

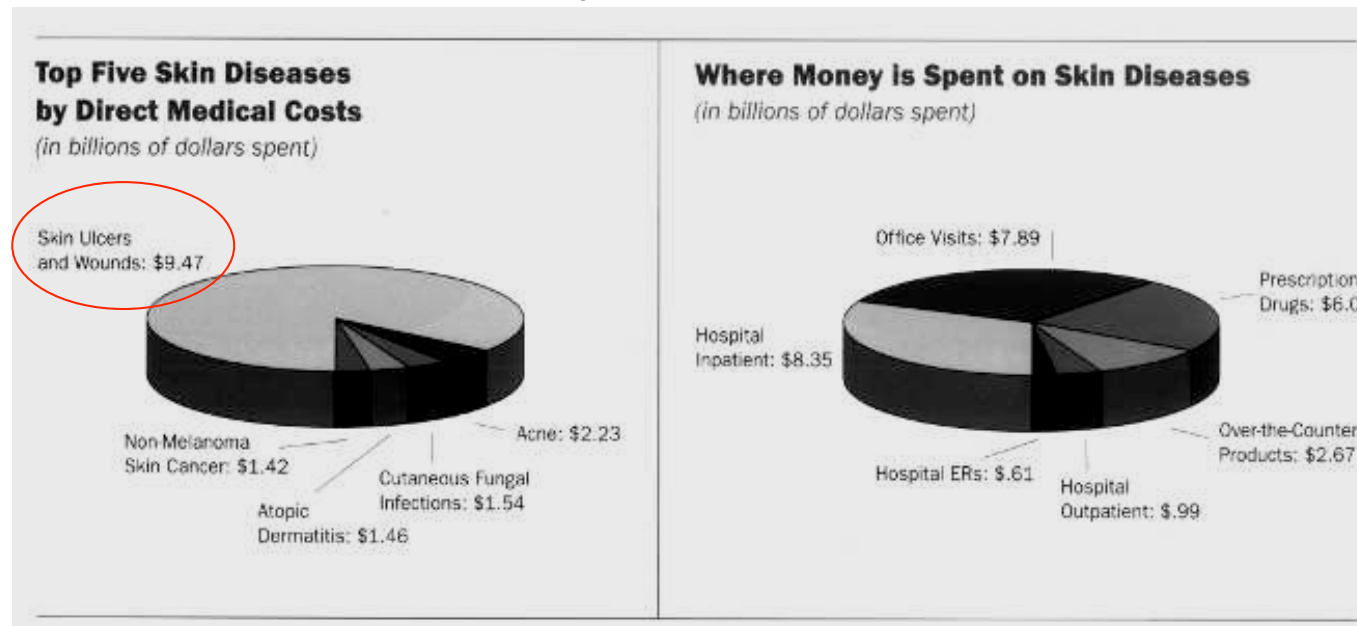


Update on Munich Plasma Project

G. Isbary and everybody listening right now

Chronic wounds are a major burden for the health system

- Prevalence ~ 1-2 % in German Population (> 1.000.000 patients)
- High costs for the community 1-2 % of annual health care budget*
- Venous ulcers require an average of 24 weeks to heal, 15% never heal, recurrence is found once or multiple times in 15-71% of cases** ***



American Academy of Dermatology Report 2005

*Etufugh CN, Phillips TJ. Venous ulcers. *Clin Dermatol* 2007; **25**: 121-30.

**Kurz et al. VEINES Task Force Report, *Int Angiol*. 1999;18(2):83-102.

***Heit et al. Venous thromboembolism epidemiology *Semin Thromb Hemost*. 2002;28(suppl 2):3-13

Infections and Resistance - Facts

- „Bacteria can become resistant to antibiotics“ warned Alexander Fleming, when he landed the Nobel prize in Medicine in 1945.
- European Antimicrobial Resistance Surveillance System (EARSS) 2007: Resistance is becoming a larger problem year after year (especially for *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia Coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*)
- Global Health Care Associations consider multiresistant germs like MRSA as a global threat*
- 19,5 % of all *Staph. aureus* detected in German hospitals are MRSA (EARSS 2008)
- Worrying is the raising resistance against so called reserve drugs within the last 6 years – e.g. Vancomycin (EARSS 2007)
- „Gold standard“ Vancomycin with failure rates of 23-52%!
- November 2008 launch of DART (Deutschen Antibiotika-Resistenzstrategie)

*Grundmann H, Aires-de-Sousa M, Boyce J et al. Emergence and resurgence of methicillin-resistant *Staphylococcus aureus* as a public-health threat. *Lancet* 2006; **368**: 874-85.

Worldwide prevalence of MRSA displayed by country (The Lancet 2006)

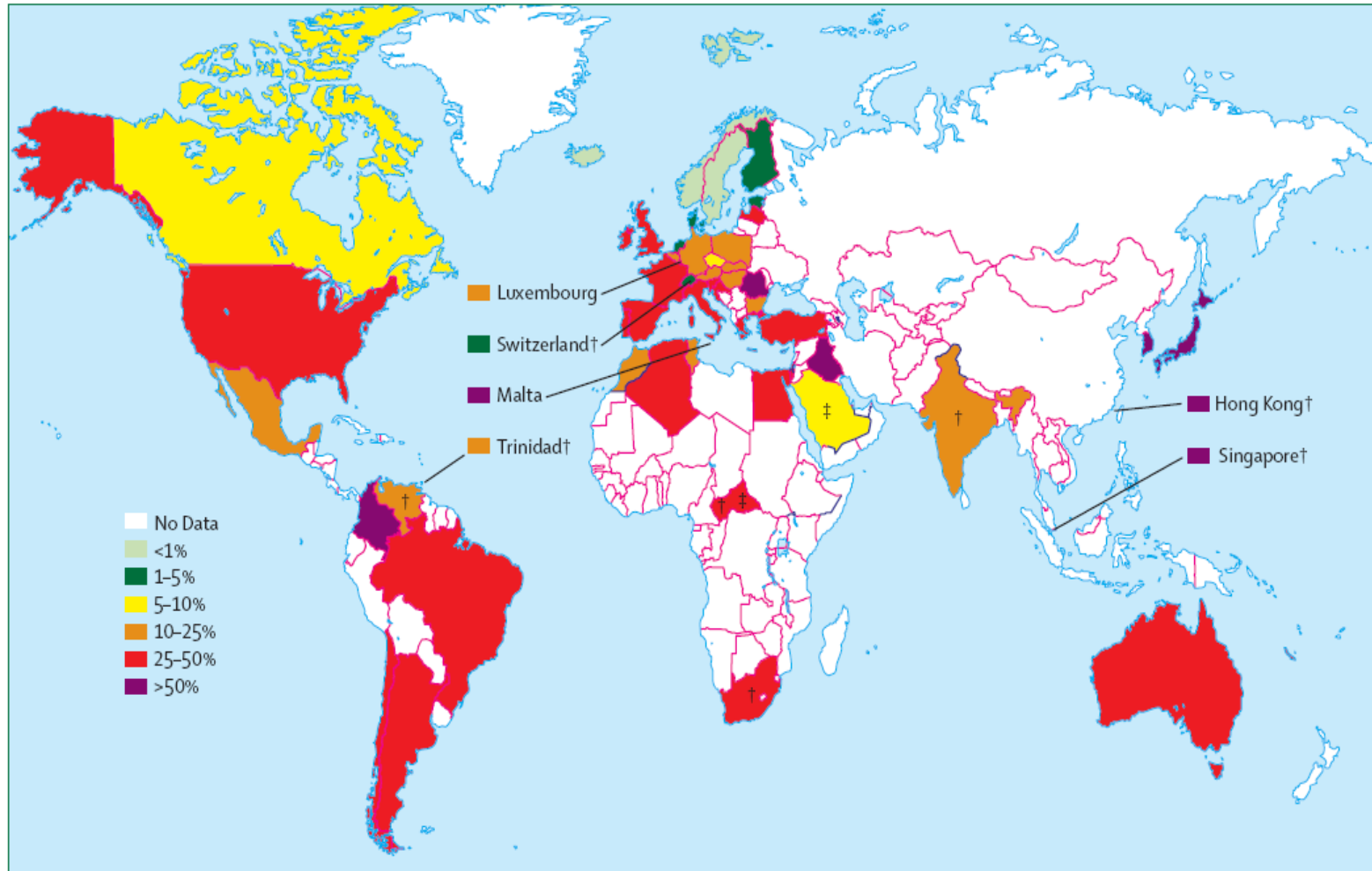


Figure 1: Worldwide prevalence of MRSA displayed by country*

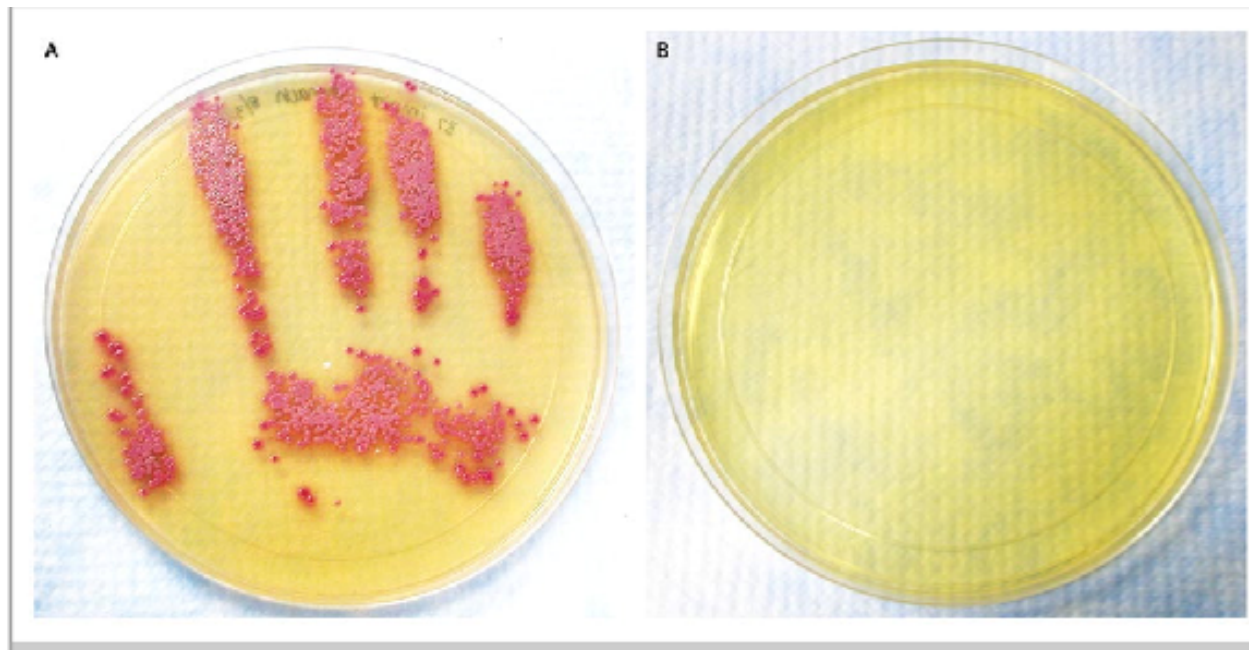
*All presented MRSA proportions are from peer-reviewed studies undertaken since 1998.³²⁷⁴⁻⁸⁵ Prevalence estimates for Morocco, Algeria, Tunisia, Egypt, Jordan, Lebanon, and Turkey are from the antimicrobial resistance in the Mediterranean region website⁸⁶ at www.slh.gov.mt/armed/earss.asp. Studies providing most recent estimate of the MRSA proportion taken into account. If more than one study reported over same period, study including different types of clinical isolates was preferred over studies including only one specific type of specimen. †=Prevalence estimates are based on a study that included only one hospital. ‡=Prevalence estimates are based on studies between 1993 and 1997.



The NEW ENGLAND
JOURNAL of MEDICINE

The Hands Give It Away

Curtis J. Donskey, M.D. and Brittany C. Eckstein, B.S.
N Engl J Med 2009; 360:e3 | January 15, 2009



The importance of hand hygiene to prevent the transfer of germs and resistance.

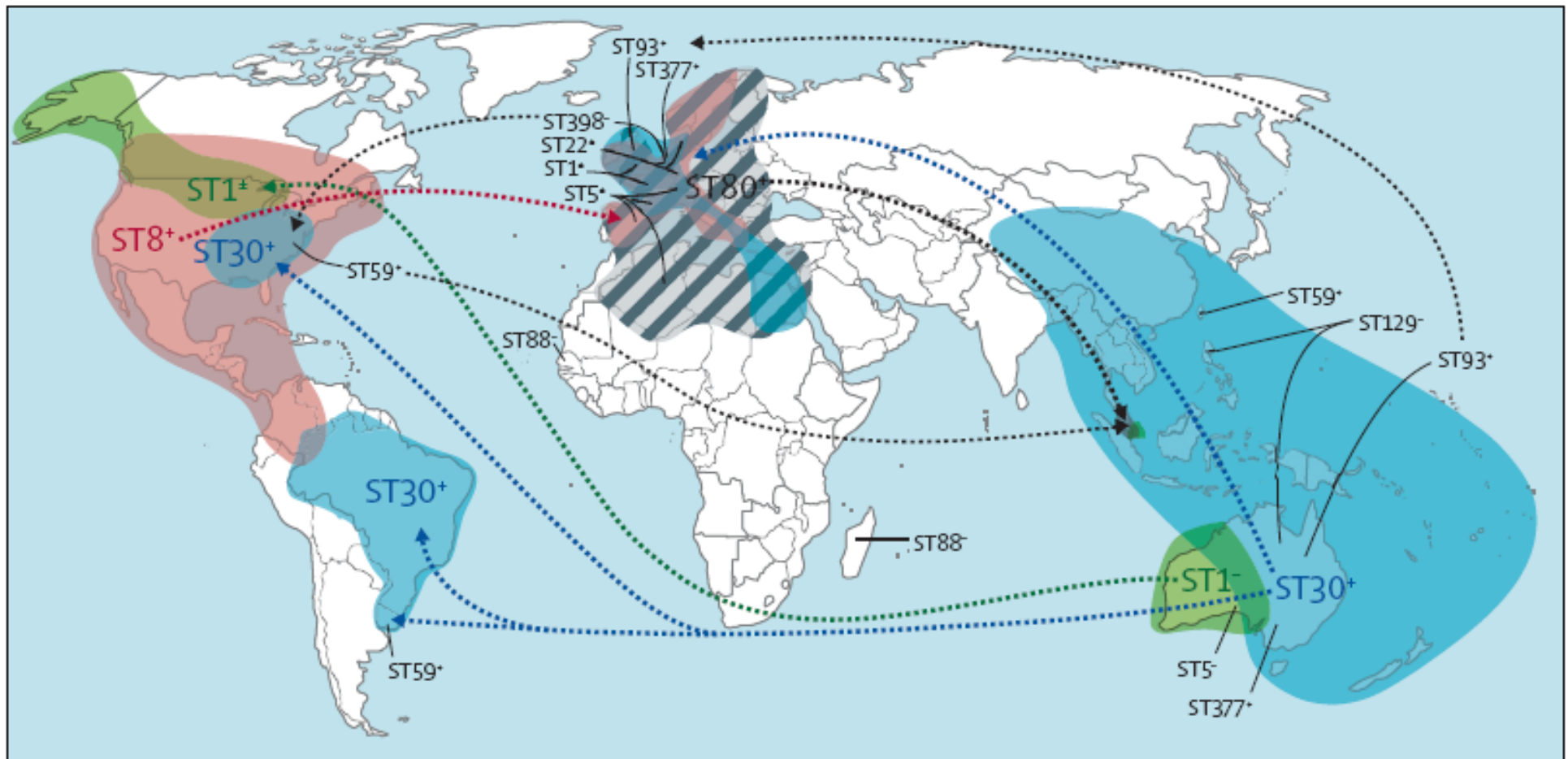


Figure 1: Global distribution of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) by multilocus sequence type (ST). Dotted lines indicate possible route of dissemination of the CA-MRSA strains. Estimates of the areas are shown in which infections with the main strains—ie, ST1 (green), ST8 (red), ST30 (blue), and ST80 (grey hatched)—have been reported. +=Panton-Valentine leukocidin (PVL)-positive strains. -=PVL-negative strains. ±=combination of PVL-positive and PVL-negative strains.

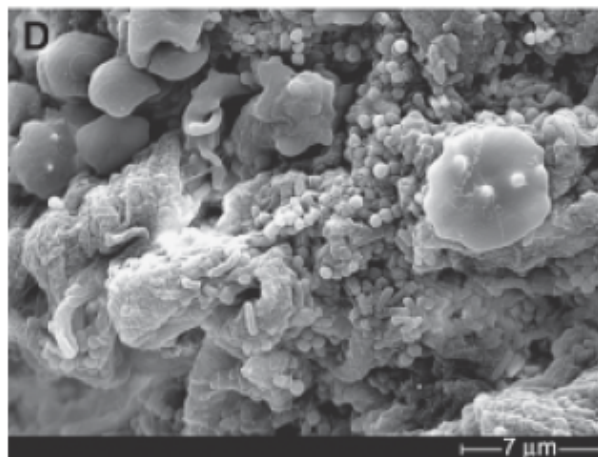
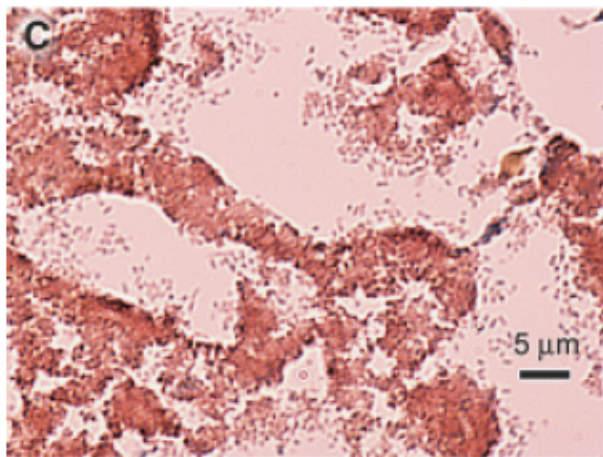
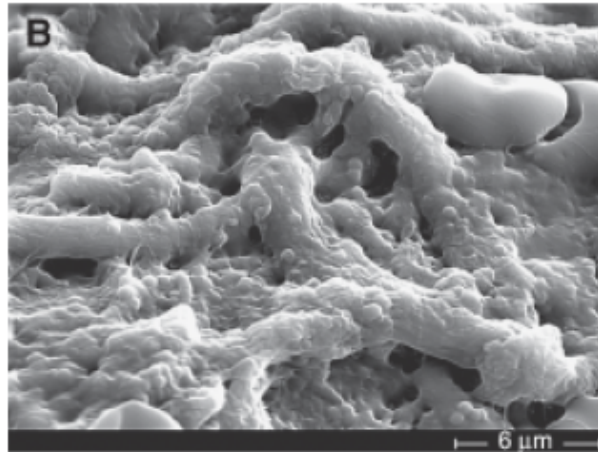
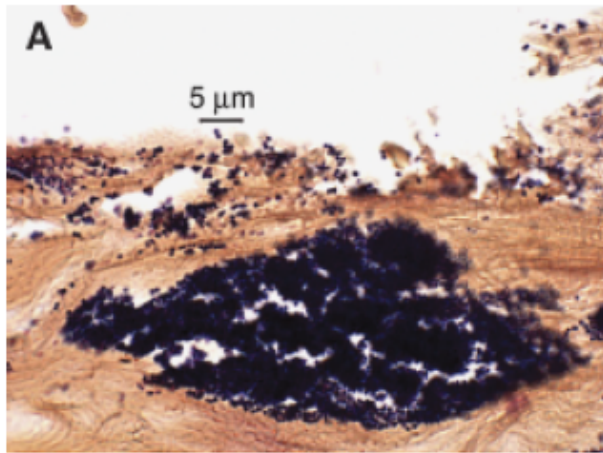


Figure 1. Microscopic images from chronic wounds. (A) Photomicrograph of a Gram-stained thin section from a pressure ulcer specimen showing a biofilm formed by Gram-positive cocci near the tissue surface. Gram-positive cocci were commonly observed in samples examined using light microscopy, which agreed with culture analysis that revealed the predominance of *Staphylococcus* and *Enterococcus*. (B) Scanning electron micrograph of pressure ulcer specimen showing a biofilm of coccoid bacterial cells colonizing collagen bundles within the wound. The bacterial cells are blanketed in extracellular polymeric substance, which had collapsed onto the cells during the dehydration steps of specimen preparation. (C) Photomicrograph of a Gram-stained thin section from a diabetic foot ulcer specimen showing a biofilm formed by Gram-negative rods near the tissue surface. (D) Scanning electron micrograph of pressure ulcer specimen showing bacteria of different morphotypes (rods and cocci) colonizing the wound within close proximity.

Infections and Resistance - Facts

- 1999 – 2005 rate of Staphylococcus aureus-related hospitalizations increased 62%*
- In the same period MRSA-related hospitalizations more than doubled (119%, respectively ~14% per year)*
- Infections with MRSA kill ~19000 hospitalized patients in the U.S. annually (similar to the number of deaths caused by AIDS, tuberculosis and viral hepatitis combined!)**
- 40.000 deaths in 2006 due to infections (including all germs) in Germany (14% Increase 2002-2006)***
- Antimicrobial drug-resistant infections do increase death, illness, and direct costs by 30-100%***

*Klein E, Smith DL, Laxminarayan R. Hospitalizations and deaths caused by methicillin-resistant Staphylococcus aureus, United States, 1999-2005. *Emerg Infect Dis* 2007; **13**: 1840-6

Klevens RM, Morrison MA, Nadle J et al. Invasive methicillin-resistant Staphylococcus aureus infections in the United States. *Jama* 2007; **298: 1763-71

*** Report Deutsche Antibiotika-Resistenzstrategie

****Cosgrove SE, Carmeli Y. The impact of antimicrobial resistance on health and economic outcomes. *Clin Infect Dis* 2003; **36**: 1433-7.

Side effects of antibiotics

- ~10% of hospitalized patients present an allergy against penicillin (but only 10% of those actually have allergic reactions during treatment)*
- Problematic is the cross-reactivity, which averts the use of many other antibiotics, e.g. cephalosporins*
- Antibiotic associated diarrhea occurs in about 5-30% during therapy or even two month after ending the treatment**, ***

*Greenberger PA. Drug allergy. Part B: Allergic reactions to individual drugs: low molecular weight. *Patterson's Allergic Diseases* 2002: 335-59

McFarland LV. Epidemiology, risk factors and treatments for antibiotic-associated diarrhea. *Dig Dis* 1998; **16: 292-307

***Wistrom J, Norrby SR, Myhre EB et al. Frequency of antibiotic-associated diarrhoea in 2462 antibiotic-treated hospitalized patients: a prospective study. *J Antimicrob Chemother* 2001; **47**: 43-50

New antibiotic drugs

- „Effective antibiotic treatment becomes as precious as clean drinking water“
- 2003 - 13.Mio prescriptions of antibiotics by dermatologists in the US
- Genomic derived or target based antibiotics need a lot of time to brought to the market:
 - for gram + strains ~ 2012*
 - for gram – strains ~ 2016 - 2021*

*Payne DJ, Gwynn MN, Holmes DJ et al. Drugs for bad bugs: confronting the challenges of antibacterial discovery. *Nat Rev Drug Discov* 2007; **6**: 29-40

Deadly Germs Largely Ignored By Drug Firms

By ANDREW POLLACK
Published: February 26, 2010

Gram-negative bacteria are practically built to withstand drugs, which is one reason few drug makers have rushed to pursue treatments.

Related

[Rising Threat of Infections Unfazed by Antibiotics](#)
(February 27, 2010)

The bacteria have a double cell membrane to shield them, compared with Gram-positive organisms, which have a single membrane. They can make various enzymes that break down antibiotics. And some,

particularly *Pseudomonas aeruginosa*, have powerful pumps that can expel the drugs.


The bacteria also readily exchange genes, even across different species, that confer drug resistance.


It is likely to be several years before new drugs to treat Gram-negative infections are available. A report last September by European health authorities found only six novel drugs in clinical trials that might work against at least one Gram-negative organism, compared with 13 for Gram-positive bacteria.

A separate study released about a year ago by the Infectious Diseases Society of America found no drugs in middle- or late-stage clinical trials directed specifically at Gram-negative organisms. There were eight drugs in those trials that developers hoped might work against both Gram-negative and Gram-positive microbes.

The difficulty of killing Gram-negative germs is not the only reason for the dearth of new

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New antibiotic drugs

- „Effective antibiotic treatment becomes as precious as clean drinking water“
- 2003 - 13.Mio prescriptions of antibiotics by dermatologists in the US
- Genomic derived or target based antibiotics need a lot of time to brought to the market:
 - for gram + strains ~ 2012*
 - for gram – strains ~ 2016 - 2021*
- New antibiotic drugs face same problems like usual ones (resistance, allergic reactions and other side effects)

*Payne DJ, Gwynn MN, Holmes DJ et al. Drugs for bad bugs: confronting the challenges of antibacterial discovery. *Nat Rev Drug Discov* 2007; **6**: 29-40

Cold atmospheric plasmas are ideal antibiotics

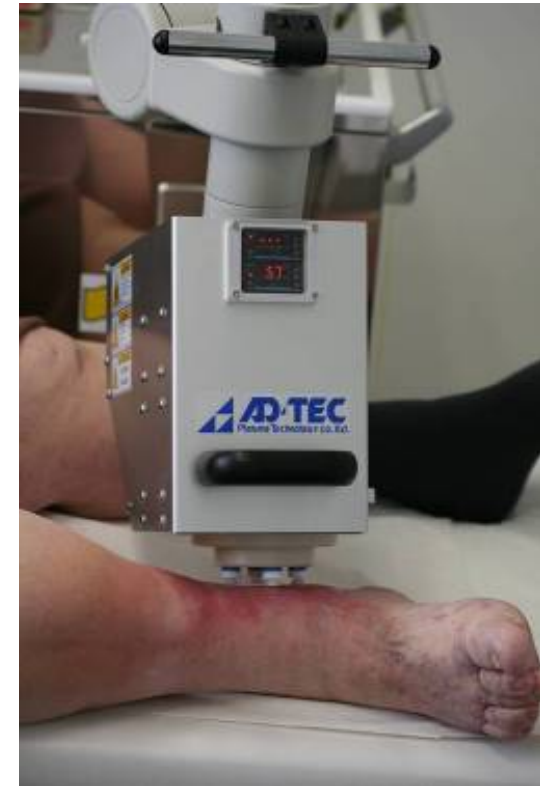
Low temperature argon plasma:

- Allows in-vivo application, without damaging tissue
- Medical cocktail – can be tuned for different purposes
- Waste-free (only electricity required) and economical (running cost, maintainanance)
- Contact free application, reaches “rough” surfaces down to micrometer scale
- Bactericidal (fungicidal and virucidal)
- Physical-chemical therapy → Resistance and allergic reactions are less feasible
- Enhanced wound healing

Phase II study: MicroPlaSter

(ADTEC Plasma Technology Co. Ltd., Hiroshima/London)

MaryMcGovern@adtec.eu.com



Chronic wounds in dermatology



Venous diseases



Arterial diseases



Infections



Diabetes mellitus



Carcinoma

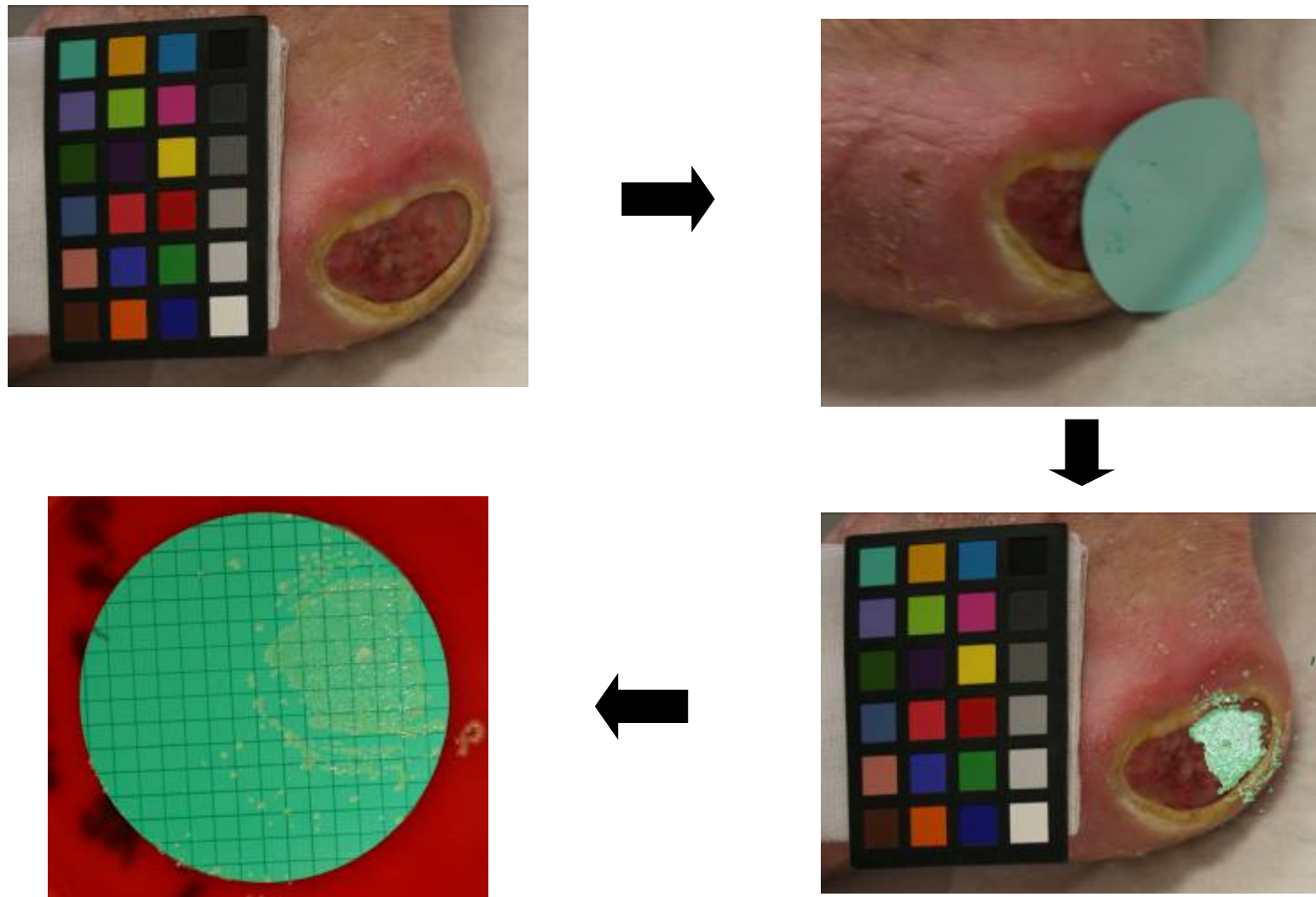


Pyoderma gangraenosum

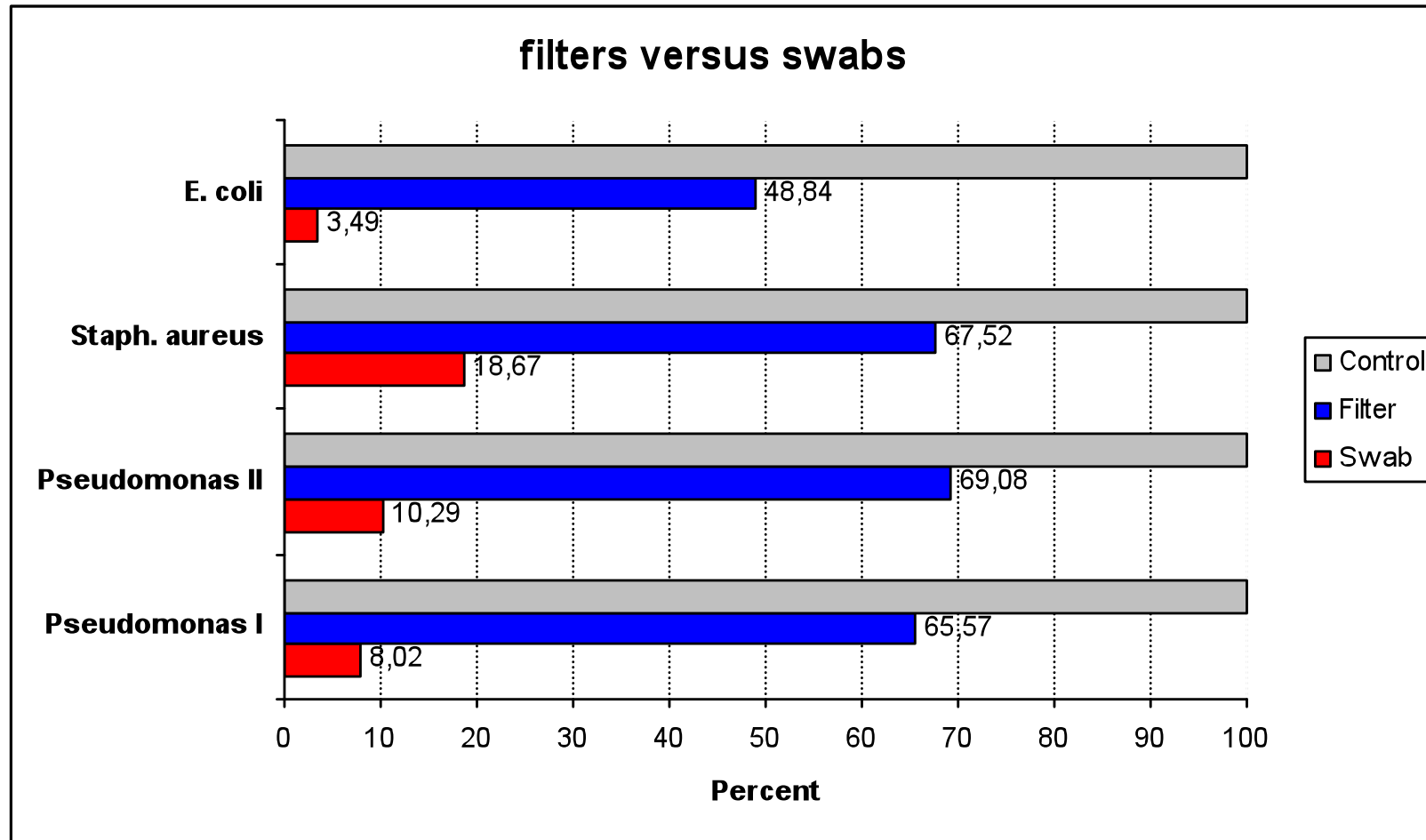
Common swab techniques failed in accuracy and reproducibility of bacterial loads



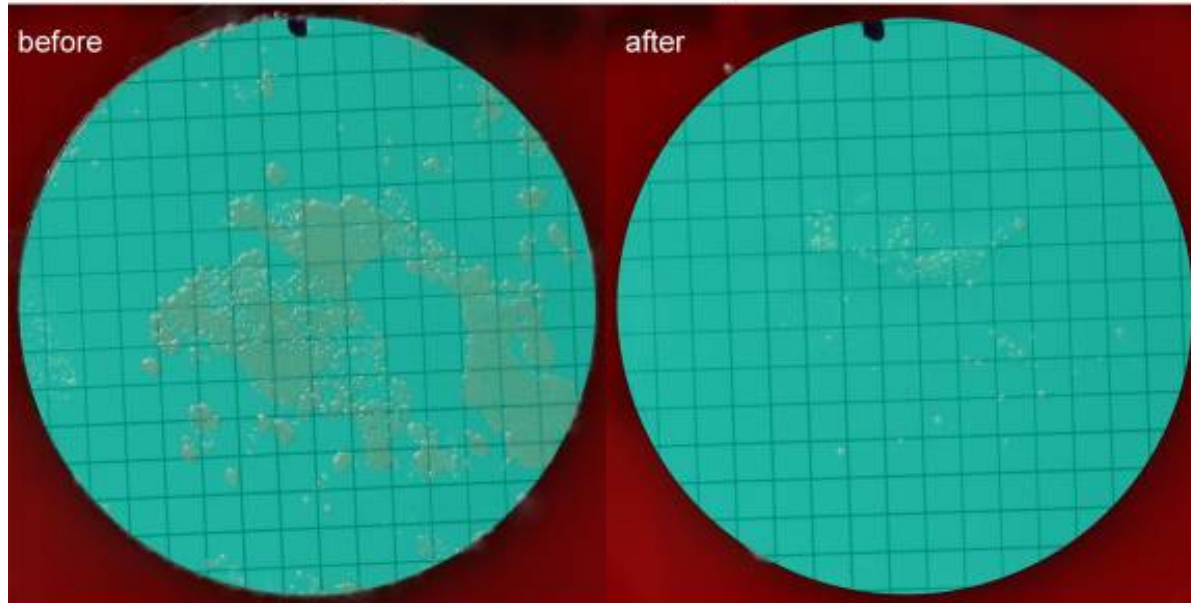
Nitrocellulosis filters revealed a higher accuracy and reproducibility



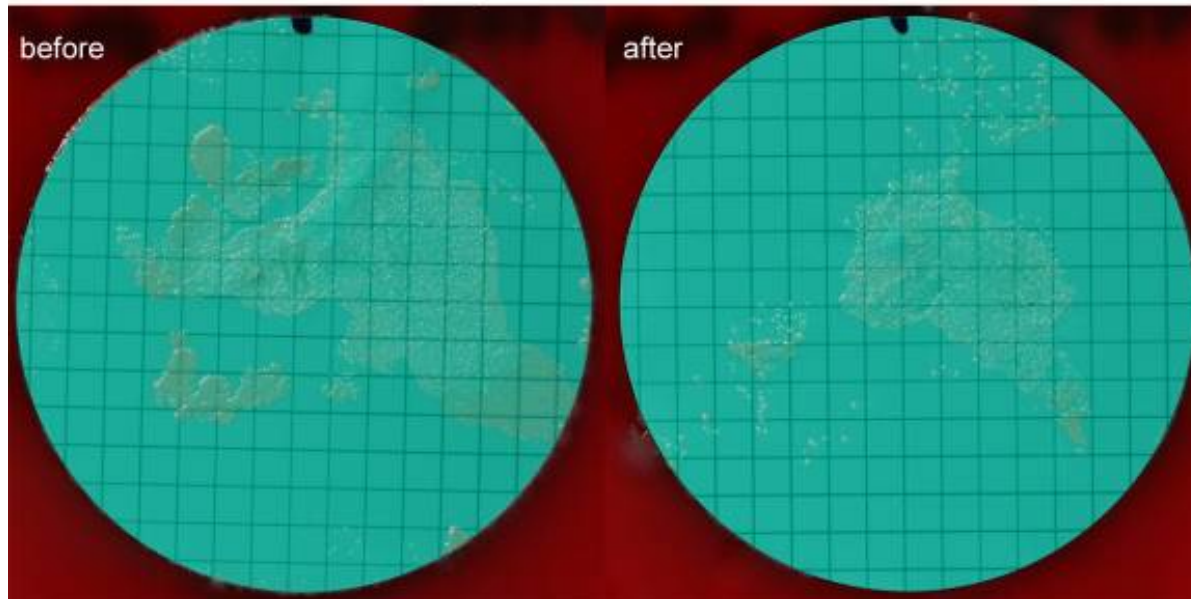
Evaluation of accuracy and reproducibility of swabs vs. nitrocellulose filters



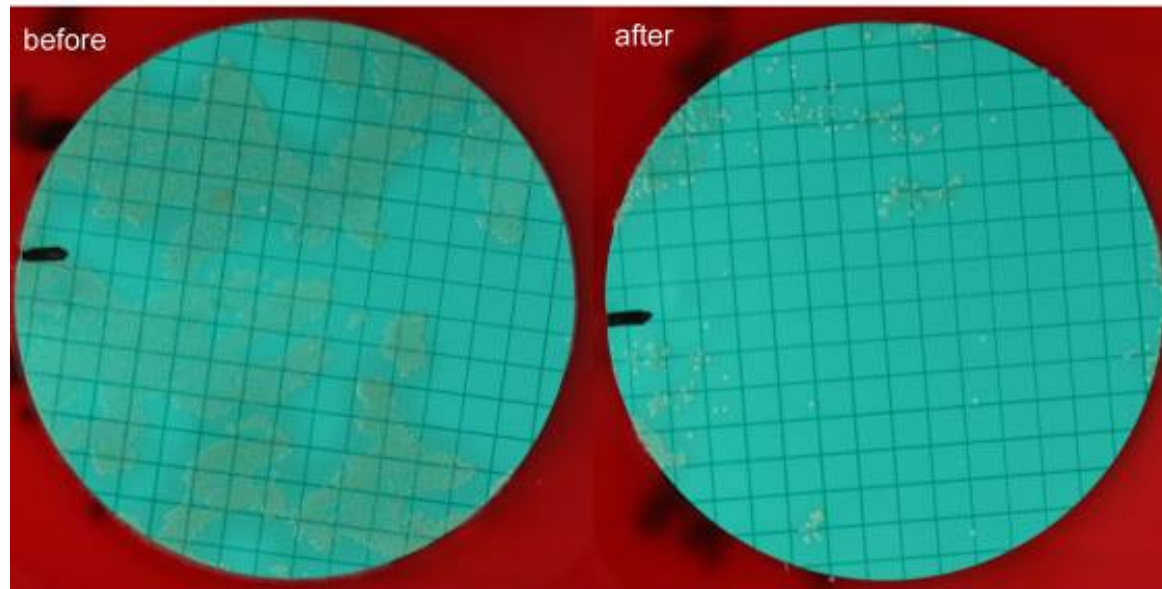
PSAE changes before and after plasma treatment



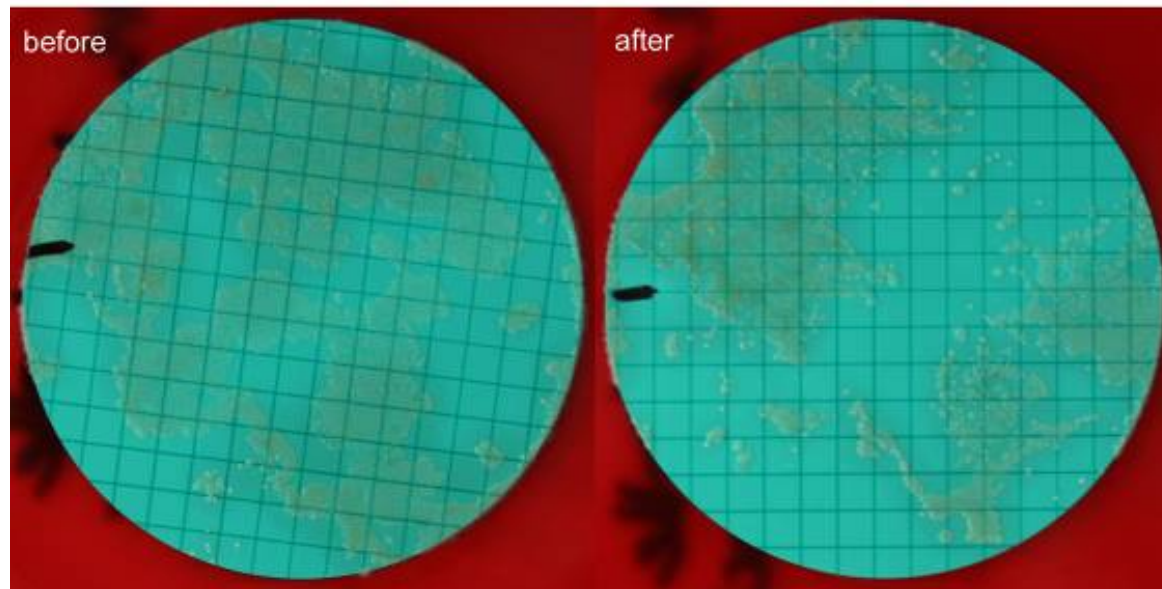
PSAE changes before and after control



MRSA before and after plasma treatment



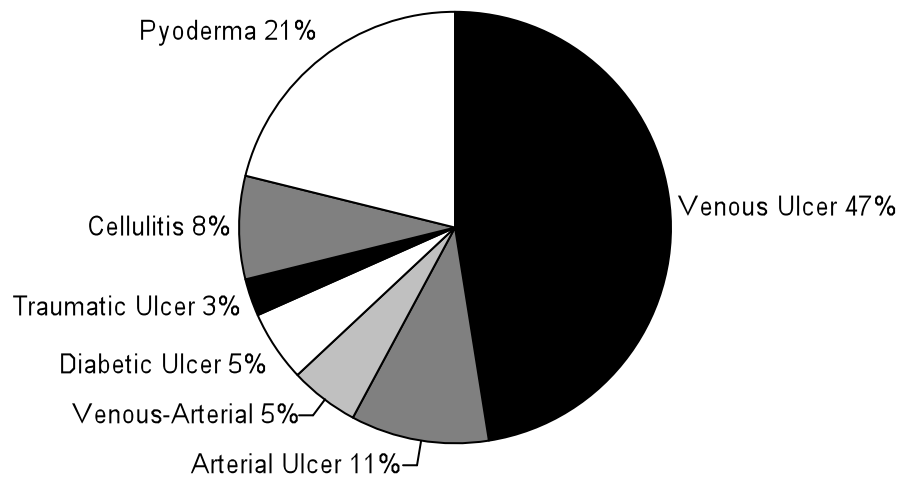
MRSA before and after control



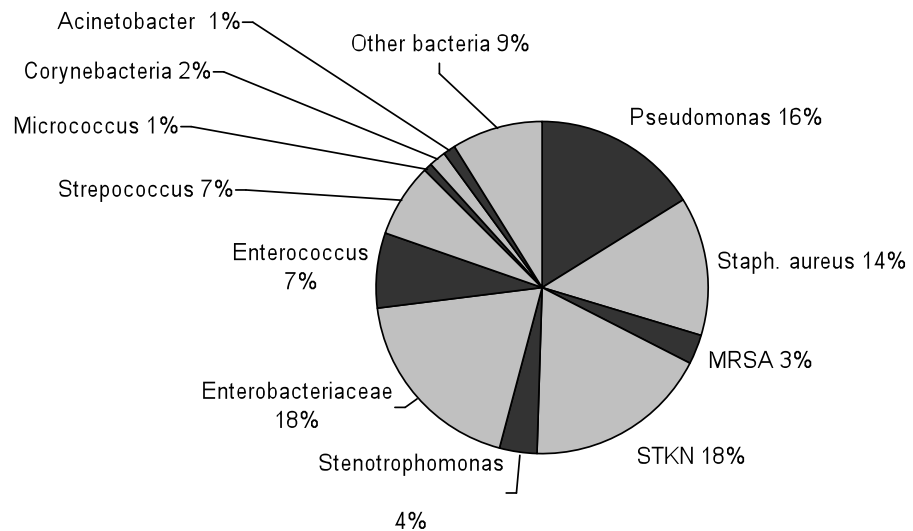
Interim analysis (efficacy of plasma treatment)

- 36 patients
- 291 treatments
- 5 min treatment time
- Primary aetiology of wounds: venous ulcers (47%)
- Filter taken before and after treatment

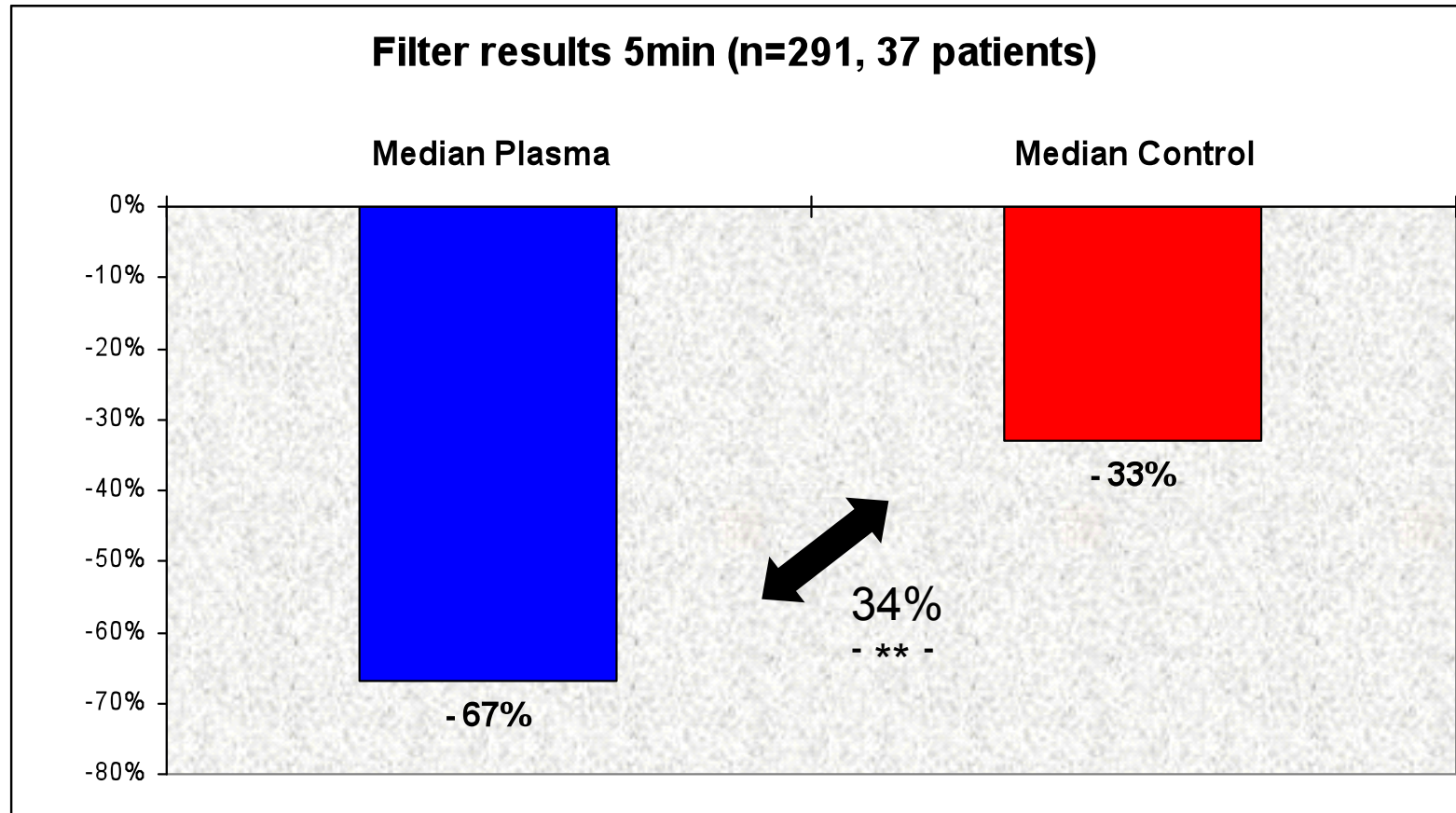
primary aetiology of ulcers



Germs located on wound

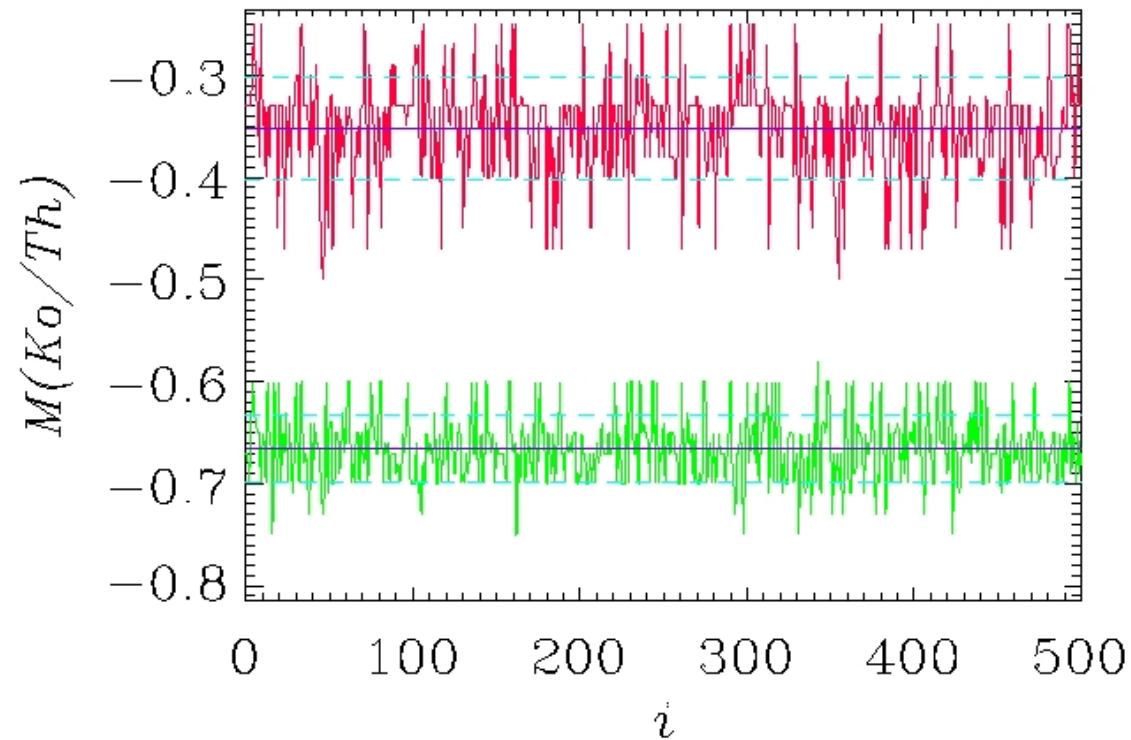


Results: 5 min treatment time



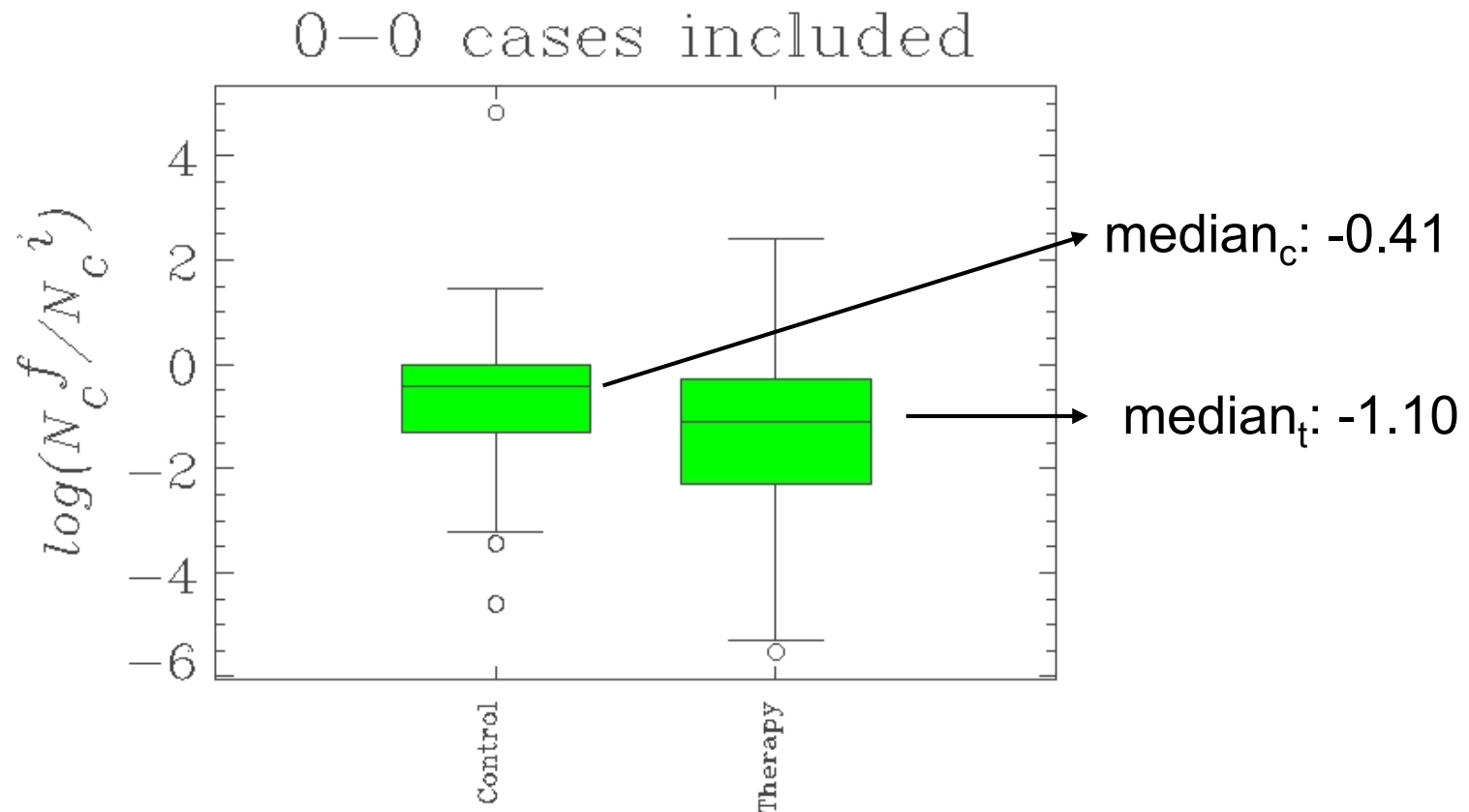
Highly significant ($p < 10^{-6}$) higher germ reduction (34%) in plasma treated area

Summary of Phase II - Results 5min of treatment time



Results from the corresponding bootstrap-test

Summary of Phase II - Results 5min of treatment time



Corresponding results displayed as box plots using the log return

Background of treatment time reduction: UV-measurements of argon plasma

- There are no regulations and studies about long-term effects of plasma treatment
- We do produce UV, and to some parts UVC as well, which is known to be carcinogenic

To have a „safe“ distance to the aforementioned limits/recommendations we decided to reduce treatment time to 2 min

FDA approved UVC devices (254nm)



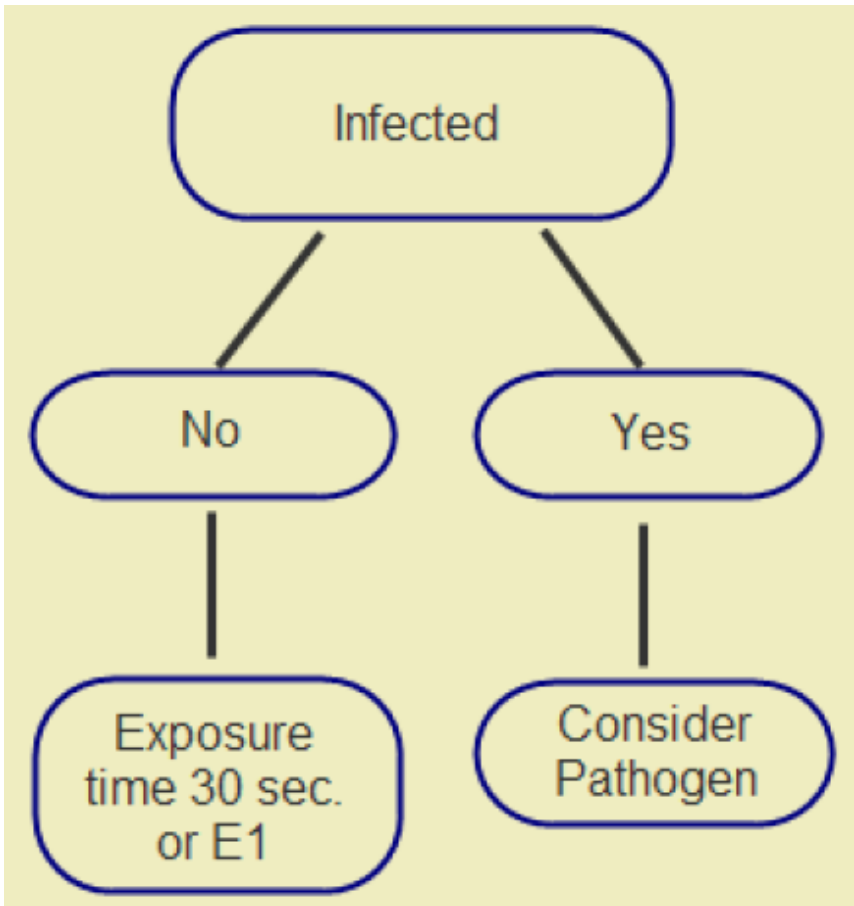
MedFauxx



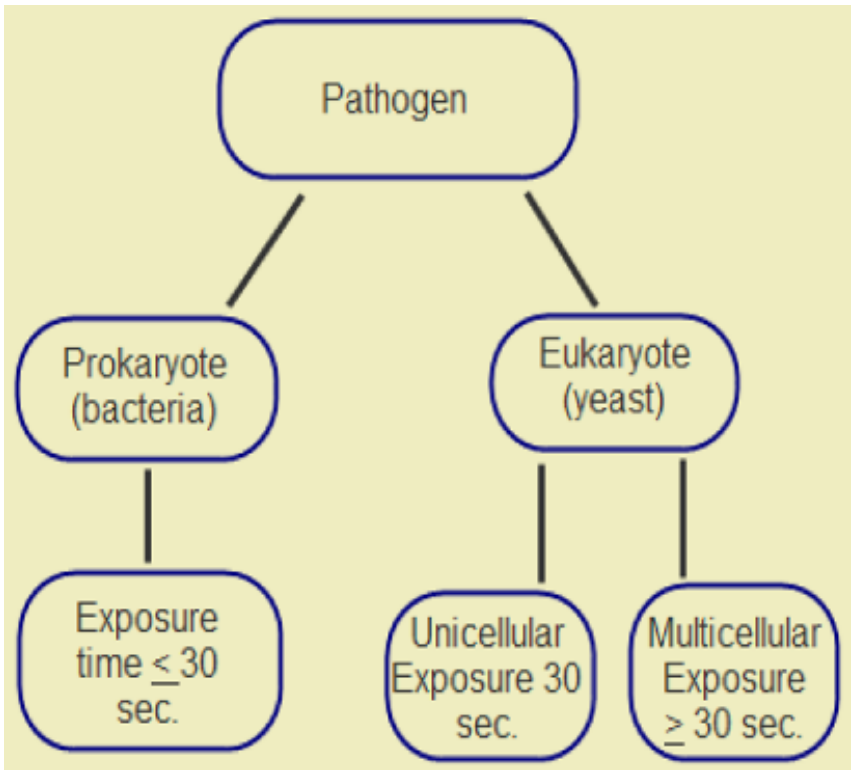
National Biological

UV Power ~ 5-20 $\mu\text{W}/\text{cm}^2$ (16 $\mu\text{W}/\text{cm}^2$ preferred)

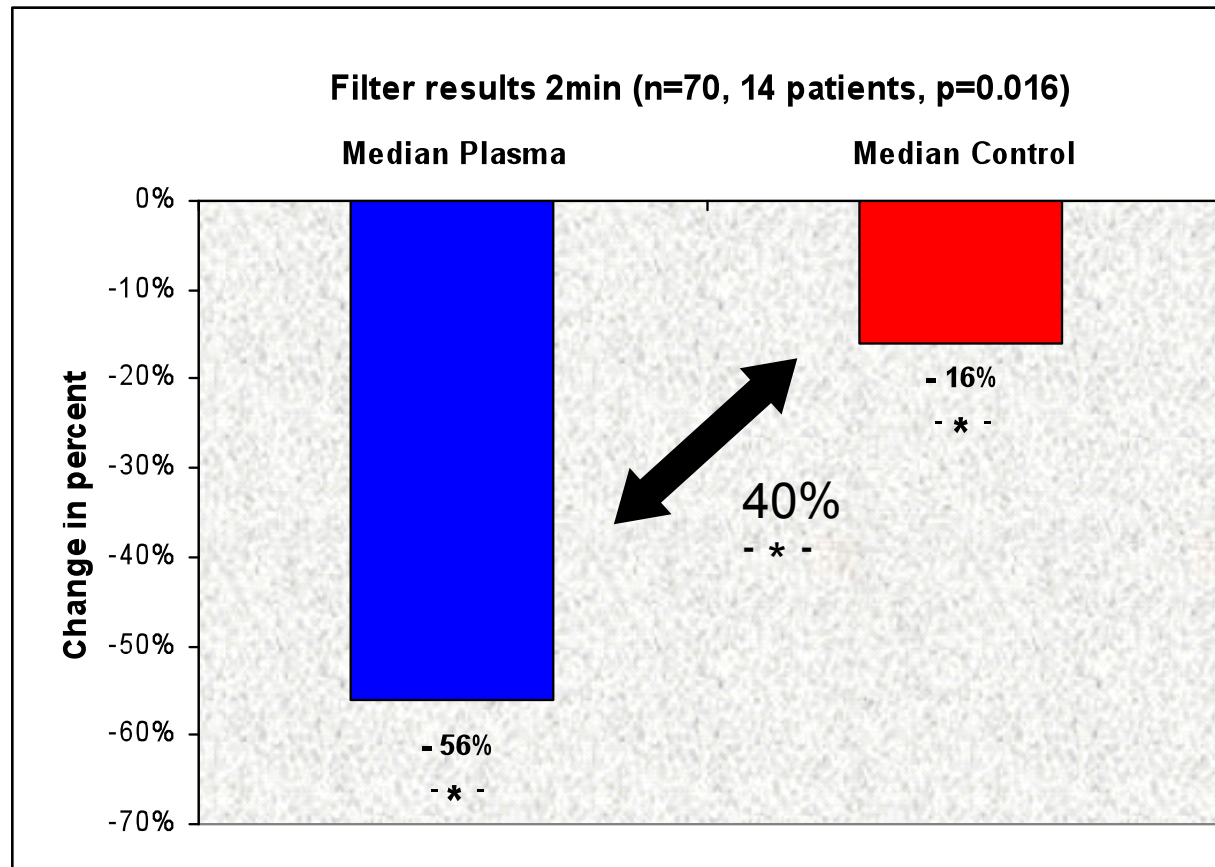
MicroPlaSter UVC 10-16 $\mu\text{W}/\text{cm}^2$



UVC treatment algorithm (Conner-Kerr)

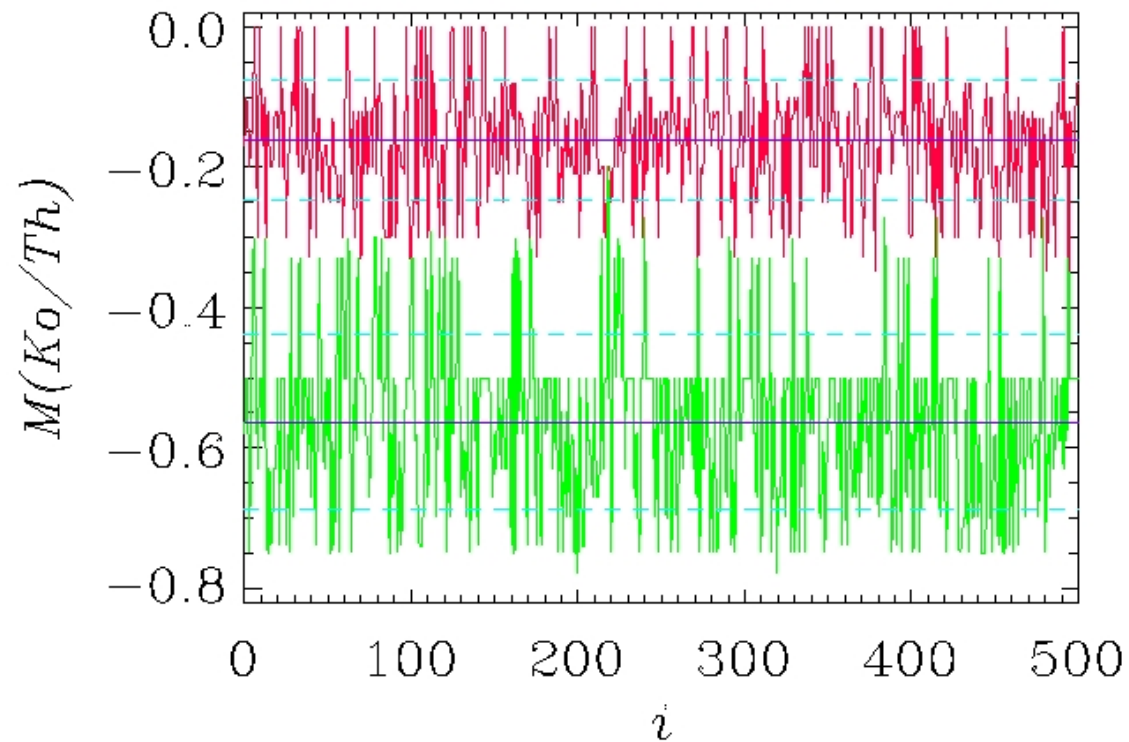


Results: 2 min treatment time



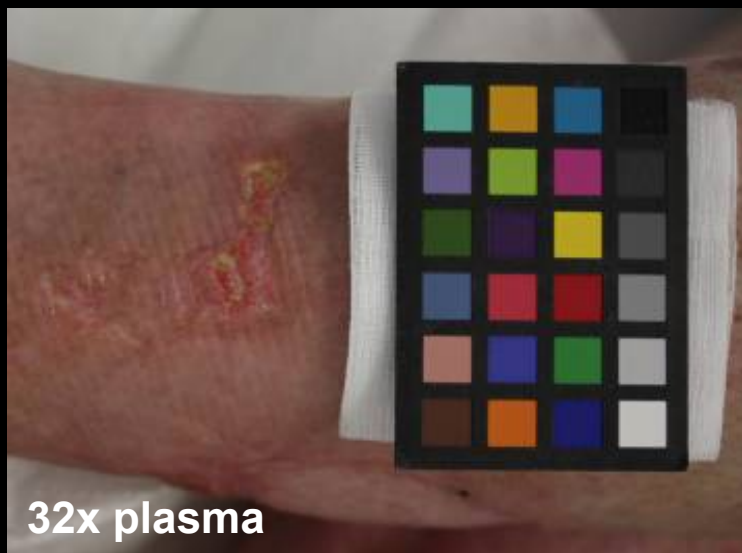
Significant ($p < 0.016$) higher germ reduction (40%) in plasma treated area

Summary of Phase II - Results 2min of treatment time



Results from the corresponding bootstrap-test

Good results of plasma therapy



Good results of plasma therapy



Insufficient result of plasma therapy



Poor result of plasma therapy

13x plasma



33x plasma



Other therapy options – V.A.C.®



07.07.2010



07.07.2010 V.A.C.



12.08.2010

MESH graft



12.08.2010

V.A.C. 125mmHg



12.08.2010

>80% accepted graft



15.09.2010

Donor site



15.09.2010

Results

- A highly significant (34%, $p < 10^{-6}$) higher germ reduction in 5 min plasma treated area vs. control area
- A significant (40%, $p = 0.016$) higher germ reduction in 2 min plasma treated area vs. control area
- No side effects occurred until now, and the treatment is well tolerated
- The use of nitrocellulosis filters revealed a higher accuracy and reproducibility than common swab techniques

Hailey-Hailey Disease

- syn: familial benign chronic pemphigus

- autosomal recessive

- mutation in *ATP2B1*

- characteristic

recurrent

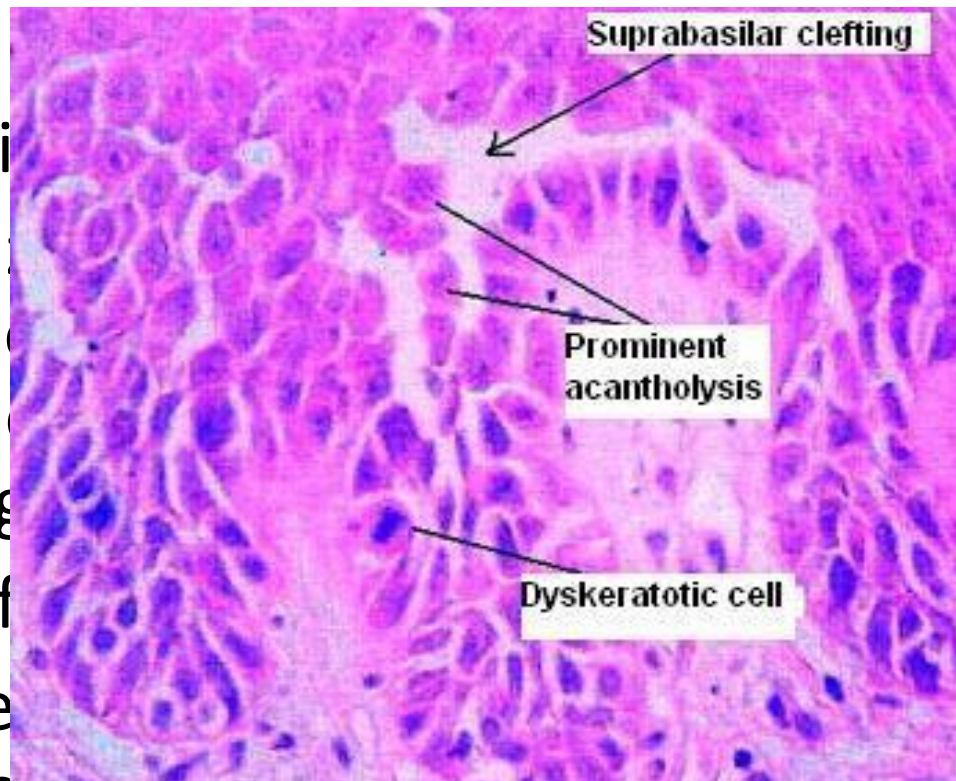
intertriginous

and during

- problem: flare-ups

- Topical treatment

antibiotics, antifungals, immunosuppressive



der

some 3q21.1

and leads to

in

periods

ds,

ive

03.05.2010

axilla before

14.05.2010

axilla after 8 plasma treatments

03.05.2010

ledge before

07.05.2010

ledge without treatment

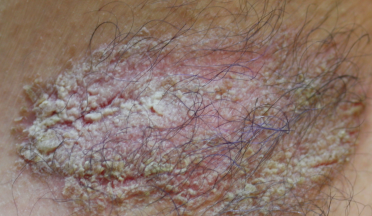
10.06.2010



10.06.2010



14.06.2010



axilla after 4 plasma treatments

25.06.2010



axilla after 11 plasma treatments

14.06.2010



ledge after 4 plasma treatments

25.06.2010



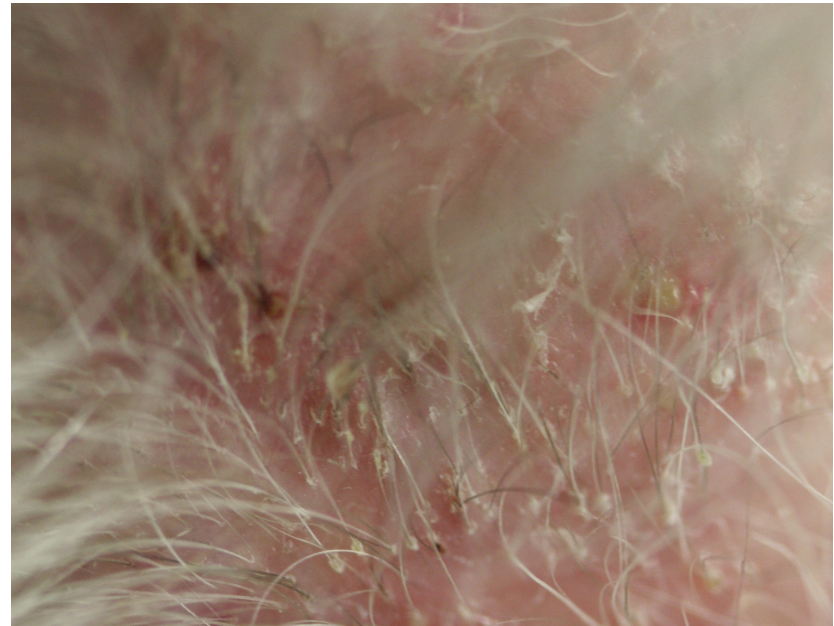
ledge after 11 plasma treatments

Staphylococcus aureus infected secondary eczema



Folliculitis decalvans

- deep folliculitis of the scalp leading to scarring alopecia
- hair follicles are no longer present, hair loss is permanent
- aetiology unknown, but *Staph. aureus* frequently detected



13.04.2010

3x plasma



26.04.2010

Folliculitis decalvans



12.04.2010

12.05.2010

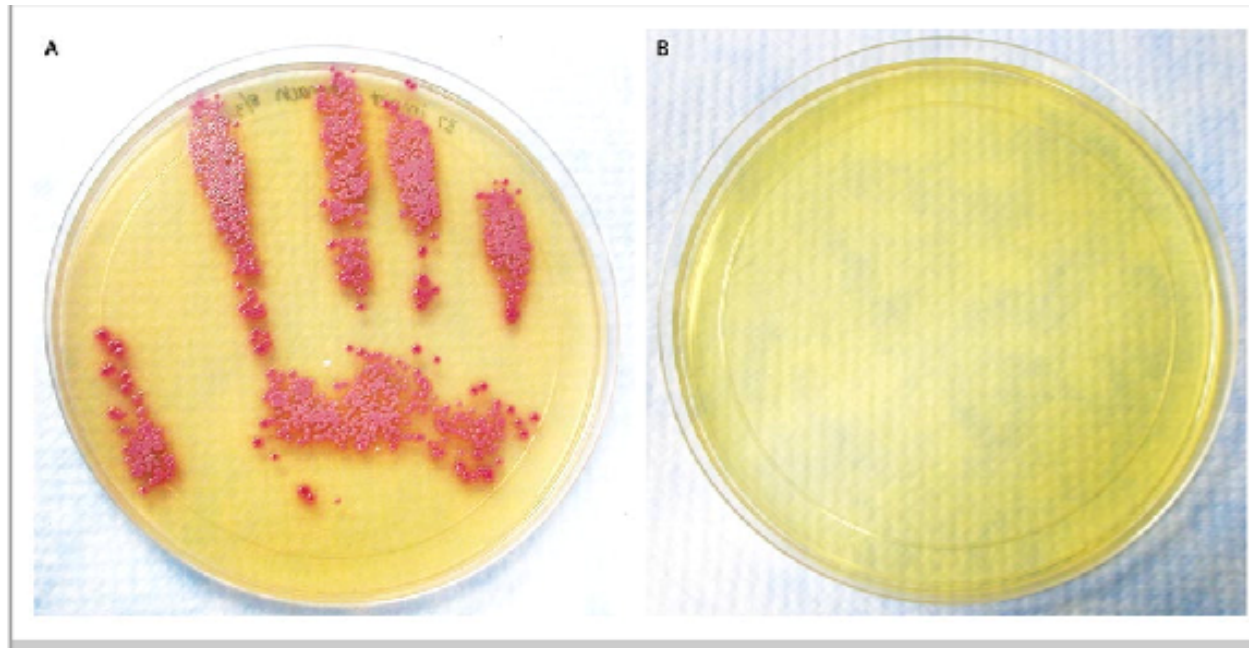
15x plasma



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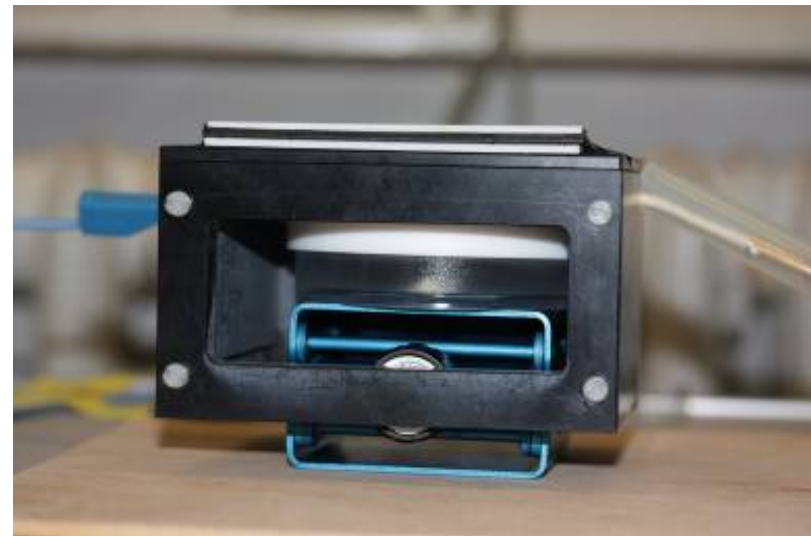
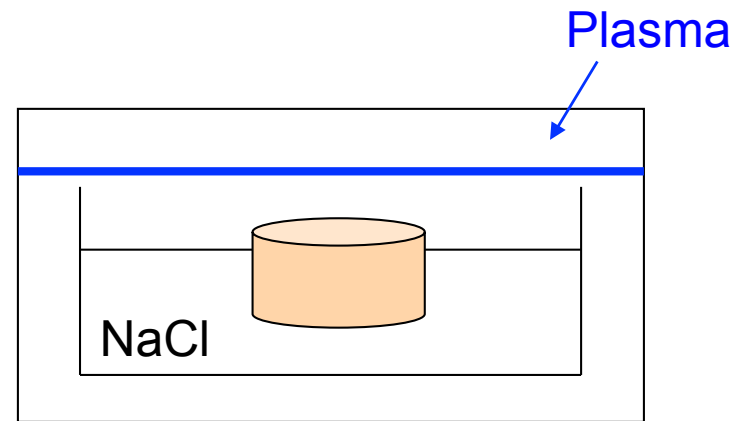
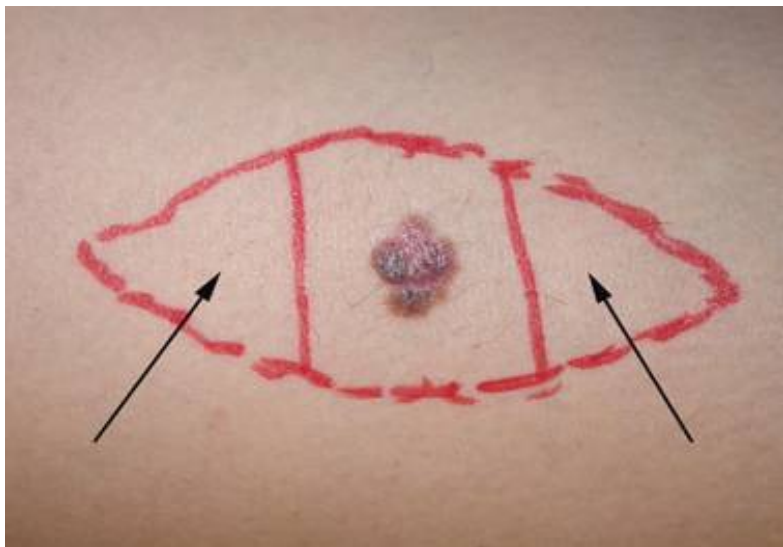
The Hands Give It Away

Curtis J. Donskey, M.D. and Brittany C. Eckstein, B.S.
N Engl J Med 2009; 360:e3 | January 15, 2009



The importance of hand hygiene to prevent the transfer of germs and resistance.

HandPlaSter – cutaneous tolerance



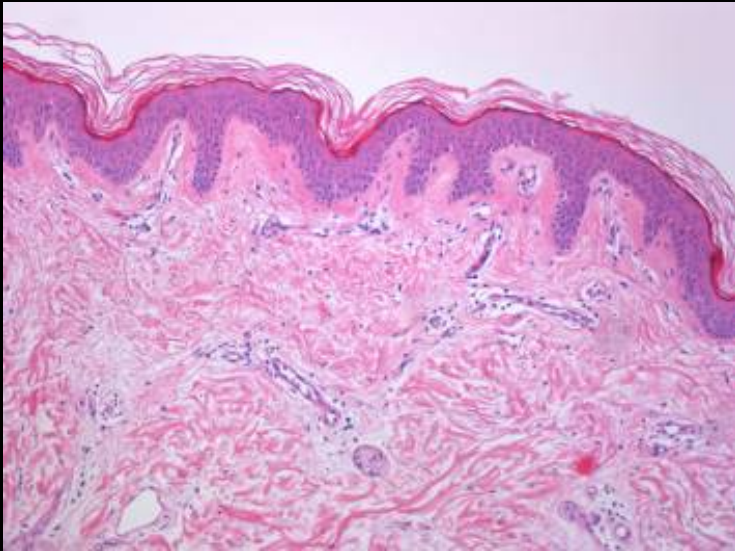
HandPlaSter – Patient 1

Plasma

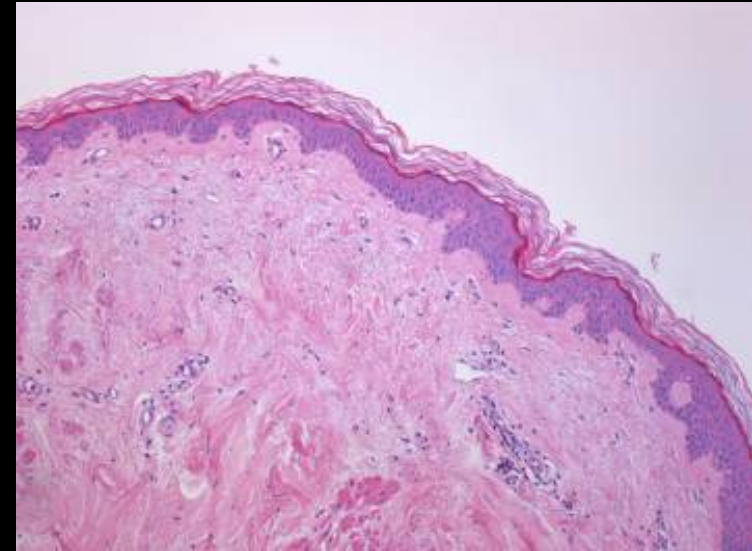
treatment-time

Control

10x

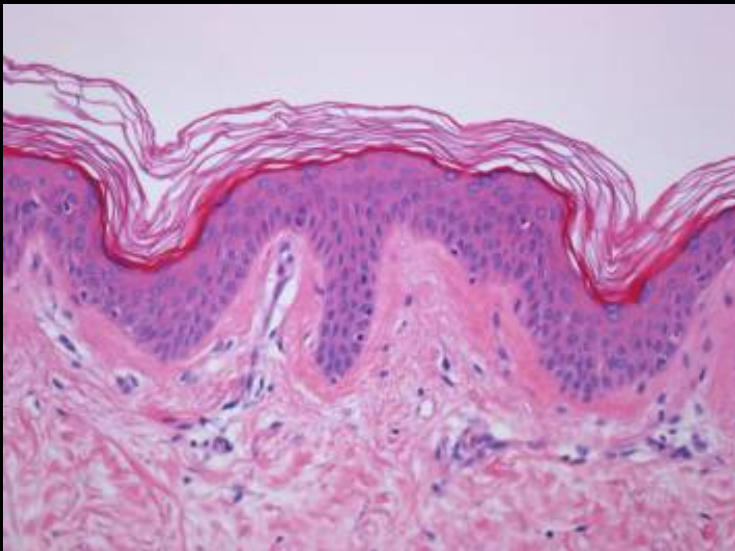


10x

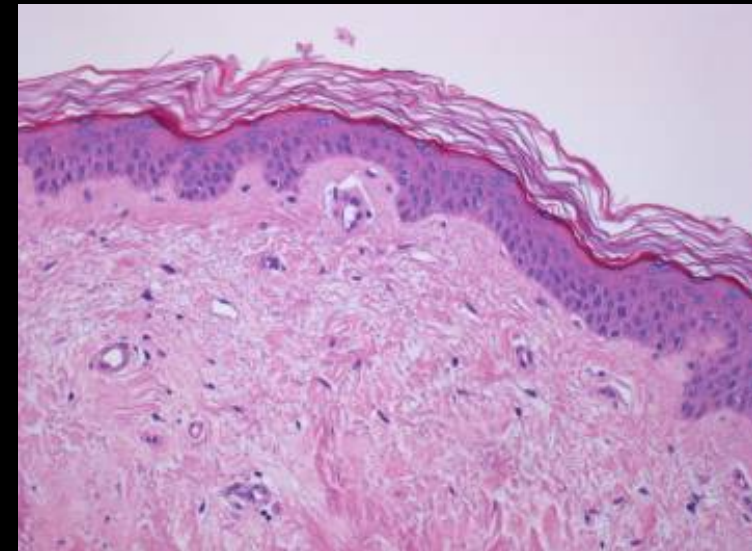


30s

20x



20x



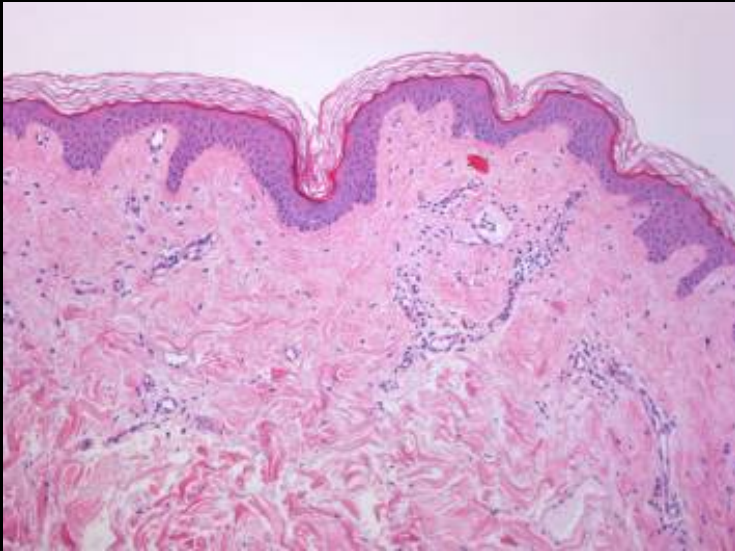
HandPlaSter – Patient 1

Plasma

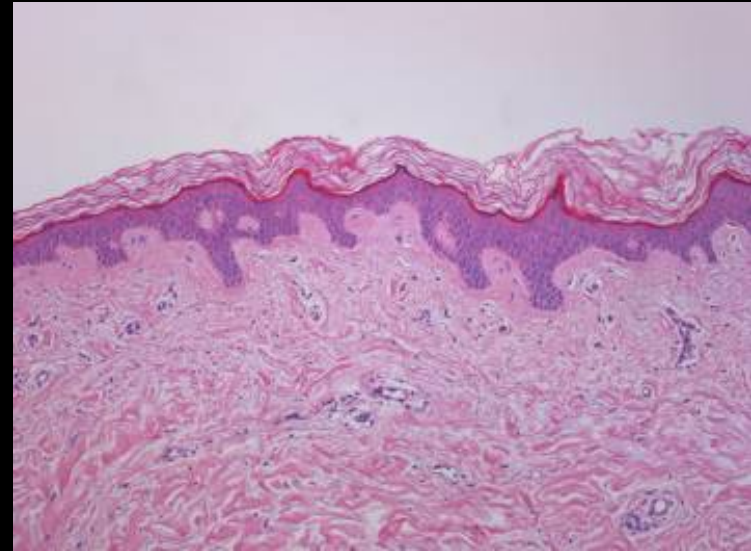
treatment-time

Control

10x

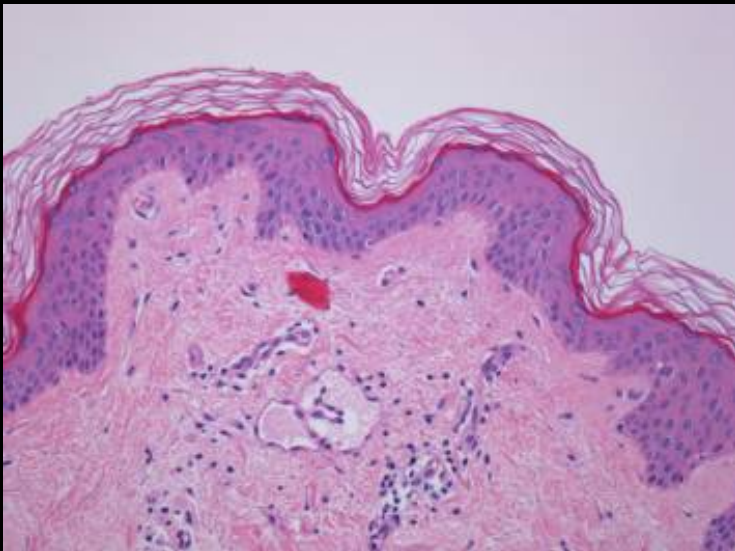


10x

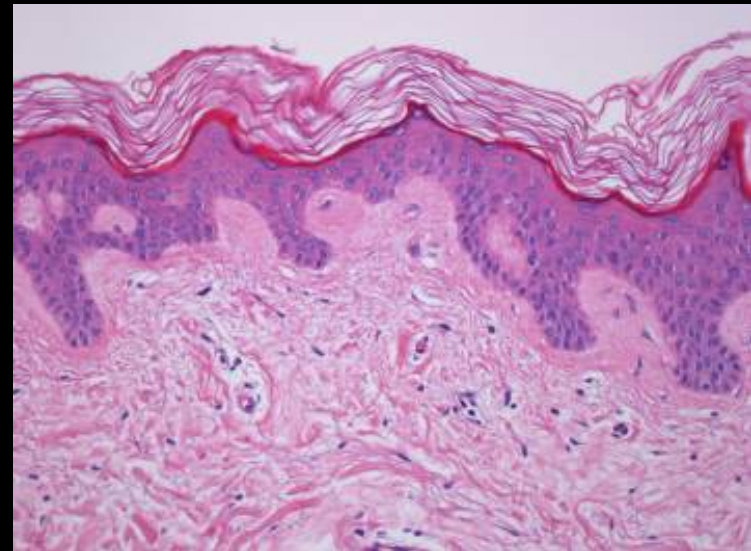


60s

20x



20x



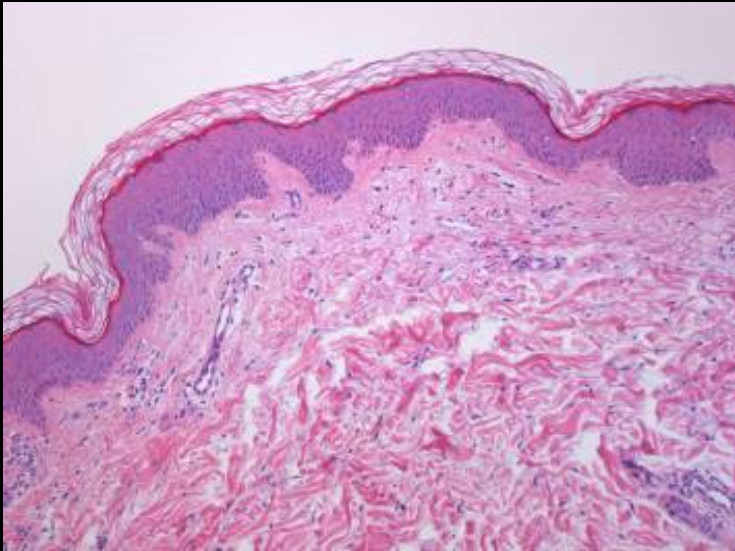
HandPlaSter – Patient 1

Plasma

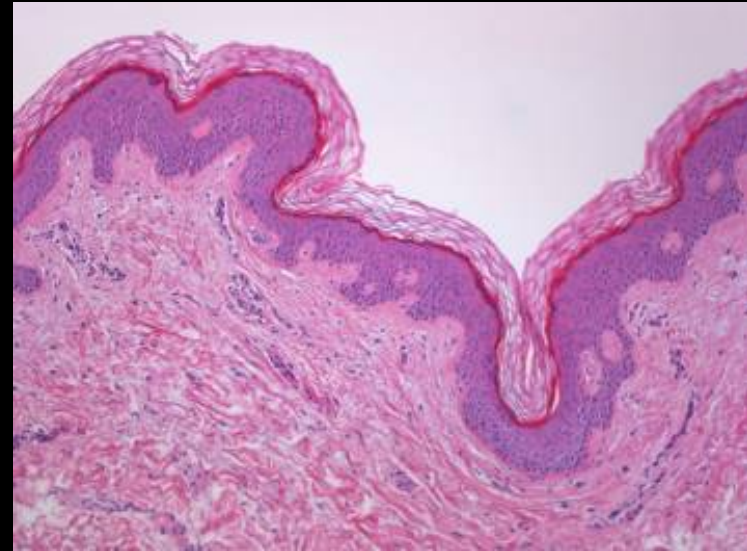
treatment-time

Control

10x

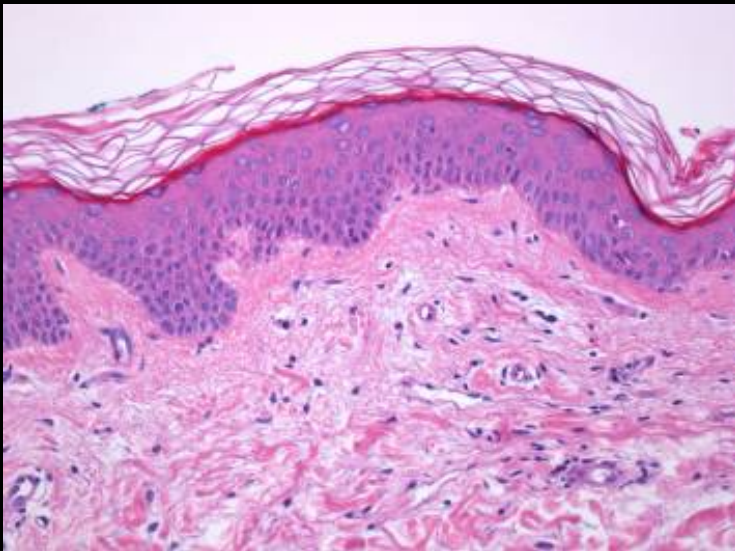


10x

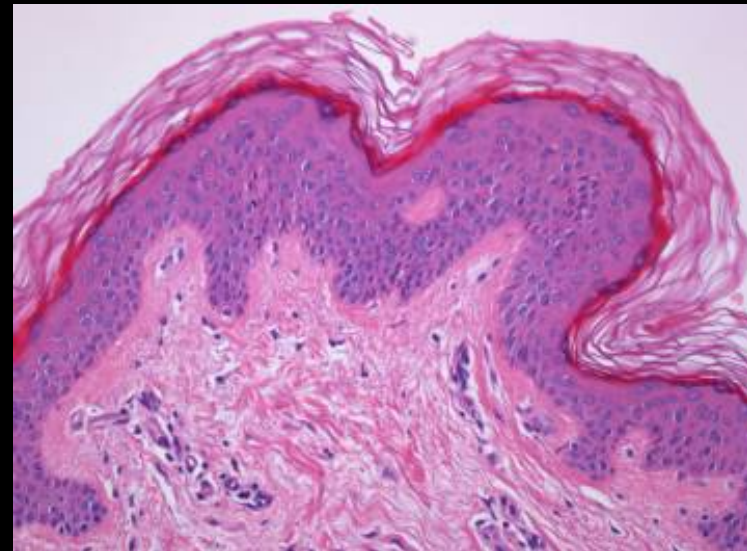


120s

20x



20x



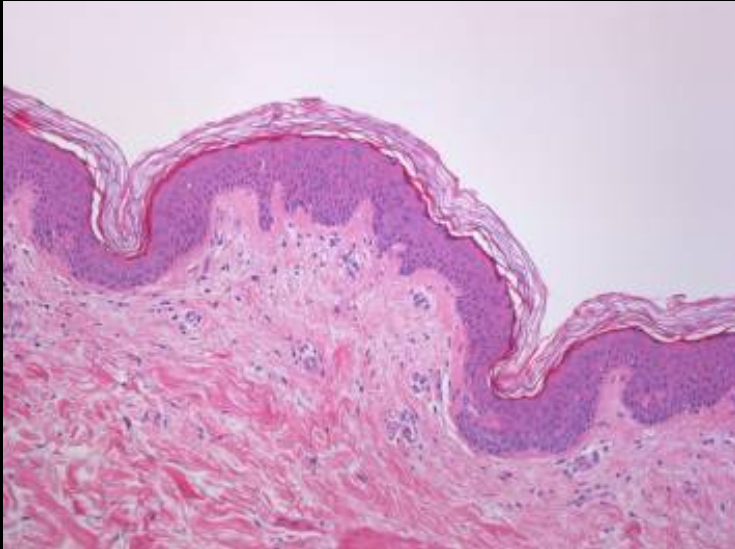
HandPlaSter – Patient 1

Plasma

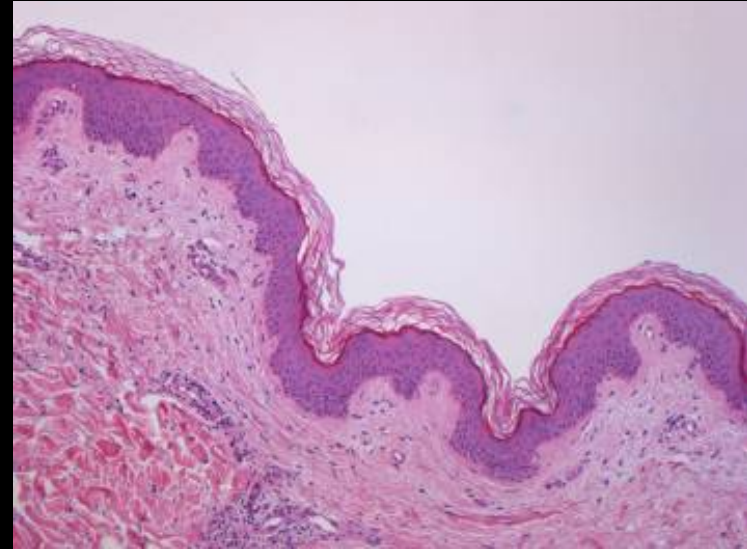
treatment-time

Control

10x

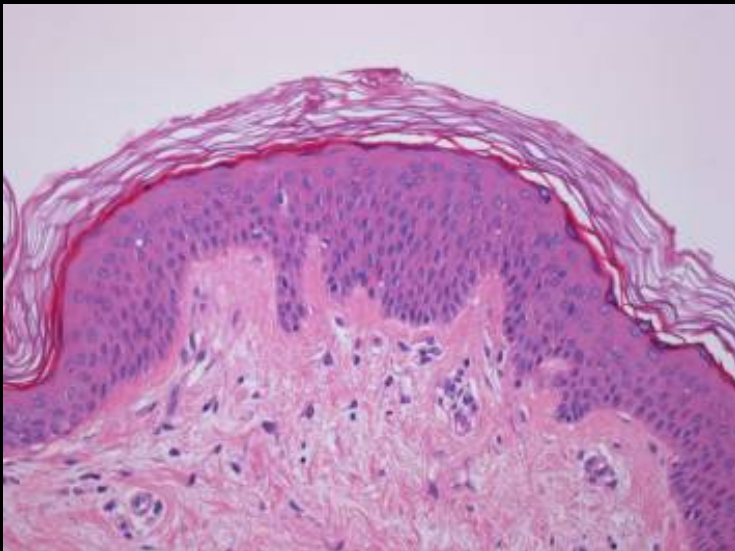


10x

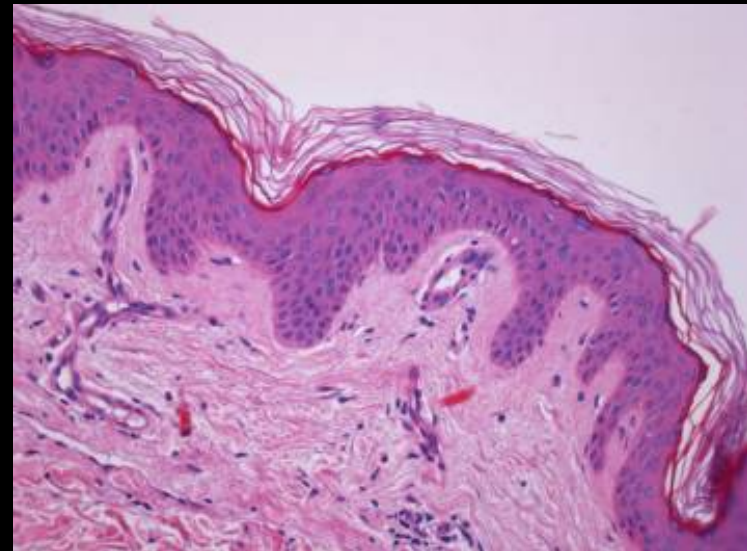


300s

20x



20x



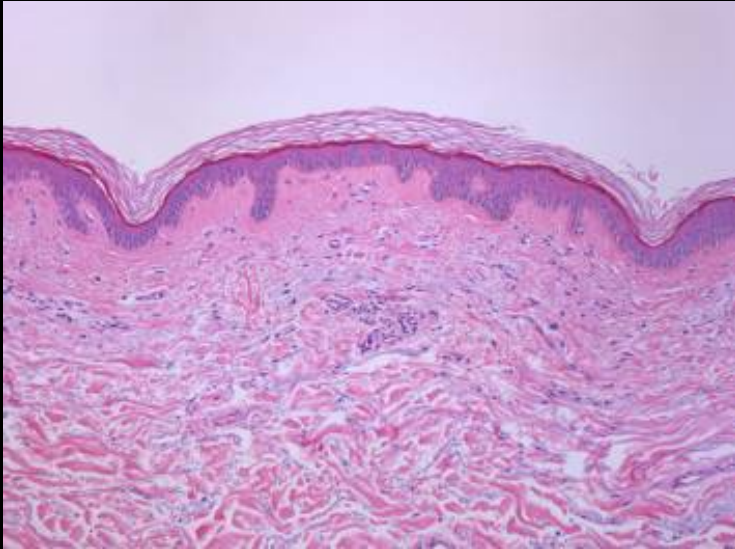
HandPlaSter – Patient 2

Plasma

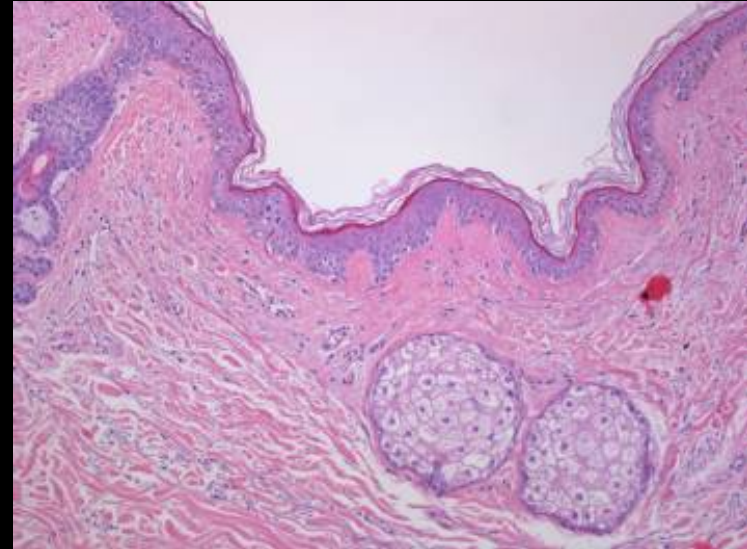
treatment-time

Control

10x

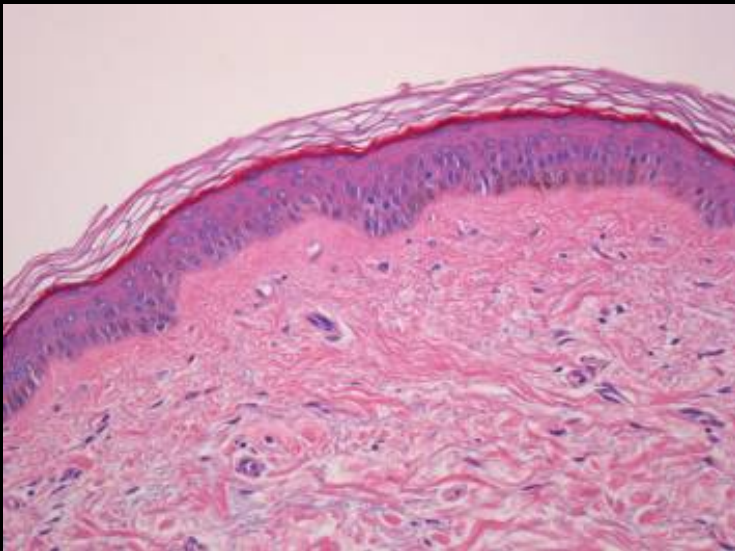


10x

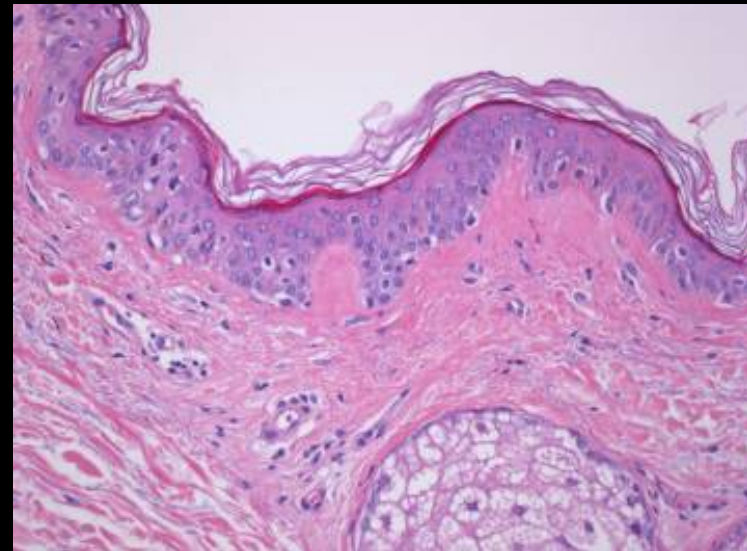


60s

20x



20x



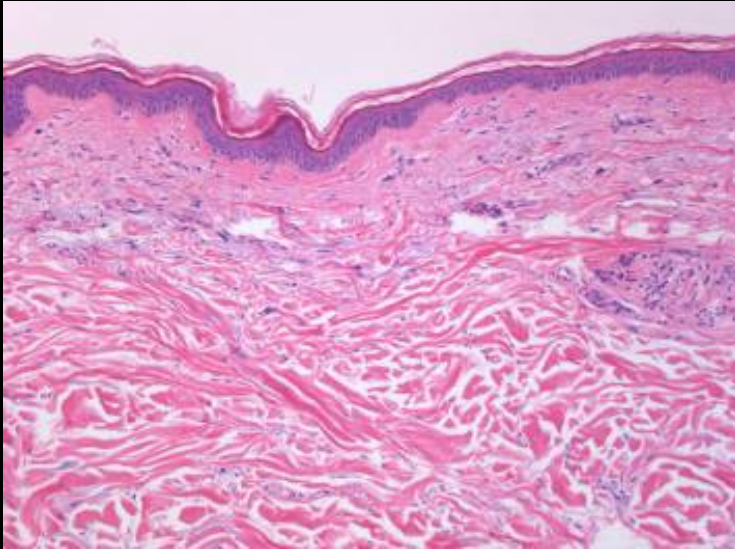
HandPlaSter – Patient 2

Plasma

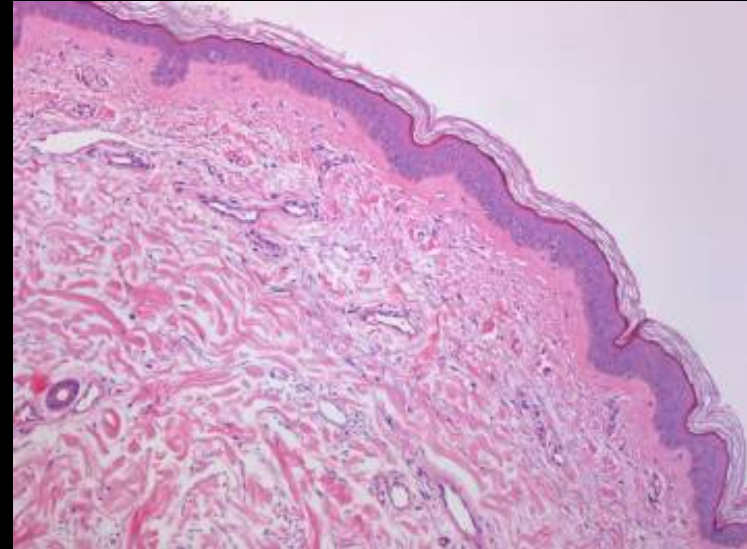
treatment-time

Control

10x

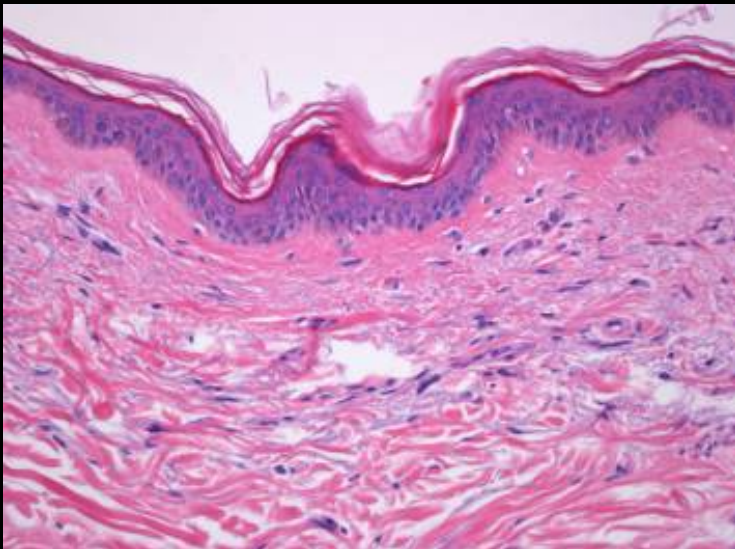


10x

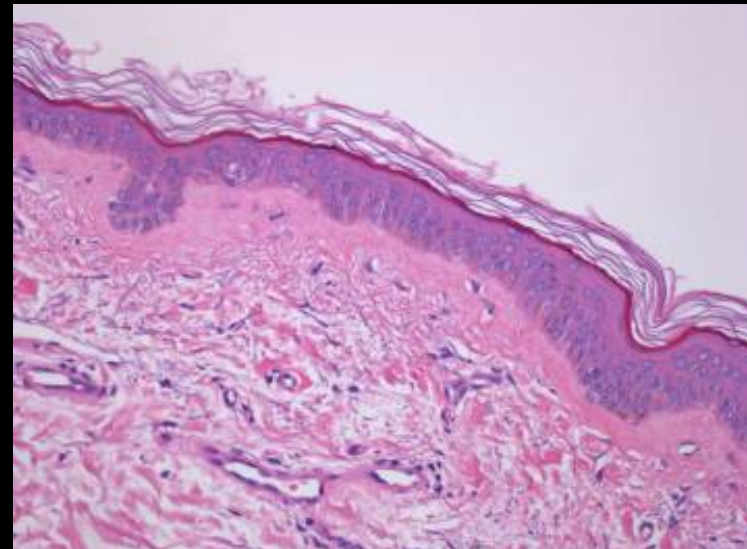


120s

20x



20x



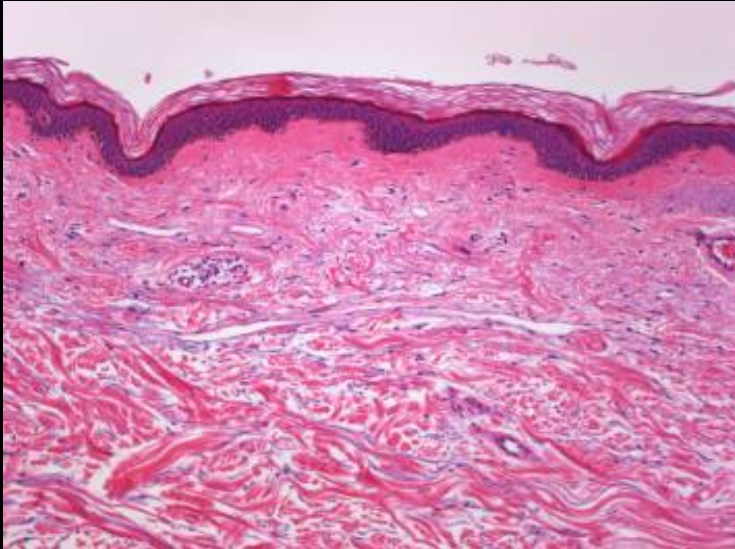
HandPlaSter – Patient 2

Plasma

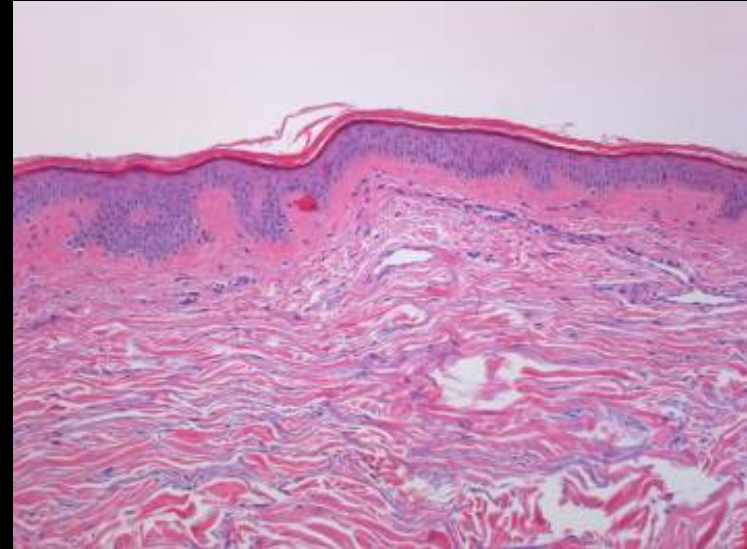
treatment-time

Control

10x

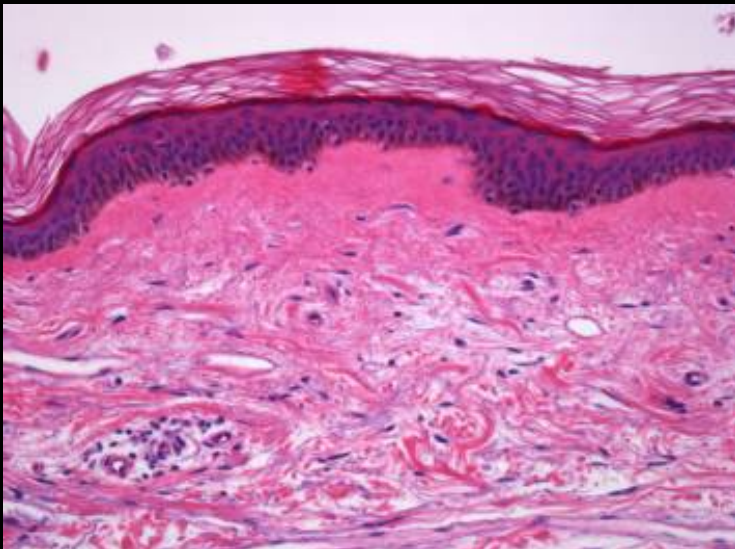


10x

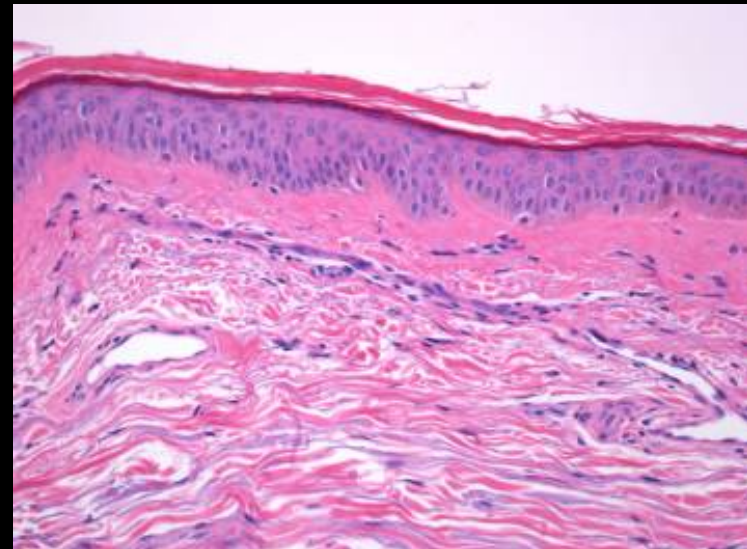


300s

20x



20x



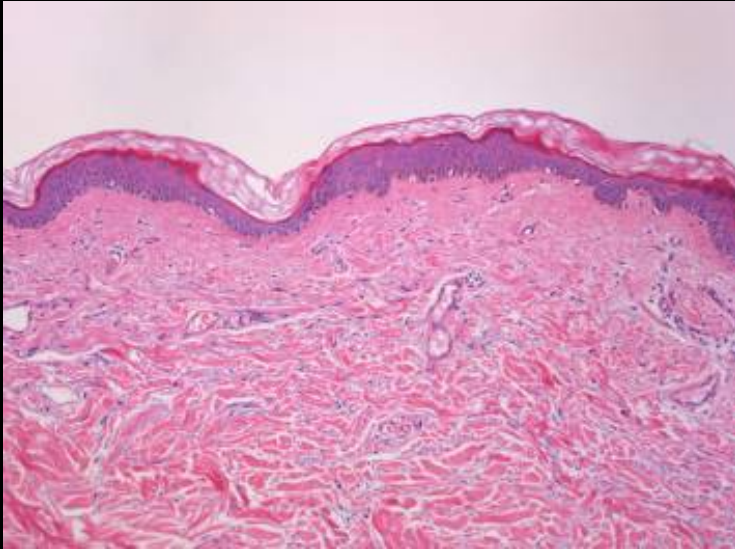
HandPlaSter – Patient 2

Plasma

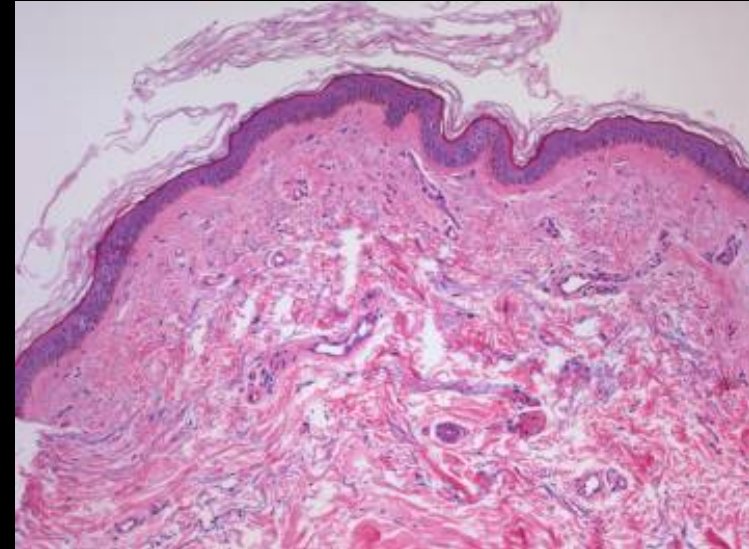
treatment-time

Control

10x

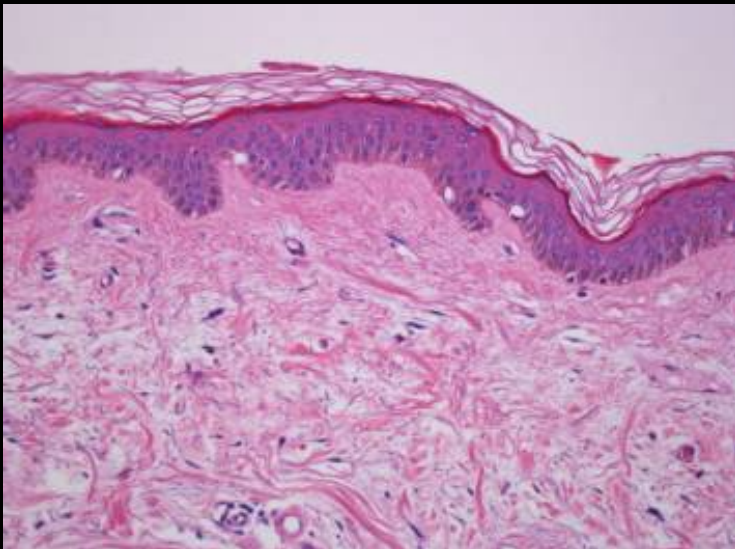


10x

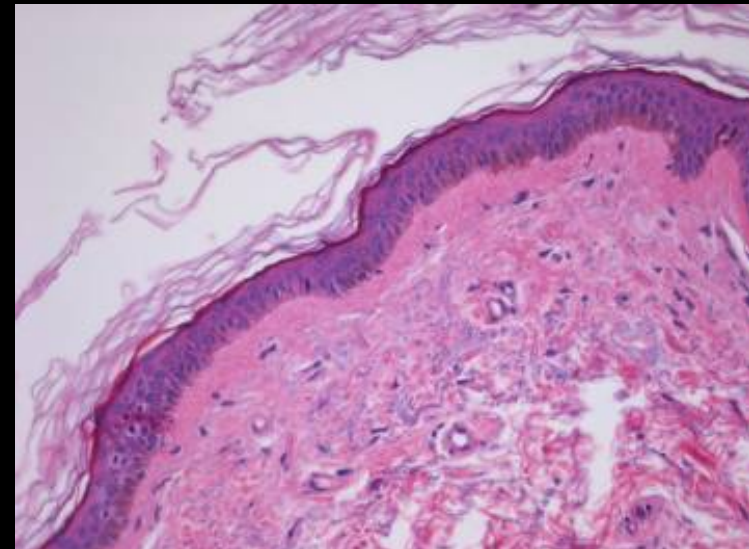


600s

20x



20x



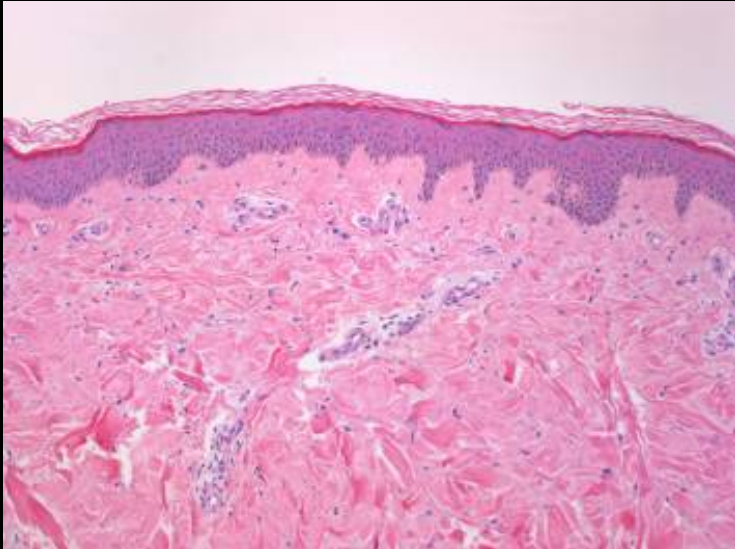
HandPlaSter – Patient 3

Plasma

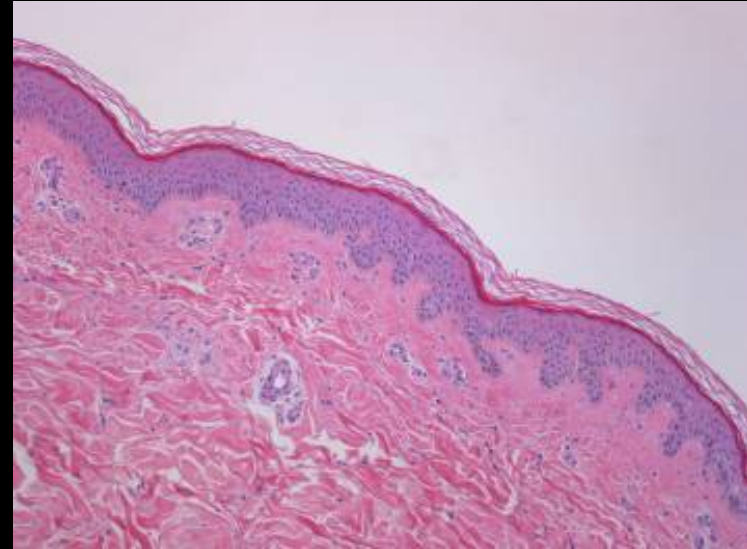
treatment-time

Control

10x



10x

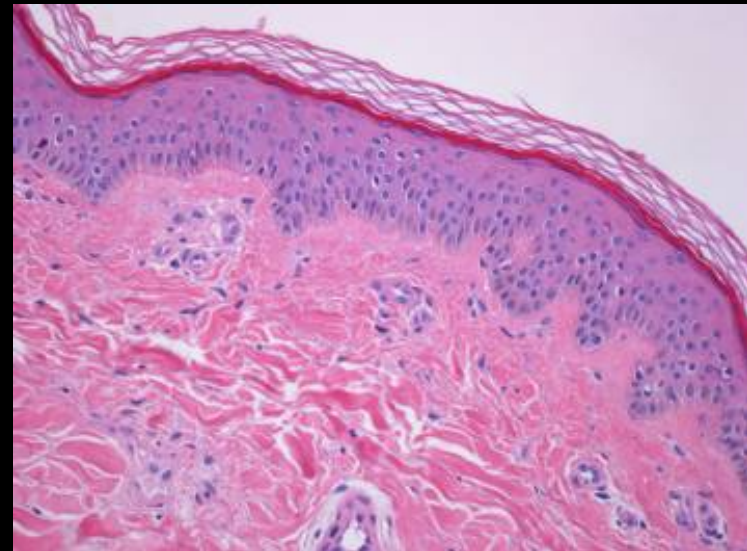


600s

20x



20x



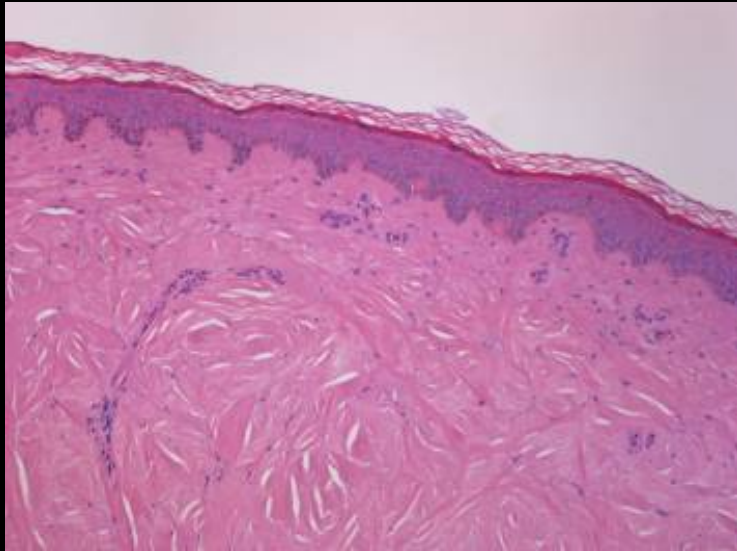
HandPlaSter – Patient 3

Plasma

treatment-time

Control

10x

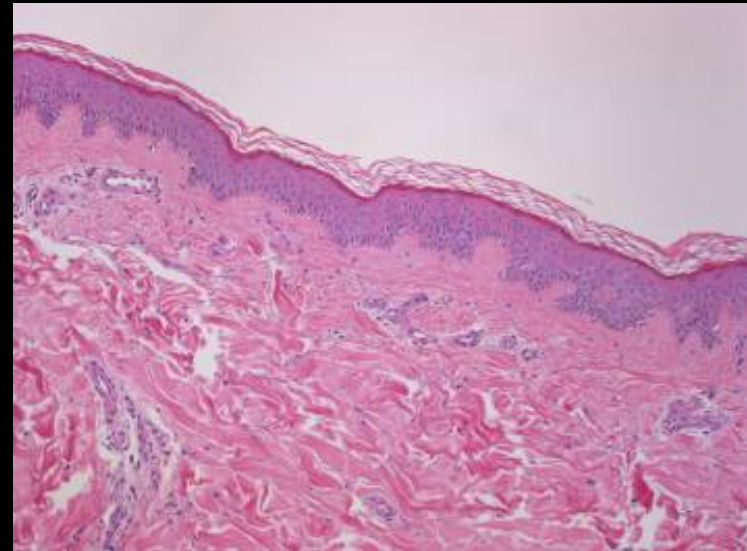


600s

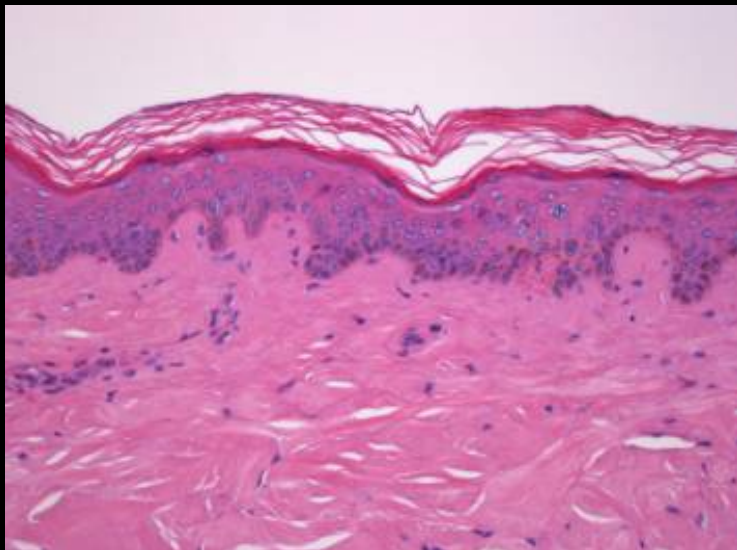
break 300s

+ 600s

10x



20x



20x

