinct from inflammatory nodules [70; 71; 150].

Foreign body granuloma formation can involve biofilm which, protected from host immune response, remains semidormant until activated months or years later by host conditions that favor replication (e.g., new filler injection, dental/medical surgery, local or remote infection, trauma). Activated biofilm can cause an immune response, granulomatous inflammation, abscesses, or nodules, and flu-like illness can precede late-onset nodules [19; 22; 69].

Thus, late-onset nodules or granuloma may represent an immune/inflammatory response secondary to biofilm-colonized filler. Clinical differentiation is challenging. Foreign material in the dermis or sub-dermis can lead to sterile abscesses, granulomas, cellulitis, or nodules. Infection months or years after injection may have similar signs, varying from erythema, edema, inflammatory nodules, and pain/itching to systemic responses [165].

Therapy for late-onset nodules or granuloma consists of [19; 68; 69; 150]:

- Oral antibiotics with immunomodulatory and anti-inflammatory efficacy, with a macrolide (e.g., clarithromycin) or a tetracycline (e.g., minocycline or doxycycline)
- Systematic and intralesional corticosteroids
- Topical tacrolimus (0.1%) or pimecrolimus (1%)
- Intralesional 5-fluorouracil
- Laser treatment
- Surgical excision

Biofilm in Dermal Filler Infections

Biofilm as an increasing concern is reflected in surgical and infectious disease practice guidelines; uptake in cosmetic/aesthetic medicine is more recent. The skin is understood as a microbiota ecosystem, colonized by diverse micro-organisms. In normal skin flora, most bacterial constituents are harmless. Some are beneficial, such as *Staphylococcus epidermidis*, which inhibits the growth of pathogenic *Staphylococcus aureus* [169; 170].

S. aureus, the most commonly isolated pathogenic bacteria in surgical-site infections, colonizes tissue and artificial surfaces and is found on 30% to 60% of healthy Americans. A disturbed balance of the skin ecosystem can favor *S. aureus* proliferation and biofilm [171; 172; 173; 174].

On unbroken skin, *S. aureus* can remain asymptomatic; on injection sites, it can seed infections. The needle breaks the skin barrier, picking up bacteria that are delivered into the dermal filler and setting up infection in the tissue. Preoperative skin preparation for open surgery fails to remove 20% of resident skin flora [21; 165; 175].

Dermal filler skin prep is less stringent than presurgical site prep. However, it is important to remember that Isopropyl alcohol, chlorhexidine, and povidone iodine are demonstrably insufficient in preventing *S. aureus* biofilm transfer to tissue during filler injection [165; 170].

S. aureus biofilm-seeded hyaluronic acid injections have been linked to bacterial infection in studies comparing subjects who developed late infection to complication-free subjects, matched on age and hyaluronic acid treatment (e.g., filler properties, injections, volume). Bacterial skin flora were cultured from nasal swabs in both groups and filler injection sites in patients with late bacterial infection repeatedly over 12 months [164]. *S. epidermidis* dominated the bacterial flora on facial skin in 100% of subjects without complications, but pathogenic *S. aureus* and *Klebsiella* spp. dominated the bacterial flora on the facial skin of subjects with late bacterial infection. Late bacterial infection was diagnosed a mean 5.5 months after filler injection; pus and inflammatory tissue cultures were negative for bacterial growth. No subjects consented to biopsy, but exhaustive exclusion of other etiologies suggested bacterial biofilm infection [164].



EVIDENCE-BASED
PRACTICE
RECOMMENDATION

To minimize the risk of contamination and infection, the Australasian College of Dermatologists asserts that stringent hygiene, including the use of antiseptic non-touch technique at all times, is essential when fillers are injected. Because

filler injections necessitate using hands to stabilize or pinch the skin, clinicians should perform antisepsis frequently during the procedure. They also note that sterile gloves may provide a false sense of security; therefore, they advocate changing gloves after preparing syringes for injection and marking the face.

(<https://onlinelibrary.wiley.com/doi/full/10.1111/ajd.13273>. Last accessed March 26, 2021.)

Level of Evidence: Expert Opinion/Consensus Statement

Concerns of Antibiotic Resistance

Bacteria in a biofilm matrix exchange DNA mutations to spread antibiotic-resistant genes and biodiversity. As biofilms mature, antibiotic and antimicrobial resistance strengthens [162; 172; 173; 175]. A lack of biofilm-specific biomarkers has made noninvasive detection and diagnosis very difficult [174].

Biofilms are very difficult to treat and can require antibiotic concentration over 32 times that necessary for planktonic bacteria. Even the highest tolerable antibiotic dose can be insufficient [176]. Filler explant may be needed, putting the patient at risk for tissue scarring, deformity, and nerve or structural damage. Minimally biodegradable fillers have higher rates of delayed-onset infection [165].

MRSA is a serious concern because few remaining antibiotics are effective. Vancomycin-resistant *S. aureus* has also emerged—a potentially incurable infection [174]. In the general U.S. population, 20% are persistently colonized with *S. aureus* (i.e., carriers) and 2% are MRSA carriers. MRSA carriage among surgical staff (4.5%) and healthcare workers (5%) is higher, and many studies support MRSA transmission from healthcare workers to patients [170; 177]. As such, MRSA carriage screening and decolonization of surgical staff and patients can reduce MRSA surgical infections. However, no protocols or data are available on plastic surgeon MRSA carriage, association with filler-site infections, or decolonization [178; 179].

Management of biofilm infection consists of oral antibiotics with immunomodulatory and anti-inflammatory efficacy [19; 22; 143; 150]. The first-line choice is a macrolide (e.g., clarithromycin) or a tetracycline (e.g., minocycline or doxycycline) for two weeks. Second-line therapy is dual macrolide- and tetracycline-class therapy. The addition of a quinolone (e.g., ciprofloxacin) is reserved as third-line therapy due to potential serious class-wide adverse events. Patients with systemic symptoms or more severe local infection may require hospitalization and IV antibiotics.

Additional treatment options include hyaluronidase, laser, surgical drainage of the abscess, and filler excision. Note that intralesional hyaluronidase requires extreme caution, as it can facilitate the spread of active infection into adjacent tissues.

Another strategy for treating biofilm is low-dose triamcinolone injection mixed with 5-fluorouracil at regular intervals until resolution. The efficacy of 5-fluorouracil may involve its interaction with *ariR*, a regulatory gene that inhibits biofilm formation [34].

CONCLUSION

The importance for primary care clinicians to understand aesthetic medicine, patient variables, and market factors is brought to light by the increasing rates of aesthetic injections performed by non-board-certified physicians, nurses, and minimally trained aestheticians at inadequately equipped clinics, office settings, and spas [20]. Primary care providers are well-placed to importantly inform their patients about many aspects related to aesthetic medicine but benefit from educational intervention to become most effective in this role.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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