Injectable Soft Tissue Fillers: Practical Applications

Karol A Gutowski, MD, FACS
Disclosures

Angiotech/Surgical Specialties - Advisory Board
AxcelRx Pharmaceuticals - Advisory Board
Suneva Medical - Instructor

Will discuss off-label uses
Will use brand names for ease of understanding
Objectives

- Understand basic facial aging assessment
- Compare differences between fillers
- Identify anatomic sites for injection
- Learn to avoid & manage complications
- Review regulatory issues
## Fillers Used & Locations

### Most Common Sites
- Malar & cheeks
- Lips & perioral
- Tear troughs & periorbital
- Nasolabial folds
- Temples, hands, nose

### Most Common Filler
- Radiesse
- Restylane products
- Bellafill
- Juvederm products
- Belotero
- Sculptra
New Concepts

**Old School**
- Face starts looking old
  - Wait a little longer
  - Surgery (Facelift)

**Modern Approach**
- Prevention
  - Address each problem
    - Injections & skin treatments
    - Less invasive procedures
    - Maintenance
What Happens with Aging?

• Skin changes
  – Thickness
  – Pigment
  – Lines

• Loss of facial volume (fat)

• Muscle descent

• Changes in facial bones
Address Each Problem Area

• **Skin Changes**
  – Medical facials & peels
  – Light therapy & lasers
  – Block muscles that cause lines
  – Fill in fine lines
  – Tighten skin

• **Loss of Volume**
  – Add volume
Twin Comparison: Body Mass Index
Twin Comparison: Body Mass Index

Age 58

Perceived 5 years older
BMI 15 points lower

Guyuron, 2009
Facial Bone Changes

Bones in the midface and jaw become less prominent causing loss of structural support which leads to a sunken appearance.
Facial Bone Changes

Bones around the eye become larger causing loss of structural support which leads to aged appearance.
Injectable Options
## Soft Tissue Filler Trends

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Botulinum Toxin Type A (Botox, Dysport)**</td>
<td>6,757,198</td>
<td>6,673,608</td>
<td>786,911</td>
<td>1%</td>
<td>759%</td>
</tr>
<tr>
<td>Cellulite treatment (Velosmooth, Endermology)</td>
<td>30,810</td>
<td>29,243</td>
<td>23,952</td>
<td>5%</td>
<td>29%</td>
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<tr>
<td>Chemical peel</td>
<td>1,310,252</td>
<td>1,250,059</td>
<td>1,149,457</td>
<td>5%</td>
<td>14%</td>
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<tr>
<td>Intense Pulsed Light (IPL) treatment</td>
<td>646,592</td>
<td>621,724</td>
<td>*</td>
<td>4%</td>
<td>*</td>
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<tr>
<td>Laser hair removal</td>
<td>1,116,708</td>
<td>1,112,046</td>
<td>735,996</td>
<td>0%</td>
<td>52%</td>
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<tr>
<td>Laser skin resurfacing</td>
<td>569,458</td>
<td>543,731</td>
<td>170,951</td>
<td>5%</td>
<td>233%</td>
</tr>
<tr>
<td>Ablative</td>
<td>159,795</td>
<td>152,478</td>
<td>*</td>
<td>5%</td>
<td>*</td>
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<tr>
<td>Non-ablative (Fraxel, etc.)</td>
<td>409,663</td>
<td>391,253</td>
<td>*</td>
<td>5%</td>
<td>*</td>
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<tr>
<td>Laser treatment of leg veins</td>
<td>207,862</td>
<td>207,790</td>
<td>245,424</td>
<td>0%</td>
<td>-15%</td>
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<tr>
<td>Microdermabrasion</td>
<td>800,340</td>
<td>881,905</td>
<td>868,315</td>
<td>-9%</td>
<td>-8%</td>
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<tr>
<td>Sclerotherapy</td>
<td>322,280</td>
<td>323,609</td>
<td>866,555</td>
<td>0%</td>
<td>-63%</td>
</tr>
<tr>
<td>Soft Tissue Fillers</td>
<td>2,440,724</td>
<td>2,295,647</td>
<td>652,885</td>
<td>6%</td>
<td>274%</td>
</tr>
<tr>
<td>Calcium hydroxylapatite (Radiesse)</td>
<td>256,256</td>
<td>257,953</td>
<td>*</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Collagen</td>
<td>14,353</td>
<td>16,023</td>
<td>587,615</td>
<td>-10%</td>
<td>-98%</td>
</tr>
<tr>
<td>Porcine/bovine-based (Evolence, Zyderm, Zyplast)</td>
<td>14,353</td>
<td>16,023</td>
<td>*</td>
<td>-10%</td>
<td>*</td>
</tr>
<tr>
<td>Fat</td>
<td>70,283</td>
<td>67,609</td>
<td>65,270</td>
<td>4%</td>
<td>8%</td>
</tr>
<tr>
<td>Hyaluronic acid (Juvederm Ultra, Juvederm Ultra Plus, Perlane, Restylane, Belotero)</td>
<td>1,951,692</td>
<td>1,802,247</td>
<td>*</td>
<td>8%</td>
<td>*</td>
</tr>
<tr>
<td>Polylactic acid (Sculptra)</td>
<td>130,089</td>
<td>134,471</td>
<td>*</td>
<td>-3%</td>
<td>*</td>
</tr>
<tr>
<td>Polymethyl-methacrylate microspheres (Artefill)</td>
<td>18,051</td>
<td>17,344</td>
<td>*</td>
<td>4%</td>
<td>*</td>
</tr>
</tbody>
</table>

**TOTAL COSMETIC MINIMALLY-INVASIVE PROCEDURES** | 14,202,224 | 13,939,362 | 5,500,446 | **2%** | **158%** |
The Typical Liquid Facelift
The Atypical Result
The Fillers
Latest FDA Approvals

- 2016    Volbella    Lips & perioral lines
- 2014    Restylane Silk       Lips & perioral lines
- 2013    Voluma        Cheek augmentation
- 2012    Restylane L     + lidocaine
- 2011    Belotero       NLF & Perioral
- 2011    Restylane      + lip indication
- 2009    Sculptra       + aesthetic indication

Not much compared to worldwide fillers
More **Options** for Filler Duration
- Short-term degradable
- Long-lasting degradable
- Permanent

More **Mechanisms** of Action
- Volumetric
- Structural
- Fibroplastic

More **Volume** being Injected
More **Sites** being Treated
Types of Lines

Lines at Rest (Static)

Lines with Movement (Dynamic)
Cause of Lines

Muscle contractions cause skin folds

Over time persistent lines form
Where & What to Inject

- **Neuromodulator** (Botox, Dysport, Xeomin)
  For wrinkles **with movement**

- **Filler** (Juvederm, Restylane)
  For wrinkles **at rest**
  For small volume deficits

- **Stimulator** (Sculptra, Bellafill)
  For replacing regional volume loss
Injectable Tissue Filler Options

- **Hyaluronic Acids**
  - Juvederm, Voluma, Volbella, Restylane, Belotero
  - Reversible

- **Animal Collagen**
  - Zyderm, Zyplasty, Evolence

- **Human Collagen**
  - CosmoDerm, CosmoPlast, Fascian, Autologen, Cymetra, LaViv

- **Stimulators**
  - PLLA (Sculptra)
  - PMM (Bellafill)

- **CaHA (Radiesse)**

- **Silicone**

- **Fat**
## Soft Tissue Filler Classifications

### Source
- Autologous
- Biological
- Synthetic

### Longevity/duration of effect
- Temporary: < 6 months
- Long lasting: 6 to 24 months
- Semi permanent: 2 to 5 years
- Permanent: > 5 years

### Risk profile
- Injection expertise needed
- Depth of injection
Temporary Fillers: Collagen

**Bovine collagen**
- First FDA approved nonautologous dermal filler (1981)
- Treatment of wrinkles, smile & frown lines, acne, postsurgical scars
- Double skin testing required (up to 3% positive)
- Allows for connective tissue ingrowth
- Excellent long-term safety profile
- Injected into dermis
- Last for 3 to 6 months
Collagen 1980s

**Zyderm 1** 35 mg/mL collagen + 0.3% lidocaine
- Injected into superficial papillary dermis
- 100% **overcorrection** recommended because of water loss

**Zyderm 2** 65 mg/mL collagen + 0.3% lidocaine
- Injected into mid-dermis
- 50% **overcorrection** recommended

**Zyplast** 35 mg/mL collagen + 0.3% lidocaine
- Longer-lasting due to cross linking (less immunogenic)
- Injected into deep dermis
- **No** overcorrection
Collagen New Millennium

**CosmoDerm**  Human-derived collagen equivalents of Zyderm
**CosmoPlast**  Human-derived collagen equivalents of Zyplast
- FDA approved 2003
- No skin testing

**Evolence**  35-mg/mL type I collagen
- FDA approved 2008
- Cross-linked porcine collagen (skin testing not required)
- No overcorrection, lasts up to 1 yr
- Correction of moderate to deep wrinkles & folds (NLF)
- Not into lips (nodule formation)
- Discontinued late 2009 (tough market)
Temporary Fillers: Hyaluronic Acid

- Glycosaminoglycan biopolymer
- Found in all connective tissue
- Chemically the same for all species
  - Low risk for allergic reactions
  - Skin testing is not required
- Hydrophilic - provides matrix to retain dermal moisture
  - One gram of HA can bind up to 6 L of water
- Hyaluronic gels (Hylans) = Cross-linked to increase longevity
Hyaluronic Acid Properties

Unique to hylan fillers

• Dynamic viscosity
  – Decreasing viscosity as shear rate increases
  – Upon injection hylans pass through needles more easily
  – When force removed, viscosity increases, gel thickens to minimize migration

• Isovolemic degradation
  – As it degrades, the remaining HA bind more water
  – Overall volume remains the same
  – Maintain 95% of initial filling volume until all is resorbed
Hyaluronic Acid Products

Animal Based HAs from dermis of rooster combs

• Hylaform
  – First HA available (but approved 2004)
  – Mid to deep dermis for moderate to severe wrinkles & folds (NLF)

• Hylaform Plus
  – Larger particle size (750 vs 500 mm) & greater gel hardness
  – Greater ability to deform surrounding tissues to correct defects
  – Intended for deeper injections
Hyaluronic Acid Products

Non-Animal Based HAs from *Strep equi*

- **Restylane**
  - First FDA approved filler (2003)
  - Correction of moderate to severe wrinkles and folds (NLF)
  - 20 mg/mL, uniform 400 mm particles, 1% cross-linked
  - 6 month duration
  - More viscous & less elastic than Hylaform

- **Restylane Silk** for lips & lip lines

- **Restylane Lyft** for deeper folds

- **Belotero Balance** for perioral & NLF, fine lines
Hyaluronic Acid Products

- **Juvederm Ultra** (2006)
  - Mid to deep dermis for moderate to severe wrinkles & folds (NLF)
  - Higher HA concentration (24 mg/mL) than Restylane
  - More crosslinking than Restylane to increase longevity
  - Last up to 12 months

- **Juvederm Ultra Plus**
  - Larger particle size & more cross-linking
  - Thicker gel for volumizing deeper injections

- **Juvederm “XC”** includes 0.3% lidocaine

- **Voluma** (2013)
  - More “lift” for cheek elevation
  - Lasts up to 18 months
Does HA Stimulate Collagen?

Fillers and Neocollagenesis

Jean D. A. Carruthers, MD, FRCSC, FRCOphth, * J. Alastair Carruthers, MBBS, MRCP, FRCPC, † and Shannon Humphrey, MD, FRCPC, FAAD‡

HA fillers show increased collagen around injection site for at least 3 months
### HA Filler Physical Properties

<table>
<thead>
<tr>
<th></th>
<th>Hylaform</th>
<th>Hylaform Plus</th>
<th>Prevelle</th>
<th>Restylane</th>
<th>Perlane</th>
<th>Juvederm 30 HV</th>
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<tbody>
<tr>
<td>Total HA concentration (mg/mL)</td>
<td>5.5</td>
<td>5.5</td>
<td>5.5</td>
<td>20</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>Gel-to-fluid ratio</td>
<td>98:2</td>
<td>98:2</td>
<td>98:2</td>
<td>75:25</td>
<td>75:25</td>
<td>60:40</td>
</tr>
<tr>
<td>HA gel concentration (mg/mL)</td>
<td>5.4</td>
<td>5.4</td>
<td>5.4</td>
<td>15.0</td>
<td>15.0</td>
<td>14.4</td>
</tr>
<tr>
<td>Degree of HA modification (%)</td>
<td>23</td>
<td>23</td>
<td>23</td>
<td>3</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Percentage cross-linked HA</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>1.2</td>
<td>1.4</td>
<td>2</td>
</tr>
<tr>
<td>Dilution durability/percentage swelling</td>
<td>&lt;25</td>
<td>&lt;25</td>
<td>&lt;25</td>
<td>50</td>
<td>50</td>
<td>300</td>
</tr>
<tr>
<td>G’ modulus (Pa)</td>
<td>140–220</td>
<td>140–220</td>
<td>230–260</td>
<td>660</td>
<td>588</td>
<td>105</td>
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<tr>
<td>Average particle size (μm)</td>
<td>500</td>
<td>700</td>
<td>350</td>
<td>300</td>
<td>650</td>
<td>300</td>
</tr>
</tbody>
</table>

**HA products are NOT interchangeable**
# Filler Rheology

## Basics of Dermal Filler Rheology

*Sébastien Pierre, PhD,* Steven Liew, MD,* and Aude Bernardin, PhD*

<table>
<thead>
<tr>
<th>Filler</th>
<th>$G'$ (Pa)</th>
<th>$G''$ (Pa)</th>
<th>Tan δ</th>
<th>Compression (gmf)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juvederm Ultra XC</td>
<td>207</td>
<td>80</td>
<td>0.39</td>
<td>96</td>
</tr>
<tr>
<td>Juvederm Ultra Plus XC</td>
<td>263</td>
<td>79</td>
<td>0.30</td>
<td>112</td>
</tr>
<tr>
<td>Juvederm Voluma XC</td>
<td>398</td>
<td>41</td>
<td>0.10</td>
<td>40</td>
</tr>
<tr>
<td>Juvederm Volift with lidocaine†</td>
<td>340</td>
<td>46</td>
<td>0.14</td>
<td>30</td>
</tr>
<tr>
<td>Juvederm Volbella with lidocaine†</td>
<td>271</td>
<td>39</td>
<td>0.14</td>
<td>19</td>
</tr>
<tr>
<td>Restylane-L</td>
<td>864</td>
<td>185</td>
<td>0.21</td>
<td>29</td>
</tr>
<tr>
<td>Perlane-L</td>
<td>977</td>
<td>198</td>
<td>0.20</td>
<td>32</td>
</tr>
<tr>
<td>Belotero Balance</td>
<td>128</td>
<td>82</td>
<td>0.64</td>
<td>69</td>
</tr>
</tbody>
</table>
## Filler Rheology

\[ G' = \text{Elastic behavior (modulus)} \]
How much it can recover after a stress force

<table>
<thead>
<tr>
<th>Filler</th>
<th>( G' ) (Pa)</th>
<th>( G'' ) (Pa)</th>
<th>( \tan \delta )</th>
<th>Compression (gmf)</th>
</tr>
</thead>
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<td>0.64</td>
<td>69</td>
</tr>
</tbody>
</table>
Filler Rheology

Shear: $G^*$
Relaxation: $G' = G^*$, $G'' = 0$
Visco-elastic: $G' < G^*$
Dermal fillers

Compression:
- High cohesivity
- Medium cohesivity
- Low cohesivity
- Non cohesive
Elastic Modulus* (G prime)

*Mathematical description of product’s tendency to be deformed elastically
May not match clinical results
All 3 have 20 mg HA per mL
Particle size is different
Particle Size & Injection Depth

Silk

Small particle hyaluronic acid

Small gel particle hyaluronic acid

Large gel particle hyaluronic acid

Restylane

Lyft

Epidermis

Dermis

Subcutaneous tissue
Rheology & Filler Choice

- **Midface**
  - Use higher $G'$ products
  - Lift & fill

- **Fine lines & wrinkles**
  - Use low-moderate $G'$ products
  - Easy to mold
  - Less visible
Water Absorption

Prevelle Silk

Less Swelling

Restylane and Lyft

More Swelling

Juvéderm Ultra Plus
Long Lasting Fillers: PLLA

Poly L Lactic Acid

• Biodegradable, nontoxic, synthetic, inactive material from corn starch
• Used in sutures, stents, other biomedical implants
• Growth of type I collagen into injection sites
• Metabolized to CO$_2$ & glucose
• **Sculptra** (2004) HIV-related facial lipoatrophy then cosmetic indications
  – Up to 2 year duration
  – Provides true **volumization**
  – Not an instant results filler
  – Requires temporary overcorrection
  – Reassess at 4-6 weeks
Semipermanent Fillers: CaHA

**Calcium Hydroxylapatite**
- Mineral component of bone
- Non immunogenic & biocompatible
- Scaffold for collagen in-growth
- Dental, orthopedic, urologic, & vocal cord applications
  - Spheres (24 - 45 µm) suspended in carboxymethylcellulose gel
  - Highly viscous
  - Predisposed to nodule formation, especially in lips
  - 9 to 18 month duration but may last 2 to 5 years
Permanent Fillers

**Autologous Fat** - The original filler

**Silicone** - Controversial

**Polymethylmethacrylate** (PMMA, Plexiglas, Lucite, acrylic glass)
- Used in bone cement, lenses, dental work, pacemakers
- **Bellafill** (2015, **Artefill** 2003) correction of nasolabial folds (**Artecoll** in Europe)
  - Microspheres (30 - 42 mm) in 3.5% **bovine collagen** + 0.3% lidocaine
  - Skin test needed
  - Collagen stimulation & ingrowth as bovine collagen dissolves
  - Off the market in 2008 (Artes out of business), back in 2009

**Aquamid** (World wide use, not FDA approved)
- Acrylic polymer hydrogel
Scaffold for Collagen Deposition

- 5 days
- 2 wks
- 1 mo
- 3 mo
- 5 mo
- 6 mo
- 1 yr
- 2 yr
- 3 yr

Percent Implant Volume

- PMMA Microspheres
- Injected Collagen
- Autologous Connective Tissue
PMMA Encapsulation after 3 Months

Multiple fibroblasts & connective tissue encapsulation of individual microspheres
## PMMA Variability

<table>
<thead>
<tr>
<th>Product</th>
<th>Country of Origin</th>
<th>SEM Analysis (Particle shape, surface finish, size, gross size distribution, and anomalies)</th>
<th>SEM Image</th>
</tr>
</thead>
</table>
| Artefill 2007 | USA               | - Size: 30 to 50 microns, with negligible small sizes.  
- Shape: Smooth surfaced microspheres with scant if any sediment.  
- The only FDA approved PMMA-enhanced dermal filler |           |
| Artecoll 2005 | Canada            | - Size: 30 to 50 microns, with negligible small sizes.  
- Shape: Smooth surfaced microspheres with slight surface irregularity, scant sediment. |           |
| Artecoll 2001 | Europe            | - Size: 32 to 40 microns, but with larger variation in particle sizes  
- Shape: presence of nanoparticles on the surface of microspheres.  
- There are sub-20 micron particles and some sub 5 micron particles, some sediment. |           |
| Metacrill 2006 | Brazil            | - Size: 0.2 to 60 microns. Many sub-20 micron particles, and many are sub-5 micron.  
- Shape: Many irregular shapes, some non spherical, jagged edges, poor surface. |           |
| NewPlastic 2006 | Brazil           | - Size: 0.2 to 70 microns. Some large spheres > 70 microns and some very small.  
- Shape: Some are non spherical, and conjoined, many small spheres and particles. |           |
Contaminant Elimination
Production control to insure MS are round & smooth

Uniform particle size (30 – 50 µm)
<1% are <20 µm per FDA
Silicone

- 1992: FDA bans liquid injectable silicone
- 1994 & 1997: FDA approves AdatoSil (Adaptosil) 5000 & Silikon 1000 (highly purified silicone) for retinal detachment
- 1997: FDA Modernization Act allows off label use of devices
- Filler indication is strictly off-label
- Liability carriers have regulations on liquid injectable silicone
Silicone

Largest report of Silikon 1000

• 916 patients over 6 years
• 5246 treatments during 3307 visits
  – 3.5 visits per patient
  – 1.6 treatments per visit

• Adverse events
  – Overcorrection in 11 patients (1%)
  – Retrospective chart review limitations

Hevia 2009
Silicone for Acne Scars

Barnett 2010
Silicone for HIV Facial Atrophy

Barnett 2010
Silicone Summary

- FDA studies underway to assess safety & efficacy
- Silicone injections remain controversial
- Inherently unpredictable, adverse events
  versus
- Safe & effective, giving superior aesthetic results if:
  - Use highly purified silicone
  - Microdroplet technique (0.01 cc into subdermal plane 2-4 mm intervals)
  - Small volumes ($\leq 0.5$ cc for smaller defects, $\leq 2$ cc for facial lipoatrophy)
  - Limit injections to once monthly (allow fibroplasia augmentation)
- May be ideal filler if injected correctly
- Complications similar to other FDA approved fillers
Aquamid

2.5% Cross-linked polyacrylamide (PAAG)
- Homogeneous gel, no microparticles
- No foreign body reaction to achieve augmentation
- Permanent results (up to 11 years)
- Approved in Europe (2001)
- NLF, lips, cheeks, nose, facial lipoatrophy
Adverse reactions following injection with a permanent facial filler polyacrylamide hydrogel (Aquamid): causes and treatment

• Prospective study of 40,000 case reports between 2003
• 55 were reported to have experienced adverse events (AE)
  – AEs occurred mainly in lips and nasolabial folds
  – 55 patients, with 51 requiring treatment
  – The time from last injection to AE: 2 to 364 days (median of 12 days)
  – High dose broad-spectrum antibiotic effective for a short time
  – Steroids & NSAIDs (NSAIDs) aggravated symptoms & prolong treatment time

• Conclusions: Nodules or swellings later than 1 week and less than 1 year should be treated immediately
  – Broad-spectrum antibiotic (quinolone) in high dosage
  – Steroids & NSAIDs contraindicated

Christensen 2006
Tingling, redness, swelling or other changes in the first weeks are usually sign of infection. In the event of complications, suspect an infection - these are NOT an allergic reaction.

Never corticosteroids

- Complications, such as swelling, should NEVER be treated with corticosteroids or NSAIDs as they are absolutely contraindicated because they prolong recovery time.

Treat with antibiotics (high-dose & broad spectrum)

- Clarithromycin 500 mg + Moxifloxazin 400 mg BID, at least 10-14 days.
- If no reduction after 3 days, change to Clindamycin 600 mg + Tetracyclin 500 mg BID.
  - This combination may act against bacteria resistant to Clarithromycin + Moxifloxacin.

Prophylactic antibiotics

- If you choose to use a prophylactic treatment, the following is recommended: Azithromycin 500 mg + Moxifloxacin 400 mg 2 - 6 hours prior to injection.
Aquamid Abscess

Acute swelling 3 years after Aquamid injection

Recurrent abscess
Platelet Rich Plasma (PRP)
PRP: What is it?

Autologous blood plasma enriched with platelets
Degranulation release cytokines & growth factors
  • Platelet-derived growth factor
  • Transforming growth factor beta
  • Fibroblast growth factor
  • Insulin-like growth factors 1 & 2
  • Vascular endothelial growth factor
  • Epidermal growth factor
  • Interleukin 8
  • Keratinocyte growth factor
  • Connective tissue growth factor
PRP Production

- Collection of anticogulated whole blood
- Two-stage centrifugation
- PRP separated from platelet poor plasma & RBCs
- 5-fold increase in platelet concentration
- Broad variability in production techniques
Selphyl

PRP & Ca^{++} to activate fibrinogen to fibrin
Results in a gel matrix
Limited clinical data
Vampire Lift: PRP & HA Filler

PRP injected with Restylane or Juvederm

Proprietary methods

No clinical data
PRP in Facial Aesthetics

• 15 adults: Single PRFM (Selphyl) injection for deep nasolabial folds
• Wrinkle Assessment Scale (WAS 1-5)
  – Reduction of $1.1 \pm 0.7$ after 12 weeks
• No complications
• Holds potential for dermal augmentation

Anthony P Sclafani MD, 2010
PRP in Facial Aesthetics Follow Up

- 50 adults with mean 10 month follow up
- NLFs, acne scars, rhytides, volume loss
- Average 1.6 treatments (Range 1-5)
- “Most patients were satisfied”
NO clinical studies support stem cell use in plastic surgery
Volbella

A prospective, open-label, multicenter, observational, postmarket study of the use of a 15 mg/mL hyaluronic acid dermal filler in the lips

Wolfgang G Philipp-Dormston, MD,1 Said Hilton, MD,2 & Myooran Nathan, MBBS3

• 15 mg/mL HA filler
• Majority LMW HA
• Cross linked
• Less swelling
Volbella
Dextran Filler

Twenty-Four-Week Multicenter, Evaluator-Blinded Clinical Study of the Efficacy and Safety of a Dextran Filler in the Treatment of Nasolabial Folds

Soo Jung Shin, MD,* Young Her, MD,† Dong Soo Yu, MD,‡ Chul Woo Kim, MD,* and Sang Seok Kim, MD*
Addition of epinephrine to Belatero Balance (HA) did NOT decrease bruising
TEOSYAL Pen Injection Device

- 30 physicians, 236 patients
- 90% patient preference
- 50% pain reduction
Other Fillers Available

• Alibaba.com
  – 100’s of products

• Europe
  – Variations of US products
  – “Me Too” products
  – Entirely different products
Technique
Factors in Unfavorable Outcomes

- Patient selection
- Undertreatment
- Anatomic site
- Product selection
- Technique
- Judgment (overfill/under correction)
- Patient expectations
- Tissue damage
Assessment Scale to Set Expectation

**Wrinkle Scale**
- Grade 1 ~ 0.3 cc per side
- Grade 2 ~ 0.6 cc per side
- Grade 3 ~ 0.6 cc per side
- Grade 4 ~ 1.0 cc per side
- Grade 5 ~ 1.0 cc per side

**Questions:**
- How severe is the crease?
- How much filler is needed?
- What result to expect?
Proper Photo Documentation

Before and after 1.5 cc Radiesse injections to nasolabial folds
Before and after 1.5 cc Radiesse injections to nasolabial folds
Target the Volume Loss
3D Facial Imaging Analysis
Individualized Treatment Plan
Predicted Results
Tricks to Demonstrate Effect

Use of Xylocaine to Predict the Effect of Neuromodulators

Wirtzer, 2015
Tricks to Demonstrate Effect

Use of Saline to Predict the Outcome of Filler Injections
Patient Comfort

Minimize discomfort, redness, swelling, bruising

• Filler viscosity
  – Thicker HAs (Restylane) & CaHA (Radiesse) more pain

• Needle caliber
  – CaHA needs at least 27G needle
  – PLLA at least a 25G to 27G needle

• Anatomical site
  – Perioral, periocular & lip more painful than NLF

• Pre & postinjection cooling packs for 5 to 10 min
Patient Comfort

- No anesthetic
- Topical cooling
- Topical anesthetic
  - Applied 30 – 60 min before injection
  - Occlusive dressings (Tegaderm)
  - Injection pain may be experienced deeper than level of effect
- Injection site block
  - 0.3 cc 1% lidocaine + epi with 32G needle
- Nerve blocks
  - Infraorbital nerve: NLF & upper lip
  - Mental nerve: lower lip & marionette lines
  - May cause tissue distortion

Pain Scale:

- 0
- 2
- 4
- 6
- 8
- 10
Hyaluronic Acids + Lidocaine

- Patient-blinded, prospective, randomized, split-face design
- HA + lidocaine (Prevelle SILK) vs no lidocaine (Captique)
- 50% less pain with lidocaine than without
- No difference in NLF outcome after 2 weeks

Monheit 2010
Collagen + Lidocaine

- Dermicol-P35 (Evolence, bovine collagen)
- Split-face NLF protocol
- **Topical** 5% lidocaine vs 0.18 cc 2% lidocaine mixed in filler
- Pain scores (0 to 10)
  - 5.3 for topical lidocaine
  - 1.2 for injected lidocaine
- Both had similar efficacy

Weinkle 2010
Calcium Hydroxylapatite + Lidocaine

- Calcium hydroxylapatite (CaHA, Radiesse)
- Prospective, randomized, split-face, single-blinded
- CaHA vs CaHA + 0.2 cc 2% lidocaine for NLF
  - Can premix day in advance
- 4 point reduction in pain at time of injection

Marmur 2010
Basic Set Up

+ Gloves
Block & Tackle the Face
Injection Technique

Target the correct level

- Mid to deep dermis
  - Low G’ HAs
- Subcutaneous
  - PLLA, CaHA, PMMA
  - Higher G’ HAs
- Deep/preperiosteal
  - High G’ HAs, CaHA
Serial Puncture

Example: Tear Trough
Linear Threading

Example: Nasolabial Fold
Fanning

Example: Deep Malar Elevation
Cross Hatching

Example: Lateral Lip Frown
Placement at dermal/subdermal junction
Proper Dermal Injection

Too Superficial

Too Deep

Correct Placement

Needle lifted
Blunt Injection Cannulas
Blunt Injection Cannulas

SHARP HYPODERMIC NEEDLE vs BLUNT-TIP MICROCANNULA
Safety and effectiveness of injection of calcium hydroxylapatite via blunt cannula compared to injection by needle for correction of nasolabial folds

Kenneth R Beer, MD
Esthetic, General & Surgical Dermatology, West Palm Beach, FL, USA

- 20 patients – split face (not enough for adverse events)
- Needle side had more pain, redness, swelling
- Cannula side had better correction at 19 days
Results
## Patient Selection

<table>
<thead>
<tr>
<th>Volume Loss</th>
<th>Volume Descent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fillers</td>
<td>Facelift</td>
</tr>
</tbody>
</table>
Filler or Fat?
The Power of Volume

After fat grafting
The Power of Volume

After fat grafting
Rebuild the deep volume with fat
Then fill fine lines with a filler
After fat grafting
Hollow Temples
Hollow Temples

High G’ bolus injections
Hollow Temples

High G’ bolus injections
Manual pressure to spread filler
Lower Lids & Tear Troughs

Proceed with Caution
Tear Trough Asymmetry

Topical anesthetic
Restylane (Moderate G’)
30G needle
80% correction
Mild Fat Pad Herniation

Topical anesthetic
Juvederm (Low G’)
30G needle
80% correction
Fat Pad Herniation Correction
Fat Pad Herniation Correction
Tear Trough & Malar Support
Tear Trough & Malar Support
Tear Trough & Malar Support
Tear Trough & Malar Support

Restylane
Tear Trough & Malar Support

Restylane

Radiessse
Tear Trough & Malar Support
Filler or Blepharoplasty?

Transconjunctival Blepharoplasty
Tear Trough & Prominent Orbicularis
Tear Trough & Prominent Orbicularis

Juvederm
Low G’
Tear Trough & Prominent Orbicularis

Juvederm
1:1 Saline

Juvederm
Low G’
Tear Trough & Prominent Orbicularis
Tear Trough & Lower Lids

- Inject on periosteum
- Expect edema & ecchymosis
- Under correct
  - Touch up in 2 weeks
- Prolonged edema
  - Treat early
  - Hyaluronidase
- May persist for years

Not for novice injectors
Malar & Cheek

Best Bang for the Buck
A randomized comparison of the efficacy of low volume deep placement cheek injection vs. mid- to deep dermal nasolabial fold injection technique for the correction of nasolabial folds

Molly Goodier, BS, Kendra Elm, BS, Irmina Wallander, BA, Brian Zelickson, MD, & Sarah Schram, MD

• Does NLF need direct injection?
• Can cheek injection improve NLF?
• Split face HA (Juvederm Ultra Plus)
• Similar improvements at low volume injections
  – Average 0.6 cc per injection site
Injection Areas

NLF injection

Mid-lateral cheek injection
Improved Nasolabial Folds

Before & After: R NLF injection, L cheek injections
Improved Nasolabial Folds

Before & After: R NLF & cheek injection, L cheek injections
Malar Hypoplasia & Tissue Descent

Radiesse (High G')
1.5 cc per side
Deep 0.1 cc bolus x 4
Subdermal fanning
Hollow Cheeks

3 months after 1.5 cc Voluma (moderate G’) + 1.5 cc saline (total 3 cc) per side
Hollow Cheeks

Before and after 1 vial Sculptra per cheek
Malar & Cheeks

• Malar
  – High G’ (Radiesse or Lyft, Bellafill for long-term)
  – 0.1 cc needle bolus at 2-4 points on periosteum at malar prominence
  – Massage & shape to desired form

• Cheeks
  – Moderate to high G’ blunt cannula injection
  – Subcutaneous fanning or cross-hatching

• Treat before nasolabial folds
Nasolabial Folds

After Malar Correction
Mild Nasolabial Folds

Low to moderate G’
Blunt cannula
Subdermal injection
Mild Nasolabial Folds

Before and after **Bellafill** to nasolabial folds
2 syringes (Right 1.2 cc, Left 0.5cc)
Before and after Juvederm Ultra Plus to nasolabial folds
1 syringe (Right 0.45 cc, Left 0.55cc)
Moderate Nasolabial Folds

Before and after 1.5 cc Radiesse to nasolabial folds
Moderate Nasolabial Folds

Before and after 1.5 cc Radiesse to nasolabial folds
Lips & Perioral
Juvederm Ultra XC for Lips

- Previous indication
  - Mid to deep dermis, facial wrinkles & folds
- Has lidocaine
- Single blinded MC-RCT
  - 157 Juvederm patients + 56 controls (then crossed over)
  - Touch up at 2-4 weeks if needed
  - Validated 5 point scale
- **Total volume (initial + touch up): 2.1 cc**
  - Upper lip 0.9 cc  Lower lip 0.7 cc
  - Upper lip lines 0.2 cc  Lower lip lines 0.1 cc
  - Oral commissure 0.4 cc
Juvederm Ultra XC for Lips

Lip Fullness Responders
(≥ 1-point Improvement on Overall Lip Fullness Scale)

<table>
<thead>
<tr>
<th>Months</th>
<th>JUVÉDERM Ultra (n = 157)</th>
<th>No Treatment (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Months (Primary Endpoint)</td>
<td>79%</td>
<td>26%</td>
</tr>
</tbody>
</table>

P < 0.0001 vs No Treatment (month 3)

Percentage of Subjects Achieving Key Outcomes at Month 3

- Upper Lip Fullness Responders
- Lower Lip Fullness Responders
- Improvement in Perioral Lines Investigator
- Improvement in Oral Commissures Investigator

Lip Improvement
3 Months - 79%
1 year - 78%
Restylane Silk Approval

- RCT 221 subjects at 14 centers
- Effectiveness: $\geq 1$ grade improvement
- Injection volume
  - Upper & lower lip: Mean 2.2 cc
  - Perioral lines: Mean 0.5 cc
Restylane Silk Approval: Lips

Proportion (%) of MLFS Responders Measured by the Blinded Evaluator (Upper and Lower Lip Combined)

<table>
<thead>
<tr>
<th></th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
<th>Week 20</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restylane Silk Treatment</td>
<td>76.7</td>
<td>73.1</td>
<td>68.3</td>
<td>64</td>
<td>58.8</td>
</tr>
<tr>
<td>No Treatment</td>
<td>11.9</td>
<td>10</td>
<td>12.5</td>
<td>14.6</td>
<td>20</td>
</tr>
</tbody>
</table>
Restylane Silk Approval: Perioral Lines

Proportion (%) of Responders Measured by the Blinded Evaluator for Upper Perioral Rhytids

<table>
<thead>
<tr>
<th>Week</th>
<th>Treatment of Rhytids + Lip</th>
<th>Treatment of Lip Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>56.5</td>
<td>20.9</td>
</tr>
<tr>
<td>12</td>
<td>61.3</td>
<td>22.9</td>
</tr>
<tr>
<td>16</td>
<td>59</td>
<td>21.4</td>
</tr>
<tr>
<td>20</td>
<td>47.5</td>
<td>20.6</td>
</tr>
<tr>
<td>24</td>
<td>57.6</td>
<td>22.8</td>
</tr>
</tbody>
</table>
Lips & Corners
Lip Vermilion

Moderate G’
30G needle (or cannula)
Serial puncture
Lip Corners

Moderate to high G’
29G or 30G needle
Cross hatch
Lips & Corners

2 cc Restylane
Thin Lips & Lip Lines

1 cc Restylane
Lip Proportions: 1/3 – 2/3

1 cc Voluma
Marionette Lines
Marionette Lines

Moderate to high G’
27G or 29G needle
Fanning
Marionette Lines

0.25 cc Radiesse/side
Gummy Smile
Gummy Smile - Neuromodulator
Consider Central & Corner Lip Lift
Neuromodulator for Lip Lines
Neuromodulator for Lip Lines

2u BTA per side
Neuromodulator for Lip Lines

1 cc Restylane
Chin Fine Lines & Creases

1 cc Hydrell Intradermal
Chin Fine Lines & Creases

1 cc Hydrell Intradermal
Neuromodulator for DAO

BTA 5 u DAO + 1 cc Restylane
Lips, Perioral, Cheeks

4.6 cc Bellafill + 1 cc Restylane
Perioral area
Bellafill 2.4cc
Jaw Line & Pre Jowl Sulcus
Small Volume, Big Result
Mild Jowls
Mild Jowls

Moderate to high G’
27G needle
0.1 cc boluses pre-periosteal
Massage as needed
Mild Jowls

0.3 cc Radiesse/side
Mild Jowl & Pointing Chin

0.4 cc Radiesse/side
Jawline Enhancement

Calcium hydroxylapatite for jawline rejuvenation: consensus recommendations

Jean-Marie Dallara, MD,¹ Martine Baspeyras, MD,² Patrick Bui, MD,³ Hugues Cartier, MD,⁴ Marie-Hélène Charavel, MD,⁵ & Laurent Dumas, MD⁶

• Diminish effects of jowls on jawline
• Caution with “full” and “square” faces
• Consider saline injection test
Jawline Enhancement

Before & After 4.5 cc (total)
3 Syringes for face
Hands

Why Stop at the Face?
Aging Hands
Treating Age Spots
Hand Rejuvenation

After 3 Sculptra Vials
Hand Augmentation

Hand recontouring with calcium hydroxylapatite (Radiesse)®

Kenneth L Edelson, MD, FAACS
Private practice, New York City

Bolus Injection

FDA panel approval for Radiesse 2015

Closed Fist Massage
RCT at 6 sites
• 85 patients, maximum 3 cc Radiesse per hand
• Mean age: 53-54 years
  – Mostly white females
• 3 months
  – 75% had ≥1 point improvement (vs 3.4% of controls)
  – 76% rated “much” or “very much improved”
• Lasts up to 1 year
  – Some had retreatment
• Has lidocaine
Aging Hand
Aging Hand

High G’
Blunt cannula
Linear threading
Massage to position
Restore Dorsal Hand Fullness

Before and after 1.5 cc Radiesse to dorsum (FDA Approved)
Before and after 1.5 cc Radiesse to dorsum (FDA Approved)
Fat Graft Dorsal Volumization

Before and 6 months after Fat Grafting to dorsum
Fat Graft Dorsal Volumization

Before and 6 months after Fat Grafting to dorsum
Putting it Together
Facial Volumization
Start Superior & Lateral

0.8 cc syringe
40 to 50 passes
27G blunt cannula

Supraperiosteal Microdroplets
Volumize Inferior Orbit & Malar Area

- 0.8 cc syringe
- 40 to 50 passes
- 27G blunt cannula

- Supraperiosteal
- Subdermal
- Fanning
Treat Hollow Cheek

0.8 cc syringe
40 to 50 passes
27G blunt cannula

Supraperiosteal
Subdermal
Subdermal
Cross Hatching
Move to Lower Face
Lower Face

0.8 cc syringe
40 to 50 passes
27G blunt cannula

Subdermal
Fanning &
Cross Hatching
Facial Volumization: Bellafill 4.6 cc
Can MFUS interact with subcutaneous filler?

- Single patient with Voluma & Radiesse
- No negative effect seen on histology
- Enhanced collagen & elastin
Realistic Expectations!

YOU SHALL NOT AGE!

ITS A SYRINGE, NOT A MAGIC WAND
Complications
The Itinerant Patient

• Patient with unknown filler administered elsewhere (or abroad) requests “touch-up”
  – Additional HA can introduce bacteria & activate biofilm
  – Original filler material may be unknown (unapproved)
  – May have had more than 1 product used

• Results in complex evaluation & treatment plan
  – Patient perception: “It was just some injections...”
Filler Complication Categories

Immediate Onset (0 – 2 Days)
Early Onset (3 – 14 Days)
Delayed Onset (> 14 Days)
Immediate Complications

• Over or Under Correction

• Implant Visibility
  – Injection too superficial
    • **HA** blue discoloration
      – Massage, Hyaluronidase
    • Particulate fillers (**CaHA, PMM**) white bumps
      – Needle unroofing & evacuation

• Vascular Compromise
  – Glabella most common?
Glabellar Vascular Compromise

5 days after HA injection
Glabellar Vascular Compromise

12 days after HA injection
Glabellar Vascular Compromise

Healed
## Vascular Compromise

<table>
<thead>
<tr>
<th>Presentation Management</th>
<th>Arterial Occlusion</th>
<th>Venous Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop injection, attempt aspiration</td>
<td>Immediate or early, blanching, severe pain</td>
<td>Delayed, dull pain, dark discoloration</td>
</tr>
<tr>
<td>Massage</td>
<td>Massage</td>
<td>Massage</td>
</tr>
<tr>
<td>Warm compresses</td>
<td>Warm compresses</td>
<td>Warm compresses</td>
</tr>
<tr>
<td>2% nitroglycerin paste*</td>
<td>2% nitroglycerin paste*</td>
<td>2% nitroglycerin paste*</td>
</tr>
<tr>
<td>Injection of hyaluronidase (if caused by HA product)</td>
<td>Injection of hyaluronidase (if caused by hyaluronic acid product)</td>
<td>Injection of hyaluronidase (if caused by hyaluronic acid product)</td>
</tr>
<tr>
<td>Antibiotic therapy (topical, parenteral, or both) in cases of skin breakdown</td>
<td>Antibiotic therapy (topical, parenteral, or both) in cases of skin breakdown</td>
<td>Antibiotic therapy (topical, parenteral, or both) in cases of skin breakdown</td>
</tr>
<tr>
<td>Conservative debridement</td>
<td>Conservative debridement</td>
<td>Conservative debridement</td>
</tr>
<tr>
<td>Frequent follow-up</td>
<td>Frequent follow-up</td>
<td>Frequent follow-up</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Arterial Occlusion</th>
<th>Venous Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent</td>
<td>Smallest possible needle</td>
<td>Informed consent</td>
</tr>
<tr>
<td>Smallest possible needle</td>
<td>Smallest possible volume injected</td>
<td>Smallest possible needle</td>
</tr>
<tr>
<td>Smallest possible volume injected</td>
<td>Proper plane of injection</td>
<td>Smallest possible volume injected</td>
</tr>
<tr>
<td>Proper plane of injection</td>
<td></td>
<td>Proper plane of injection</td>
</tr>
</tbody>
</table>
Early Onset Complications

- Temporary nodules
- Persistent nodules
  - Non inflammatory
  - Inflammatory
    - Fluctuant vs nonfluctuant
    - Treat as infection
- Angioedema
- Persistent nodules
  - Non inflammatory
  - Inflammatory
    - Fluctuant vs nonfluctuant
    - Treat as infection
- May develop into chronic problem
  - Abscess, tissue loss
- Persistent malar swelling
Case Example 1

42 year old female

- HA (Restylane) injection for acne scars
- 3 hours later - white patch over injection site
- What do you do?
Case Example 1

42 year old female

- HA (Restylane) injection for acne scars
- 3 hours later - white patch over injection site
- What do you do?
  - Nitropaste
  - Warm compressed
  - Hyaluronidase

_Immediate blanching upon injection or delayed reticulated duskiness_ after injection can identify impending necrosis
42 year old female

- HA (Restylane) injection for acne scars
- 3 hours later - white patch over injection site
- 4 days later - skin slough
- Now what?
Case Example 1

42 year old female

- HA (Restylane) injection for acne scars
- 3 hours later - white patch over injection site
- 4 days later - skin slough
- Conservative skin care
  + Hydroquinone

2 years later
46 year old female

- Multiple HA* injections to lower eyelids over 3 years
- 1 month later developed periorbital swelling
- Allergy testing negative
- What now?

* Restylane & Juvederm
Case Example 2

46 year old female

- Multiple HA* injections to lower eyelids over 3 years
- 1 month later developed periorbital swelling
- Allergy testing negative
- What now? **15 units Hyaluronidase per lower lid**

* Restylane & Juvederm

4 days later
Persistent HA

Restylane persisting in lower eyelids for 5 years

Steven H Dayan, MD, FACS,¹,²,³,⁴ John P Arkins, BS,⁴ & Michael Somenek, MD²

After 5 years, fullness resolved 2 weeks after 60U hyaluronidase injected per side
HA Migration

- 3 patients with tear trough injections resulting in inferior migration years later
- Resolved with hyaluronidase
Lessons Learned from **Infraorbital** Filler Injections

- Volume replacement is challenging
- Higher potential for complications
- Eyelid skin is unforgiving (produces lumps & bumps)
- Superficial injections produce persistent fullness
- Careful injection technique (small amounts deep)
- Variable longevity in this location
- **Unpredictable edema**
67 year old female

- 1 vial (in 5cc) PLLA (Sculptra) injected
- Palpable nodules 10 months later
- What now?
Case Example 3

67 year old female

- 1 vial (in 5cc) PLLA (Sculptra) injected
- Palpable nodules 10 months later
- Steroid injection → No Effect
Case Example 3

67 year old female

- 1 vial (in 5cc) PLLA (Sculptra) injected
- Palpable nodules 10 months later
- Steroid injection ➔ No Effect ➔ Excision

Birefringent foreign material with surrounding inflammation
Case Example 3

Lessons Learned from PLLA Injections

• Use higher dilution (8-10cc per vial)
• Dilute 3-5 days in advance
• Inject in deep plane
• Subperiosteal periorbital injection
• Frequent massage
Sculptra Nodules

- Inject saline
- 5-FU
- Kenalog
Case Example 4

64 year old female

- Multiple HA injections in NLF
- What is this?
Case Example 4

64 year old female

- Multiple HA injections in NLF
- What is this? **Tyndall Effect** (Blue discoloration)
Case Example 4

64 year old female

- Multiple HA injections in NLF
- How to treat?
Case Example 4

64 year old female

• Multiple HA injections in NLF
• How to treat? 15 units Hyaluronidase
Lessons Learned from HA Injections

• Superficial injections can be visible
• Small volume injections, evaluate & re-inject if needed
• Hyaluronidase
  – 10 to 30 units (4 to 7 days to effect)
  – Local skin reactions common
    • Amphadase (bovine - skin test)
    • Hylenex (r-human)
    • Vitrase (ovine - skin test)
Case Example 5

51 year old female

- Pain, redness & swelling 2 weeks after HA injection
- Firm without fluctuance
- Treatment?
Case Example 5

51 year old female

- Pain, redness & swelling 2 weeks after HA injection
- Firm without fluctuance
- Cellulitis, no abscess
  - Antibiotics x 6 weeks
  - Minocycline + clarithromycin
Lessons Learned from Infections after HA Injections

- Sterile skin prep before injection
  - Remove make up
- Culture fluctuant nodules before antibiotics
- Steroids not useful, prolong infection
- Consider atypical mycobacteria & biofilm if infection occurs weeks after injection
  - Multiple antibiotic therapies
  - Enzymatic removal of biofilms controversial
    - Biofilm dissolution macrophage migration & antibiotic penetration versus
    - Bacterial spread
Granulomas vs Infections

• Resorbable fillers
  – Low incidence of long-lasting or late complications

• Partially or completely nonresorbable fillers
  – More anaerobic infections & granuloma reactions
  – Harder to treat

• Bacterial infection tissue swelling
  – Edema & cellular foreign-body response

• Micro particle filler swelling
  – Foreign body granuloma

Granuloma
Granulomas vs Infections

- **Infection**
  - Progress slowly
  - Anaerobic growth conditions
  - Symptoms 1 to 2 weeks after injection

- **Granuloma**
  - No detectable bacteria
  - May appear years after injection
  - Associated with microparticles fillers
Long Lasting Low Grade Infections

- Culture negative nodules
- Mistaken for foreign-body granulomas
- Bacteria in biofilm
- Cysts on US
Noninvasive therapeutic options

- Aspiration
  - Rarely works after a few months
- Excision
  - Scars & disfigurement
- Antibiotics
  - Effective only before biofilm develops
- Steroids
  - Temporary effect, rebound, skin atrophy & telangiectasias
- 5-Fluorouracil
  - Temporary effect & rebound
New Concepts on Filler Problems

Many problems assumed to be foreign body granulomas or allergic reactions on the basis of negative bacterial cultures are now thought to be due to biofilms

(Wiest, 2009)

Biofilms are almost impossible to culture using current standard culture technology and may be treated incorrectly with steroids injections, instead of 2 or 3 antibiotics

(Christensen, 2009)
Biofilms

- Aggregate of microorganisms adherent to each other or a surface
- Embedded in a self-produced matrix of extracellular polymeric substance
- Cells in a biofilm are physiologically distinct from planktonic cells
- Biofilm growth mode causes large shift in gene regulation
- Increased resistance to antibiotics & detergents
Biofilm Formation & Cycle

- Initial Attachment
- Irreversible Attachment
- Maturation I
- Maturation II
- Dispersion
Biofilm Infection Challenges

- Increased antibiotic resistance (1000x drug needed)
- Leucocytes trapped & made ineffective
- Chemical communication promotes bacterial cooperation
- Dormant (persister) cells have decreased metabolism
  - Difficult to culture
  - Resistant to antibiotics
- Clinical failure to recognize infections
- **RESULT:** Low-grade smoldering infection
  - Low host response
  - High antibiotic resistance
  - Low possibility of positive culture
Biofim Detection

• Biofilm detection requires fluorescent DNA stains or other chemical reactions
• May need 4 to 6 weeks on specific agar plates
Bacteria in Gel

H&E Stain

Gram Stain

PNA Probe

Bjarnsholt 2009
Fillers Susceptible to Biofilm Complications

**Combination Gels** (more likely)
- Collagen–PMMA suspensions (Artecoll)
- HA–PMMA suspensions (Dermalive, Dermadeep, Dermatech)
- Bioplastique (silicone in polyvinylpyrrolidone)
- Evolution (polyacrylamide-co-DADMA)
- Bio-Alcamid (polyalkylmide)
- Outline (procollagen)

**Homogenous Products** (less likely)
- Radiesse
- Silicone
- Polyacrylamides
Biofilm 2 Week Window

- 2-week period after implant placement when bacterial contamination can occur and develop a biofilm
- Timeline documented in orthopedic implants & other solid foreign body implanted material
- Avoid needle injections over the implant during the 2 weeks
- Dental procedures, facial trauma, or facial infections can introduce bacteria and produce biofilm
Lump After Filler Injection

Non painful
Non inflammatory
- Reassure if HA
- Watch
- Massage
  (Evaluate your technique & amount injected)

Painful or Inflammatory
- Immediate or Early Onset (< 1 year)
  - Oral Antibiotic: 2 - 6 weeks
  - If fluctuant: I&D + Cx*
  - Hyaluronidase (if HA filler)
  - No steroid injections

- Late Onset (> 1 year)
  - Particulate Filler
  - Assume Biofilm Activation
  - Multiple antibiotic: > 6 weeks
  - I&D + Cx*
  - Consider steroid injection (on Abx)
  - Excise or debride if possible
Antibiotic Treatment

Most Early Infections
• Clarithromycin 500 mg BID x 6 weeks
• Minocycline 100mg BID x 6 weeks

Recurrent infections suggest active biofilm
• Filler & biofilm must be removed/excised
Laser Treatment of Filler Lesions

- **Infectious lesions**
  - 532 nm lithium triborate laser
  - Removal of infected gel & pus

- **Granulomas**
  - 808 nm diode laser (intralesional technique)
  - Melt & liquefied then granuloma
  - Facilitates evacuation

- **Thin laser beam**
  - Controlled tissue

- **20 patients had reduction or complete resolution**
  - Resolution increased with repeated treatments
  - All had prior antibiotics & steroids without success

*Cassuto 2009*
Laser Treatment of Filler Lesions

- Cystic lumps 3 months after HA & dextranomer microsphere injections
- 6 weeks antibiotics & steroids no resolution
- Multiple 532 nm lithium triborate laser treatments
Laser Treatment of Filler Lesions

- Granulomas after Dermalive* & Aquamid**
- 808 nm diode laser treatment
- Drill holes for evacuation

* HA + acrylic hydrogel
** Polyacrylamide

Cassuto 2009
Unintentional Injection of Soft Tissue Filler into Blood Vessels in the Face: FDA Safety Communication
Signs & Symptoms of Intraarterial Injection

• Skin
  – Pain
  – Nausea
  – Skin blanching
  – Slow capillary refill
  – Demarcation

• Eye
  – Vision loss/blindness

• Stroke
  – “FAST”: facial drooping, arm weakness, speech impediment, time (act fast!)
# Progression of Skin Changes

<table>
<thead>
<tr>
<th>Findings</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blanching</td>
<td>Seconds</td>
</tr>
<tr>
<td>Reactive hyperemia or livedo pattern</td>
<td>Minutes up to 10 minutes</td>
</tr>
<tr>
<td>Blue-black discoloration</td>
<td>10 minutes to hours</td>
</tr>
<tr>
<td>Blister/bullae formation</td>
<td>Hours to days</td>
</tr>
<tr>
<td>Skin breakdown, ulceration, slough</td>
<td>Days to weeks</td>
</tr>
</tbody>
</table>

Low Volume Injection & Arterial Occlusion

High Injection Pressure & Retrograde Propagation

Avoid Arterial Injection & Propagation

- Withdraw before injection
- Avoid deep injection near named vessels
- Low pressure injection
- Avoiding injecting excess volume in one area
- Blunt cannulas
- Small bore
- Inject slowly in small aliquots
- Avoid injection in previously traumatized areas
- **Stop injection if complaints of pain/vision loss**

Crash Kit

- Warm compress
- Nitropaste
- Baby ASA
- Supplemental O2
- HYALURONIDASE
  - 400U into subcutaneous area (2cc in a 3cc syringe with 0.2cc plain lidocaine 2%, 27 g-needle)
Hyaluronidase

Transarterial Degradation of Hyaluronic Acid Filler by Hyaluronidase

Claudio DeLorenzi, BA, MD, FRCS

Intravascular HA liquefied in cadaver arteries & veins after 4 hours
Hyaluronidase works for
Juvederm
- Ultra & Ultra Plus
- Voluma & Volbella
Restylane
- Lyft & Silk
Belotero

Always have Hylenex available when doing HA injections
Filler Emergencies

• Soft tissue intravascular occlusion
• Stroke
  – Standard emergency stroke protocol
• Vision loss/blindness
  – Emergency ophthalmology consult
  – Retrobulbar hyluronidase injection
Retrobulbar Injection Technique

- Local anesthesia into lower eyelid over inferotemporal orbit
- Blunt, 25g cannula advanced in inferotemporal quadrant of orbit for 1 inch
  - Inferior and lateral to optic nerve
- 2 to 4cc hyaluronidase

Retrobulbar Injection Technique
Complications
Use Informed Consent Forms!
Filler Complications

• All fillers have potential complications
• Long lasting
  – More persistent
  – More difficult to treat
• Complications due to technique vs material
  – Learn technique on temporary fillers
  – Experience decreases technique complications
Recommendations

• Know the filler material you are using
• Start with temporary & reversible products
  – Hyaluronic acids
• Use sterile techniques
• Limit amount injected & areas treated
  – Easier to add than to take away
• Deal with inflammatory nodules
• Know the regulatory issues
Regulatory Issues
Fillers & the Law

- Product purchase source
- Non-FDA approved fillers
- Patient supplied fillers
- Off label filler use
- Reimporting FDA approved fillers
- Physician vs non-physician filler injector
- Non-clinical treatment settings
5 Docs Plead Guilty in Bogus Botox Rap; Stems From Toxin Research International Case

By Jim Edwards | Aug 14, 2009

Five prominent New York State doctors pled guilty this week to injecting patients with an unapproved version of Botox, and not telling those patients they weren’t getting the real thing. They face a possible year in prison and a $100,000 fine on a misdemeanor misbranded drugs charge.

The doctors bought the Botox from Toxin Research International in Arizona. The doctors maintain they thought it was the real thing, and no patients were injured.

The president of Toxin Research International is currently serving nine years in prison for fraudulently selling misbranded Botox on the web.

The case is a warning to doctors: get your supplies through established channels, not the secondary market.

These weren’t sleazy docs operating out of strip malls. Their resumes read like pillars of the community.
Non FDA Approved Fillers

Is it legal for a physician to obtain and use a product from outside of the United States that is **not approved by the FDA**?

- An individual who enters the country with a non-approved injectable filler could be sanctioned by the FDA
- A physician who orders a non-approved injectable filler through a non-US mail-order pharmacy could be sanctioned by the FDA
- State medical board involvement if any patient complaints result
- Exceptions for investigators working under FDA-approved studies
If a patient brings a non-approved drug or device to a physician, is it legal to treat the patient using this drug or device?

- Federal law prohibits such conduct
- Risk of significant liability exposure, invalidation of professional liability insurance coverage, criminal penalties and action by regulatory agencies
Off-Label Filler Use

What is the risk exposure of off-label use of approved drugs?
- Off-label use of FDA approved drugs does **not** carry the risks cited above, provided patient acceptance and understanding, and the treatment rationale, are well documented.
- For example, Botulinum toxin type A is a FDA-approved product for use in the glabellar area. Use of the product in other areas is legal and a clinical decision.

Can a physician advertise non-approved or off-label use?
- It is illegal to commercially advertise any non-approved or off-label use; only FDA-approved uses may be commercially advertised.

ASPS & ASAPS 2006
Reimported Fillers

Is it legal for a physician to purchase and use an FDA approved drug/product that is reimported from foreign sources?

• The act of importing drugs manufactured or approved in the U.S. and approved by the FDA is called “reimportation”…which remains illegal and dangerous

• Currently, only manufacturers are allowed to reimport their own drugs
Non-Physician Filler Administration

What level of training or licensure is required to administer injectables or fillers?

- Injections may be administered by a licensed professional nurse or physician assistant as determined by the supervising physician & local and state professional practice regulations
- Physician’s responsibility to ensure the non-physician possess proper education and training

What are the legal requirements for physician supervision of non-physician personnel who administer injectables and fillers?

- Supervisory regulations vary from state to state
- Physician of record is ultimately responsible
Non-Clinical Treatment Settings

- **Administration of injectables & fillers outside a clinical setting**
- **Concern about non-clinical sites where treatments offered**
  - Shopping malls, private homes, office parties, and group social gatherings
- **Inappropriate for several reasons:**
  - Inadequate patient selection
  - Possible peer pressure for an individual to consent to treatment
  - Providers who are not trained or qualified to treat or deal with complications
  - Lack of control over dosage and inadequate post-treatment supervision
  - Alcohol influencing decision making
  - Dealing with adverse event

Update In Process
PMMA Filler for Treating Acne Scars

Karol A Gutowski, MD, FACS
Acne Scar Treatment Options

- Fillers (HA, PLLA)
- Laser resurfacing
- Chemical peels
- Topical treatments
- Dermabrasion
- Subcision
- Excision
Bellafill Mechanism of Action

- Initial volumization (bovine collagen)
- Secondary autologous collagen stimulation (PMMA)
Time Line

6 to 8 weeks to final result

- Monocytes infiltrate injected area
- Capillaries and connective tissue develop
- Density and volume of collagen fibers and fibroblasts increases

Day 3:
- Monocytes differentiate into fibroblasts; fine fibrous capsule develops

Day 9:
- Collagen fibers detected

2 weeks:

3 weeks:

2 months:

4 months:
- Vascularization complete
Update on Duration of Effect

Post Marketing Study

• 145 patients followed for 5 years
• 5 year 90% patient & investigator satisfaction
Update on Duration of Effect

5 Year Safety Trial

• 1008 patients followed for 5 years
• 87% retention
• 94% “somewhat” to “very satisfied”
Atrophic Acne Scars

Rolling scars improved with skin traction

Bellafill FDA Approved for Acne Scars
Scars Improved with Traction
## Acne Scar Assessment

<table>
<thead>
<tr>
<th>Category</th>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal</td>
<td>1</td>
<td>Depth up to .5 mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Visibility = Perceptible with tangential lighting</td>
</tr>
<tr>
<td>Mild</td>
<td>2</td>
<td>Depth &gt; .5 mm to &lt;1.5 mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Visibility = Moderately detectable with tangential lighting</td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
<td>Depth ≥ 1.5 mm to &lt;2.5 mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Visibility = Easily seen with tangential lighting</td>
</tr>
<tr>
<td>Severe</td>
<td>4</td>
<td>Depth ≥ 2.5 mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Visibility = Substantial shadowing with tangential lighting</td>
</tr>
</tbody>
</table>

Study: Grade 3 & 4 rolling acne scars
Patient Selection

Study: Grade 3 & 4 rolling acne scars
ERAS Trial

- Double blinded RCT at 10 sites
- Mean age 45 yo, 2/3 female
- Average 0.1 cc per scar
  - 1.0 cc first treatment
  - 0.7 cc touch up treatment
- 80% touch up treatment
- Effectiveness: At least 50% of scars improved by \( \geq 2 \) points (4 point scale) at 1 year

Full Analysis Population (n=147)

FA Bellafill® (n=97)

FA Control (n=50)

Completed M6 (n=87; 89.7%)

Completed M6 (n=46; 92.0%)
ERAS Trial: Investigator Evaluation

Evaluated by Blinded Investigator

Responders, %

- W4: 0.3082, 26.9
- W8: 0.0078, 40.9
- M3: 0.0077, 35.7
- M6: 0.0005, 32.6
- M9: 61.5
- M12: 70.7

P =

- W4: 0.0078
- W8: 0.0077
- M3: 0.0077
- M6: 0.0005
- M9: 0.0005
- M12: 0.0005

Responder = ≥ 2-point improvement in ≥ 50% of treated scars
ERAS Trial: Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events, n (%)</th>
<th>PMMA-collagen n = 143*</th>
<th>Control n = 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reaction—lumpiness and papule (3 mild, 1 moderate)</td>
<td>4 (2.8%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>injection site bruising (2 mild, 1 severe)</td>
<td>3 (2.1%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Injection site pain (mild)</td>
<td>3 (2.1%)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Reported in > 1% of subjects
Results

2 syringes over 2 treatment sessions total for both cheeks

Only circled scars were treated
Results

Baseline

Month 6

Month 12

2 syringes over 2 treatment sessions total for both cheeks

Only circled scars were treated
Results

2.5 syringes for each cheek

Only circled scars were treated
Results

2.5 syringes for each cheek

Only circled scars were treated
Results

Only circled scars were treated
Only circled scars were treated
Results

0.4 cc for these 3 sites

Only circled scars were treated
Results

0.4 cc for these 3 sites

Only circled scars were treated
A double-blind, randomized, multicenter, controlled trial of suspended polymethylmethacrylate microspheres for the correction of atrophic facial acne scars

Jwala Karnik, MD,* Leslie Baumann, MD,† Suzanne Bruce, MD,‡ Valerie Callender, MD,§,‖
Steven Cohen, MD,¶ Pear Grimes, MD,¶ John Joseph, MD,¶ Ava Shamban, MD,¶ James Spencer, MD,¶
Ruth Tedaldi, MD,¶ William Philip Werschler, MD,¶ and Stacy R. Smith, MD¶
Santa Barbara, San Diego, Beverly Hills, and Los Angeles, California; Miami, Florida; Houston, Texas;
Glen Dale, Maryland; Washington, District of Columbia; New York, New York;
Wellesley, Massachusetts; and Seattle, Washington

Blinded Physician Evaluation

Patient GAIS Evaluation
Personal Experience

• Challenges with photo documentation
  – VISIA not useful

• Patient expectations
  – Moderate to severe rolling scars

• Multimodality approach
  – Micro-needling
  – Chemical peels
  – Fractional CO2 laser
Injectable Soft Tissue Fillers: Practical Applications

Karol A Gutowski, MD, FACS