Jan Willem Cohen Tervaert  
Professor  
Director, division of Rheumatology  
University of Alberta, Edmonton, Canada
## Faculty Disclosure

<table>
<thead>
<tr>
<th>Company</th>
<th>Nature of Affiliation</th>
</tr>
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<tbody>
<tr>
<td># InflaRx</td>
<td>• Chairman DSB (Phase II trials anti-inflammatory drugs)</td>
</tr>
<tr>
<td></td>
<td>• Company ABC, Company XYZ</td>
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### Off-Label Product Usage

# None
Organ Transplantation

- Since 1904 many attempts; failed due to rejection
- 1954: Murray successful kidney Tx (kidney from identical twin)
- 1961: use of azathioprine to suppress rejection
- 1978 introduction ciclosporin; increase of 1 yrs survival of kidney Tx from 60% to 90%
- Bone marrow, Lung, Liver, Heart Tx etc.
Medical device implantation

- Since 1898 paraffin, ivory, glass, steel balls, ground rubber, animal cartilage, foam sponges, silicone injections tried: no cosmetic success; caused breast illness
- 1962 Cronin and Gerow: silicone breast implants
  
  ..........silicones are inert
- 1964 saline breast implants
- 1967 implants not inert
- 1982 patients may develop autoimmune diseases
History silicone breast implants

- **1962**: first silicone breast implants (SBI) Cronin-Gerow Implant
- **1963-1964**: first case-reports silicone related complaints and auto-immune diseases
- **1992 - 2006**: FDA's voluntary moratorium
- **2009 - 2010**: PIP affaire
- **2011**: FDA safety warning on ALCL
- **2015**: Silimed affaire
- **2019**: France ban on textured Allergan implants
Silicone Breast Implants (SBI)

- 2-4% of women have SBI (USA and the Netherlands)
  70% cosmetic
  30% reconstructive

- Worldwide: 10 million SBI
Polydimethylsiloxane (PDMS) belongs to a group of polymeric organosilicon compounds that are commonly referred to as silicones.

PDMS is the most widely used silicon-based organic polymer, and is particularly known for its unusual rheological (or flow) properties.

PDMS is optically clear, and, in general, inert, and non-toxic
Capsular formation after breast augmentation

- Occurs in > 50% of women (Caldiero et al. 2018)
- More often after implantation of "smooth" implants; less often after implantation of "textured" implants

Smooth implants nearly never used in the Netherlands
In both animals and humans, silicone breast implants are NOT inert in vivo.

In vitro stimulation with silicones: no T cell activation.

Ex vivo analysis of the capsule: activated T cells.

FACS analysis of the T cells from the capsule: predominance of Th1/Th17 cells and failing Tregs.
Immediatedly after implantation, proteins and phagocytes are attracted; this process is histamine mediated.

*Studies by Tang et al.*
Implantation of SBI is associated with activation of the immune system

- Patients develop local complications (capsule formation)
- Patients develop symptoms such as flu-like disease, fatigue, myalgias (“breast implant illness” “human adjuvant disease” “ASIA”)
- The immune system is not able to recover from the chronic stimulation: immune deficiency resulting in frequent infections
- The immune system makes “mistakes”: auto-immune diseases, allergy and monoclonal proliferation (non-Hodgkin lymphoma such as ALCL)
Is it possible that local implantation in the breast causes systemic effects?

- SBI may rupture
  More often complaints after SBI rupture
  
  *Brown SL et al. J Rheumatol 2001*

- SBI may bleed
  
  *Snow ball on ultrasound*
  *Means silicones*
Estimated implant ages for probabilities of ruptured or indeterminate implants.

**Newer SBI implants**

- Allergan 2 yrs: 0.5%
- Mentor 3 years: 1%

**Older SBI implants**

Corroneos et al 2019

Brown SL et al. AJR 2000;175:1057-1064

Figures for gel bleed are not available
Autoinflammatory/autoimmunity syndrome induced by adjuvants (Shoenfeld’s syndrome): a new disease

Major Criteria:
- Exposure to an external stimuli (Infection, vaccine, silicone, adjuvant) prior to clinical manifestations.
- The appearance of 'typical' clinical manifestations:
  - Myalgia, Myositis or muscle weakness
  - Arthralgia and/or arthritis
  - Chronic fatigue, un-refreshing sleep or sleep disturbances
  - Neurological manifestations (especially associated with demyelination)
  - Cognitive impairment, memory loss
  - Pyrexia, dry mouth
- Removal of inciting agent induces improvement
- Typical biopsy of involved organs

Minor Criteria:
- The appearance of autoantibodies or antibodies directed at the suspected adjuvant
- Other clinical manifestations (i.e. irritable bowel syn.)
- Specific HLA (i.e. HLA DRB1, HLA DQB1)
- Evolvement of an autoimmune disease (i.e. MS, SSc)
ASIA symptoms (I)

- Always tired
- Already tired when waking up
- Post exertional malaise
- Wide-spread pain
- Myalgias and arthralgias
- Cognitive impairment
ASIA symptoms (II)

- Pyrexia
- Sicca symptoms
- Stroke or MS-like symptoms
- Raynaud and Livedo reticularis
- Lymphadenopathy
COULD YOU PLEASE TELL ME YOUR COMPLAINTS?

HERE IS THE LIST DOCTOR!!!
100 patients evaluated in Maastricht (NL) in 2014 compared with 100 patients evaluated at Baylor College (Houston) between 1985 - 1992

<table>
<thead>
<tr>
<th>Symptom</th>
<th>1994</th>
<th>2014</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Myalgia, Myositis or muscle weakness</td>
<td>91</td>
<td>54</td>
<td>&lt; .001</td>
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<td>Arthralgia, and/or arthritis</td>
<td>81</td>
<td>91</td>
<td>.04</td>
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<tr>
<td>Chronic fatigue, un-refreshing sleep</td>
<td>95</td>
<td>98</td>
<td>.25</td>
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<tr>
<td>Neurological manifestations (especially associated with demyelination)</td>
<td>32</td>
<td>20</td>
<td>.05</td>
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<tr>
<td>Cognitive impairment, memory loss</td>
<td>81</td>
<td>78</td>
<td>.60</td>
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<tr>
<td>Pyrexia</td>
<td>52</td>
<td>64</td>
<td>.09</td>
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<tr>
<td>Dry eyes and/or dry mouth (sicca)</td>
<td>72</td>
<td>73</td>
<td>.87</td>
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</table>

75% of patients with SBI related ASIA: pre-existent allergies

Maijers et al. Neth J med 2013
• Almost 4300 females with silicone breast implants reported health issues on the World Wide Web

• Prevalence of ASIA is unknown!

• Select group of predisposed (?) women

No studies performed that assessed ASIA symptoms in SBI patients compared to controls.
SELECTED PATIENTS

143 SILICONE BREAST IMPLANT PATIENTS
• Operated between 1997 – 2004*
• Maastricht University Medical Center, Maastricht; St. Anna Hospital, Geldrop; Maxima Medical Center, Eindhoven → The Netherlands

94 HEALTHY CONTROLS
• Friends of the patients of group 1
• Age- and sex-matched
• Exclusion criteria: (history of) silicone breast implants and/or (history of) breast cancer.

139 SILICONE BREAST IMPLANT PATIENTS
• Previous reported health issues!
• Registered at a Dutch foundation for women with illness due to breast implants
• Matched for the period of breast implantation to group 1.

RESPONDED PATIENTS

INCLUDED N = 222

231 FEMALES

1  N = 79
2  N = 62
3  N = 81

In non-selected SBI patients 4 x more frequent ASIA compared to HC

Colaris M, Cohen Tervaert JW. unpublished

<table>
<thead>
<tr>
<th></th>
<th>Group 1 SBI patient (n=84)</th>
<th>Group 2 Negative controls (HC) (n=48)</th>
<th>Group 3 Positive controls (MKS) (n=86)</th>
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</thead>
<tbody>
<tr>
<td>Amount of ASIA symptoms</td>
<td>2.34 ± 1.5</td>
<td>1.8 ± 1.8</td>
<td>4.06 ± 1.5</td>
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<tr>
<td>ASIA (Tree 1)</td>
<td>44 (52%)</td>
<td>14 (29%)</td>
<td>67 (78%)</td>
</tr>
<tr>
<td>ASIA (tree 2)</td>
<td>19 (23%)</td>
<td>3 (6%)</td>
<td>46 (53%)</td>
</tr>
</tbody>
</table>

**Tree 1:** Arthralgia and/or myalgia AND fatigue/sleep disturbances

**Tree 2:** Arthralgia and/or myalgia AND fatigue/sleep disturbances and/or cognitive impairment AND pyrexia and/or sicca
Multiple lymph nodes of patient 1 were filled with large quantities of multinucleated giant histiocytes in presence of possible exogenous material, suggestive of silicone A-E.

- Figure A shows a 4 µm paraffin cut stained with Hematoxylin and Eosin.
- Figure B shows a 4 µm paraffin cut stained with the MORO, positive stained material is present inside the giant histiocytes.
- Figure C shows a 1 µm toluïdin blue stain where multiple giant histiocytes are seen in presence of multiple vacuoles.
- Figure D shows a higher magnification of the toluïdin blue stain where threadlike translucent material is present inside the vacuoles.
- Figure E shows a TEM micrographs of a vacuole with dens perivacuolar material.

Often material is clearly located inside a bloodvessel, this event can be found throughout all tissues (F).

Gel Bleed and Rupture of Silicone Breast Implants Investigated by Light-, Electron Microscopy and Energy Dispersive X-ray Analysis of Internal Organs and Nervous Tissue
Figure A shows toluidine blue of the **spinal cord** high cervical, clearly visible is a structure surrounded by collagen, same structures often are positive with MORO staining, reddish plaque is visible (B)

Figures D, E and G show the droplets * found in the thoracic spinal cord of patient 1

Figure C shows the toluidin blue stained epon section, no visible droplets are detectable

Figure E shows a TEM micrograph where it is nicely demonstrated that there are actually droplets present

Figure G shows a higher magnification of a TEM micrograph were it is clearly seen that the droplets actually are located inside a vacuole and are part of the tissue

EDX analysis is performed on these droplets, figure D shows a TEM micrograph of the EDX measuring points performed on the thoracic spinal cord of patient 1

Figure F demonstrates EDX analysis Point 1 on a droplet found inside vacuolated spaces (spectra 1) = 22211 Si-counts. Point 3 is on the surrounding tissue (spectra 3) = 195 Si-counts (H)

**Silicones present in many many organs**

*Courtesy of Dr. Kappel*
Silicone breast illness

Since 1962 different “names”:
- human adjuvant disease
- adjuvant breast disease
- silicone-related symptom complex
- siliconosis
- ASIA due to silicone implant incompatibility syndrome

Similarities with fibromyalgia

Differences:
1. more often severe sicca
2. more often immune-deficiency
3. more often MS-like symptoms and/or CVA/TIA

MORE OFTEN AUTO-IMMUNE DISEASES?
Foreign body implantation results in adjuvant activity

Babensee JE. 2008
Case Report (I)

- 39 year old woman
- 2006 breast implants; new implants in 2010
- Since 5 years intermittent fever and fatigue
- Joint pain and myalgias
- Sicca complaints
- Concentration problems
- “Alzheimer-light”
- Recent onset Raynaud

“Doctor please come quick! His fever has gone from medium rare to well done!”
Is the risk of an auto-immune disease in SBI patients increased?
What about animal studies?
No evidence of AIZ in several rat and/or mice models

BUT......

Silicone gel enhances AIZ in NZB but not in BALB/c mice

Long-term Silicone implantation on type II collagen induced arthritis in mice

Schaefer et al. ARD 1999
Biomaterials induce adjuvant activity

Babensee JE. Sem Immunol 2008

**Immature DCs:**
- Localized in peripheral tissues
- Efficient antigen capturing, internalization, and processing

**Mature DCs:**
- Localized to T cell area of lymph nodes
- Efficient antigen presentation, activation and proliferation of T cells
- Upregulation of MHC and costimulatory molecules
What about AIZ and other immunologic complications in our patients?

Clinical diagnoses in 32 patients with ASIA due to SIIS (n = 32)


- Median time between implantation and complaints: 10 years (2 - 24 years)
- 8 patients: Biopsy-proven siliconosis
- 2 patients: Non-Hodgkin Lymphoma
- 15 patients: immune deficiency
  (8 x CVID; 7 x IgG subclass deficiency)
- 17 patients: systemic AI disease
- 7 patients: organ specific AI disease
Autoimmune diseases in ASIA due to SIIS


- 6 patients systemic necrotizing vasculitis
- 6 patients CTDs:
  - 2 x APS; 2 x Sjogren; 1 x SSc; 1 x SLE
- 4 x granulomatous disease:
  - 3 x sarcoidosis; 1 x Crohn’s disease
- 1 x multiple sclerosis
- 4 x pernicious anemia
- 3 x hypothyreoidism
Large cohort:

Autoimmune diseases in 100 consecutive patients with SBI induced ASIA


- RA 4
- CTD 18
- Vasculitis 5
- Granulomatous disorders 3
- Other AID 7

Silicones in breast implants
NO INCREASED RISK ??
Silicones in breast implants
NO INCREASED RISK ???
Recent meta-analysis study


Nearly all previous studies: not adequately adjusted or not adjusted for potential confounders

Decreased risk for breast and endometrium cancer, increased risk for lung cancer

Increased risk for:
- RA (RR 1.38; CI, 1.06 - 1.80)
- SS (RR 2.92; CI, 1.01 - 8.47)

Associations mainly driven by self-reported disease

Conclusion: epidemiological studies inconclusive
Relative Risk for Sjogren Syndrome (RR 2.92; CI, 1.01 - 8.47)
TABLE 3

Coroneos, Christopher; MD, MSc; Selber, Jesse; MD, MPH; Offodile, Anaeze; II MD, MPH; Butler, Charles; Clemens, Mark

DOI: 10.1097/SLA.0000000000002990

<table>
<thead>
<tr>
<th>Condition</th>
<th>Manufacturer</th>
<th>Study Events</th>
<th>Study Event Rate (Per 10,000 Person Yr)</th>
<th>General Population Event Rate (Per 10,000 Person Yr)</th>
<th>SIR</th>
<th>SIR 95% CI</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Fibromyalgia</td>
<td>Allergan</td>
<td>9</td>
<td>1.8</td>
<td>112.8</td>
<td>0.02</td>
<td>0.01–0.03</td>
<td>&lt;0.001</td>
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<td>Rheumatoid arthritis</td>
<td>Allergan</td>
<td>4</td>
<td>0.8</td>
<td>112.8</td>
<td>0.25</td>
<td>0.22–0.28</td>
<td>&lt;0.001</td>
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<td>Rheumatoid arthritis</td>
<td>Mentor</td>
<td>307</td>
<td>28.4</td>
<td>5.4</td>
<td>0.04</td>
<td>0.04–0.15</td>
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<td>Scleroderma</td>
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<td>32.2</td>
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<td>5.96</td>
<td>5.35–6.62</td>
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<td>4.2</td>
<td>5.4</td>
<td>7.00</td>
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<td>6.24–10.44</td>
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<td>Cancer</td>
<td>Allergan</td>
<td>3</td>
<td>0.6</td>
<td>5.4</td>
<td>0.11</td>
<td>0.02–0.32</td>
<td>&lt;0.001</td>
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<td>Cancer</td>
<td>Mentor</td>
<td>66</td>
<td>6.0</td>
<td>5.4</td>
<td>1.11</td>
<td>0.86–1.41</td>
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<td>Breast cancer</td>
<td>Mentor</td>
<td>80</td>
<td>16.0</td>
<td>41.3</td>
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<td>0.31–0.48</td>
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<td>Mentor</td>
<td>532</td>
<td>63.8</td>
<td>41.3</td>
<td>1.54</td>
<td>1.42–1.68</td>
<td>&lt;0.001</td>
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<td>116</td>
<td>13.9</td>
<td>12.5</td>
<td>1.11</td>
<td>0.92–1.33</td>
<td>0.26</td>
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<td>Mentor</td>
<td>5</td>
<td>0.6</td>
<td>5.2</td>
<td>0.12</td>
<td>0.04–0.27</td>
<td>&lt;0.001</td>
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<td>Brain cancer</td>
<td>Mentor</td>
<td>3</td>
<td>0.4</td>
<td>0.6</td>
<td>0.67</td>
<td>0.14–1.95</td>
<td>0.639</td>
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<td>Melanoma</td>
<td>Mentor</td>
<td>65</td>
<td>7.8</td>
<td>3.71</td>
<td>2.87–4.73</td>
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<td>Neurological disorder</td>
<td>Allergan</td>
<td>18</td>
<td>3.6</td>
<td>22.5</td>
<td>0.16</td>
<td>0.09–0.25</td>
<td>&lt;0.001</td>
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<td>394</td>
<td>35.8</td>
<td>22.5</td>
<td>1.59</td>
<td>1.44–1.76</td>
<td>&lt;0.001</td>
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<td>Multiple sclerosis</td>
<td>Mentor</td>
<td>47</td>
<td>4.3</td>
<td>2.5</td>
<td>1.72</td>
<td>1.26–2.29</td>
<td>&lt;0.001</td>
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<td>Mentor</td>
<td>17</td>
<td>1.5</td>
<td>0.8</td>
<td>1.88</td>
<td>1.09–3.00</td>
<td>0.018</td>
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*Allergan follow-up 2 years.
†Mentor follow-up 7 years.
24,651 SBI recipients and 98,604 matched SBIs free women
adjusted OR for AD 1.21, 95% CI 1.17-1.26

Figure 2. Adjusted* odds ratios (95% confidence interval) for auto-immune diseases among SBI recipients in comparison to SBI-free women in 3 different multivariate analysis

*Adjusted for: age; socio-economic status; birth place; smoking status; breast

Large recent study from Israel

_ Watad et al. 2018_
Multivariable Cox regression model: HR of 1.45 (95% CI, 1.21 - 1.73 for at least one AID
Vitamin D deficiency  IgG deficiency  Bacterial and viral infections

Smoking ?
Salt ?
Stress ?

Granulomatous inflammation  Adjuvant effect of silica  Metal allergy

AID
Case report II: Laboratory results

- ANA: pos 1: 80; SSA: pos; SSB neg
- Creat: 73; sed: no abnormalities
- ALAT:18; HCV: neg
- Cryoglobulin: negative
Silicone-induced ASIA: therapy?

- Non-invasive therapy:
  - symptomatic (e.g., pregabalin)
  - immuunsuppressive therapy (e.g., hydroxychloroquin)

- Invasive therapy
  Explantation:
  - Effectivity: 50-75%
  - Recent review 469 of 622 (75%) patients;
    in AID effective in only 16% without additional immunosuppressiv therapy

De Boer et al. Immunol Res 2017
Post-explantation Improvement

Patients in Overall ASIA-Cohort: 56% of 85 patients improve (N=48)

Patients without a well defined auto-immune disease (AID) 60% of 62 patients improve (N=37)

Patients with a well defined auto-immune disease (AID) 48% of 23 patients improve (N=11)
Case report

- Carbomer gel eyedrops
- Vitamin D suppletion
- Silicon-breast removal with capsulectomy

Case report

- Deterioration after surgery for which (temporarily) steroids were given
- Start doxycyclin maintenance therapy
- No fever anymore; 24 months follow-up
Conclusion

- Biomaterial implantation can result in systemic symptoms with signs of immune activation and/or recurrent infections as a result of immune deficiency.

- Patients with systemic symptoms often have pre-existent allergy, fibromyalgia and/or a pre-existent auto-immune disease.
Take Home Messages

- Silicone breast implants, mesh and mineral oil fillers may cause ASIA.
- In these patients more often immunodeficiency, severe allergies, auto-immune diseases and (possibly) also lymphomas.
- Explantation of the SBI results in 75% of cases in decrease of symptoms.
NOT SAFE
Acknowledgements

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Dept. of Plastic Surgery

Dr. Rita Kappel

Maastricht University
Thank you for your attention
Don`t go yet