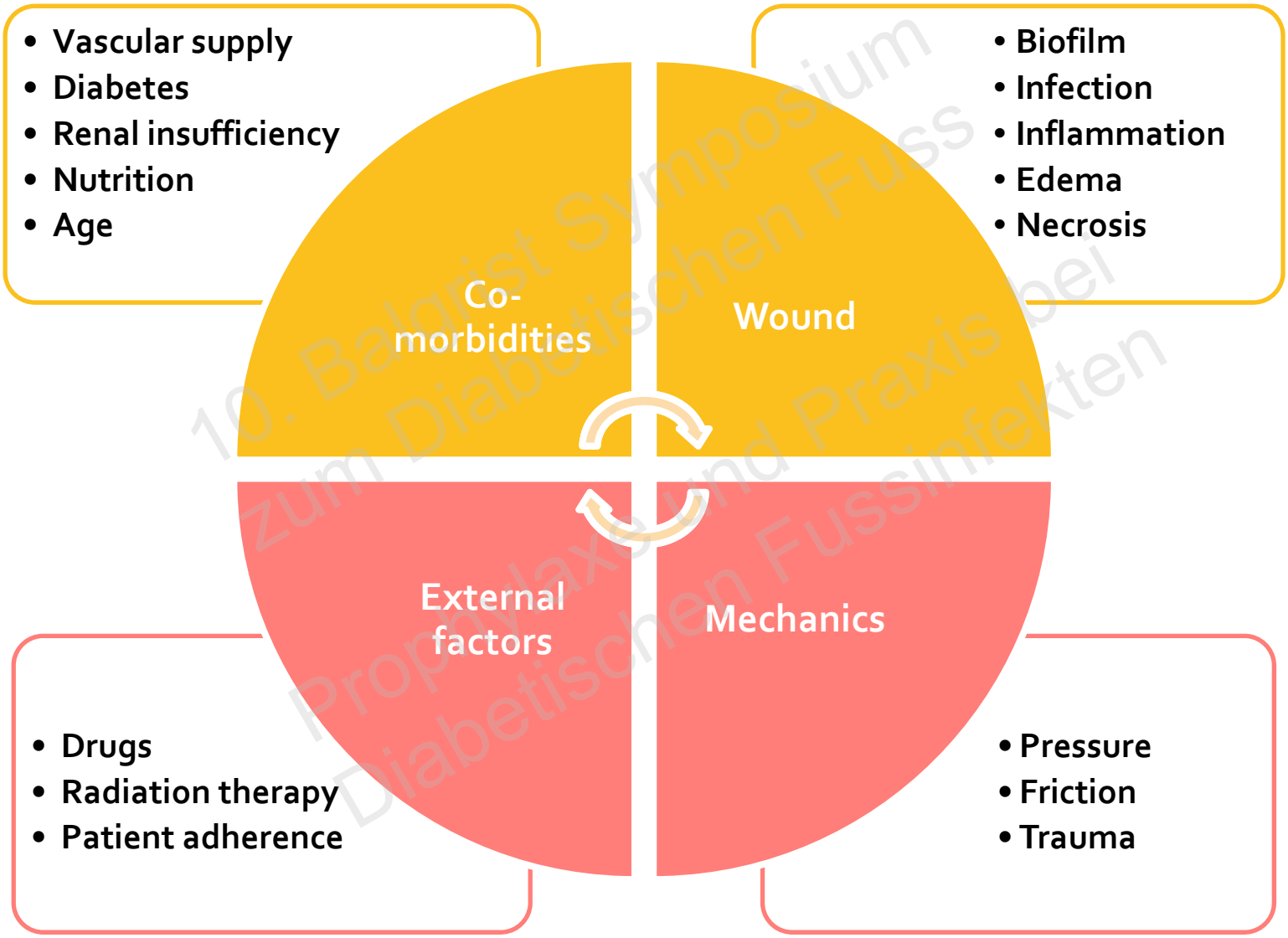
WUNDBEHANDLUNG UND - AUFLAGEN BEI DIABETISCHEN FUSSINFEKTEN

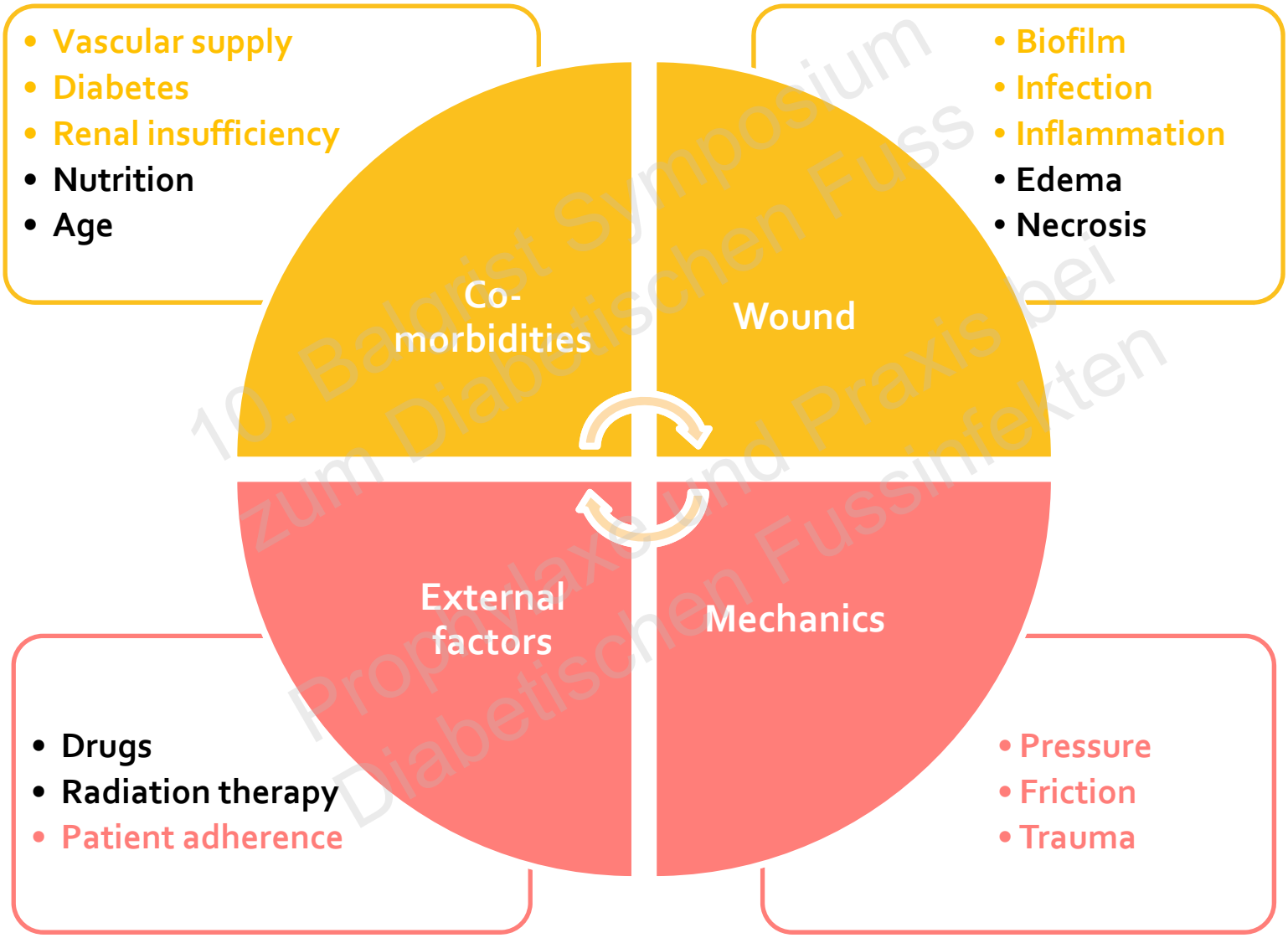
10. Balgrist Symposium zum Diabetischen Fuss
Prophylaxe und Praxis bei Diabetischen Fussinfekten
3. November 2023

PD Dr. med. Dieter Mayer, FEBVS, FAPWCA
FMH für Chirurgie und Gefässchirurgie
Experte für komplexe und nichtheilende Wunden

Checklist for Factors Affecting Wound Healing



Checklist for Factors Affecting Wound Healing



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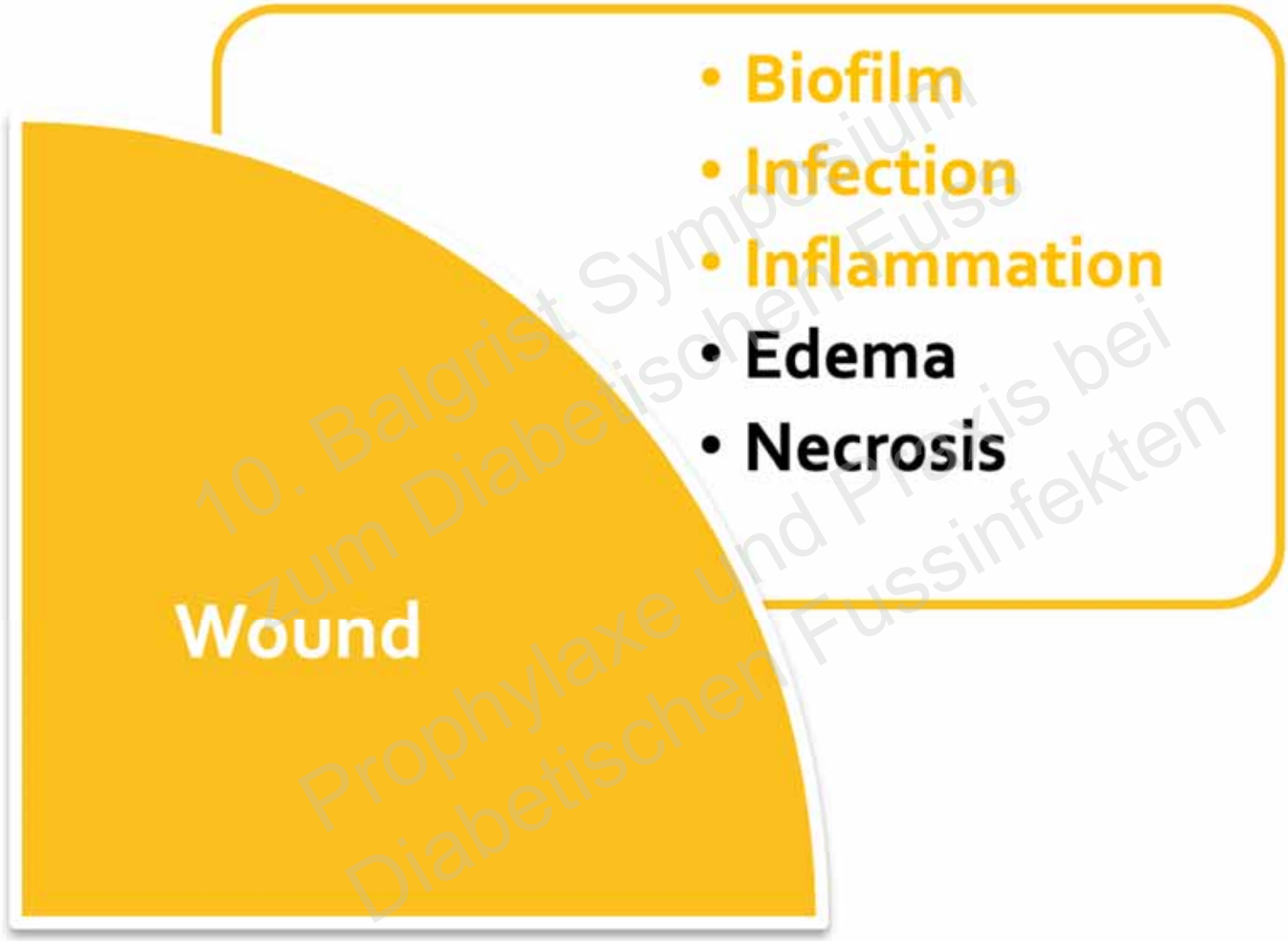


Biofilm in wound healing

From *in vitro* to *in vivo* Models of Bacterial Biofilm-Related Infections

David Lebeaux †, Ashwini Chauhan †, Olaya Rendueles ‡, Christophe Beloin *

Pathogens 2013, 2, 288-356; doi:10.3390/pathogens2020288

"Bacteria in biofilms cause up to 80% of all human infections"

ESCMID* guideline for the diagnosis and treatment of biofilm infections 2014

N. Høiby[1,2], T. Bjarnsholt[1,2], C. Moser[1], G. L. Bassi[3], T. Coenye[4], G. Donelli[5], L. Hall-Stoodley[6], V. Holá[7], C. Imbert[8], K. Kirketerp-Møller[9], D. Lebeaux[10], A. Oliver[11], A. J. Ullmann[12] and C. Williams[13], for the ESCMID Study Group for Biofilms (ESGB) and Consulting External Expert Werner Zimmerli[14]

Clin Microbiol Infect 2015;21 Suppl 1:S1-25. DOI: 10.1016/j.cmi.2014.10.024.

"Biofilm bacteria are involved in >60% of all chronic wound infections"

Biofilm - Definition

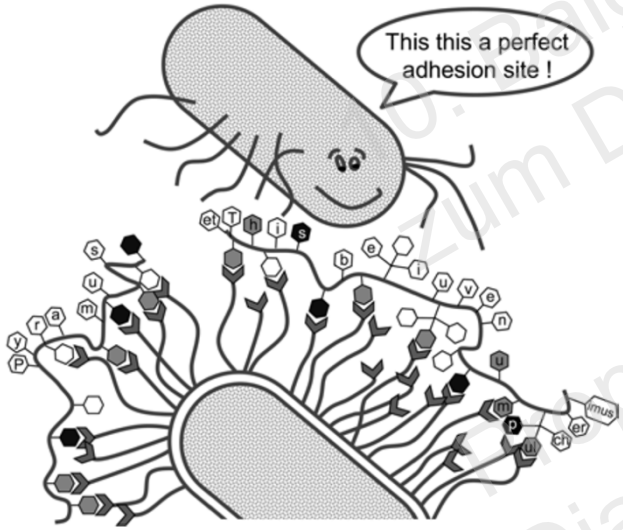
A biofilm is a microbially derived sessile community characterized by cells that

- **are irreversibly attached to a substrate or interface or to each other**
- **are embedded in a matrix of extracellular polymeric substances (EPS) that they have produced**
- **exhibit an altered phenotype in comparison to planktonic cells with respect to**
  - **growth rate and**
  - **gene transcription**

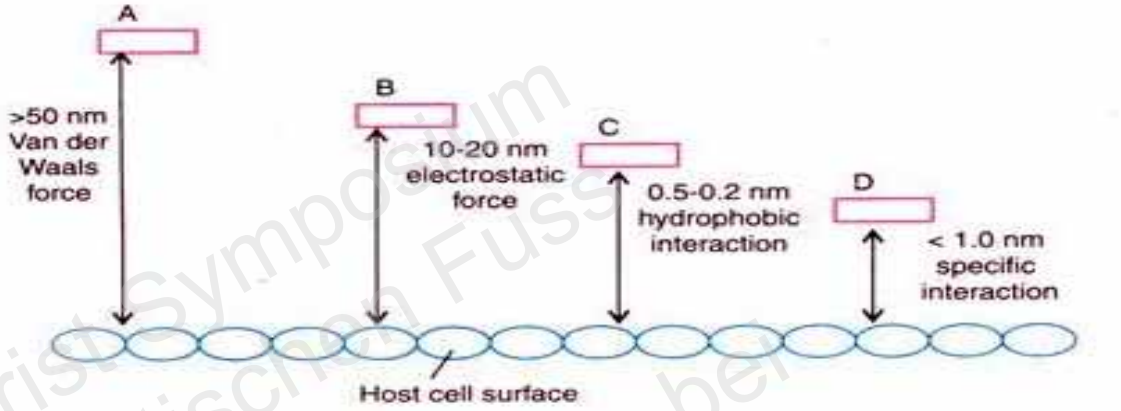
Donlan and Costerton (2002): Biofilms: Survival Mechanisms of Clinically Relevant Microorganisms. Clin Microbiol Rev, 15, 167-193

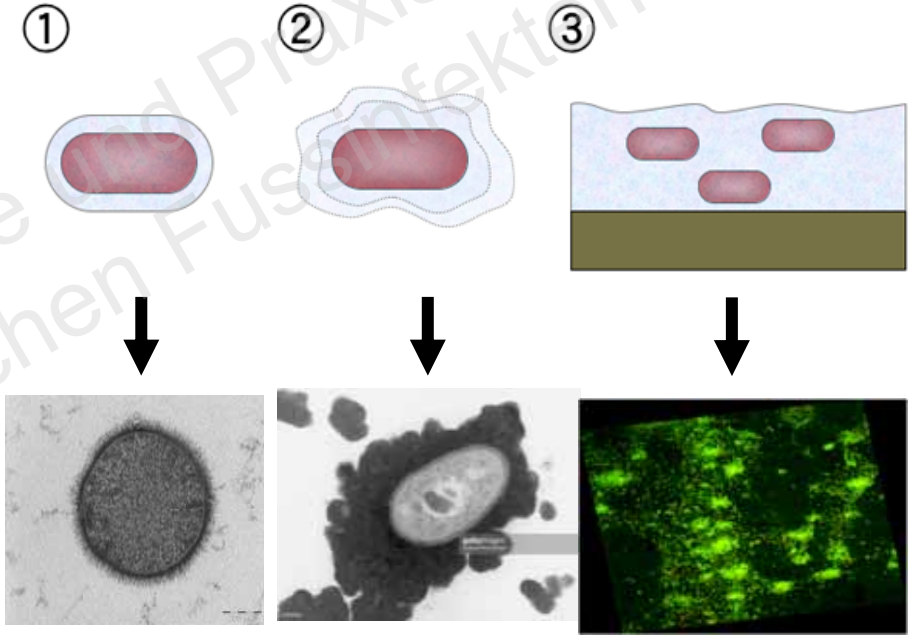
Stage 1
Conditioning

- **Conditioning… film**
  - *Glycoproteins, proteins, carbohydrates*
- **Adhesion 1 – Single cells/aggregated**



CHAPTER 1 : Small Molecule Ligands for Bacterial Lectins: Letters of an Antiadhesive Glycopolymer Code, in *Glycopolymer Code: Synthesis of Glycopolymers and their Applications*, 2015, pp. 1-16 DOI: https://doi.org/10.1039/9781782622666-00001

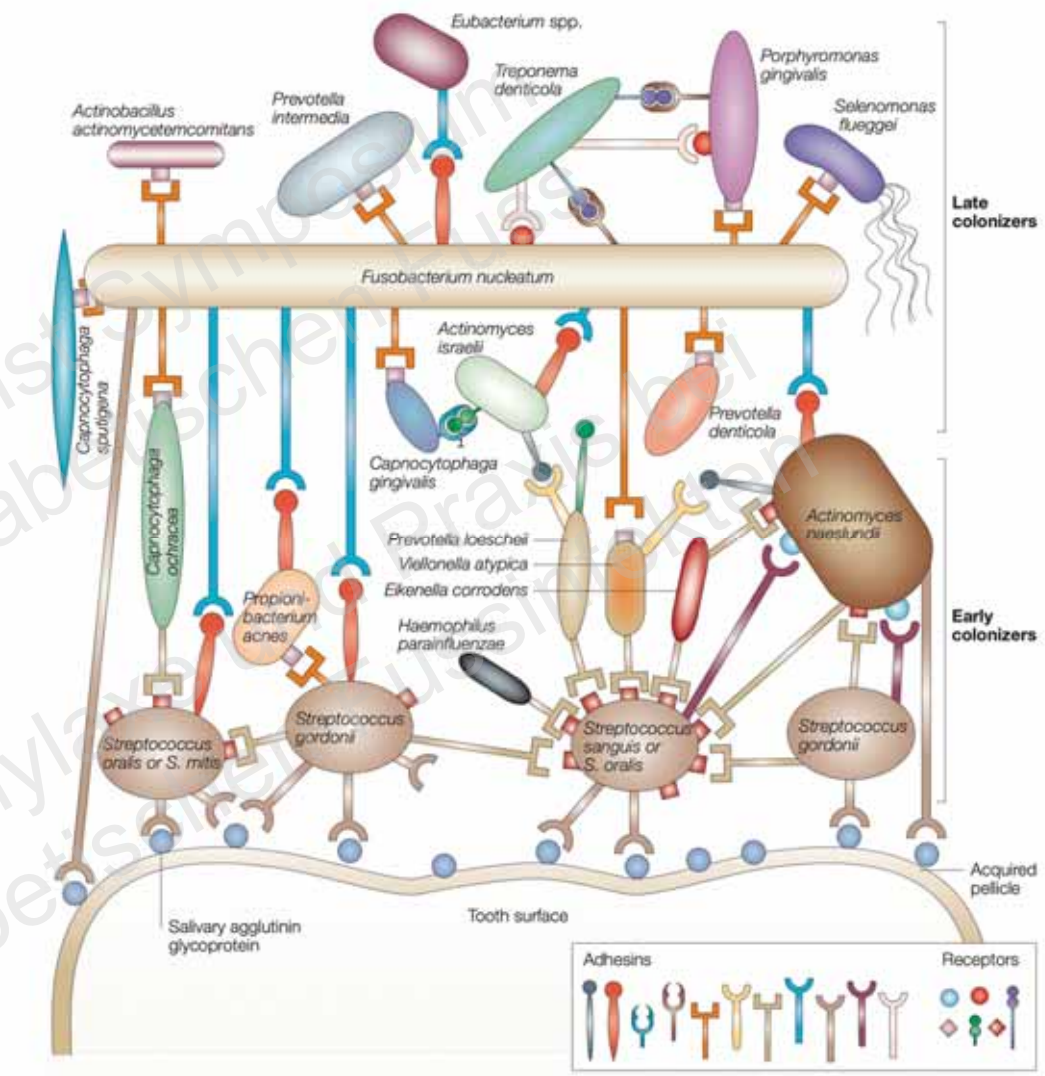




Courtesy S Percival

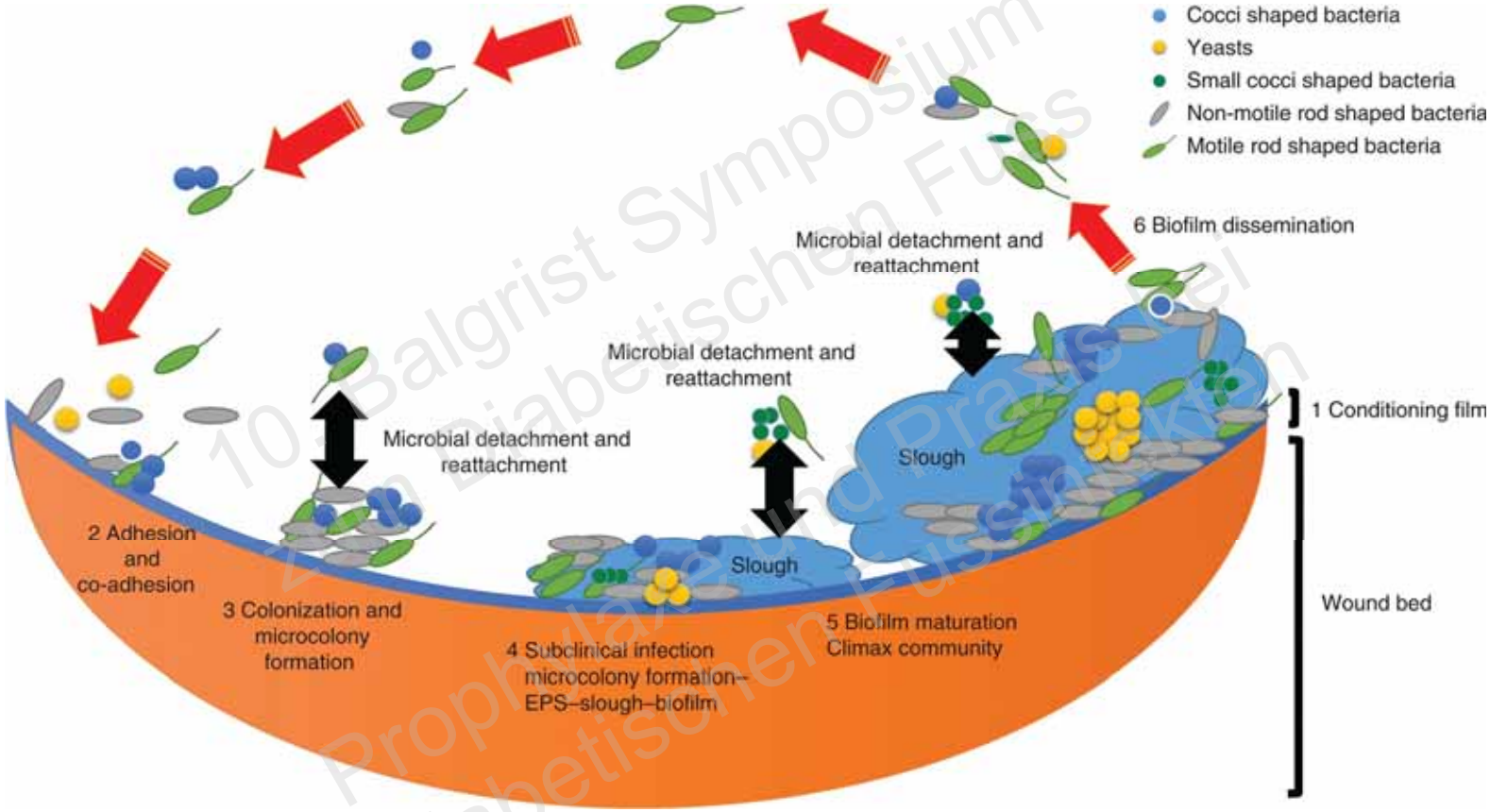
Stage 2:
Adhesion

- **The molecular and physical interactions that are involved in the adhesion process have not yet been completely understood.**
- **Microbial cells may attach to surfaces via specific and non-specific interactions**



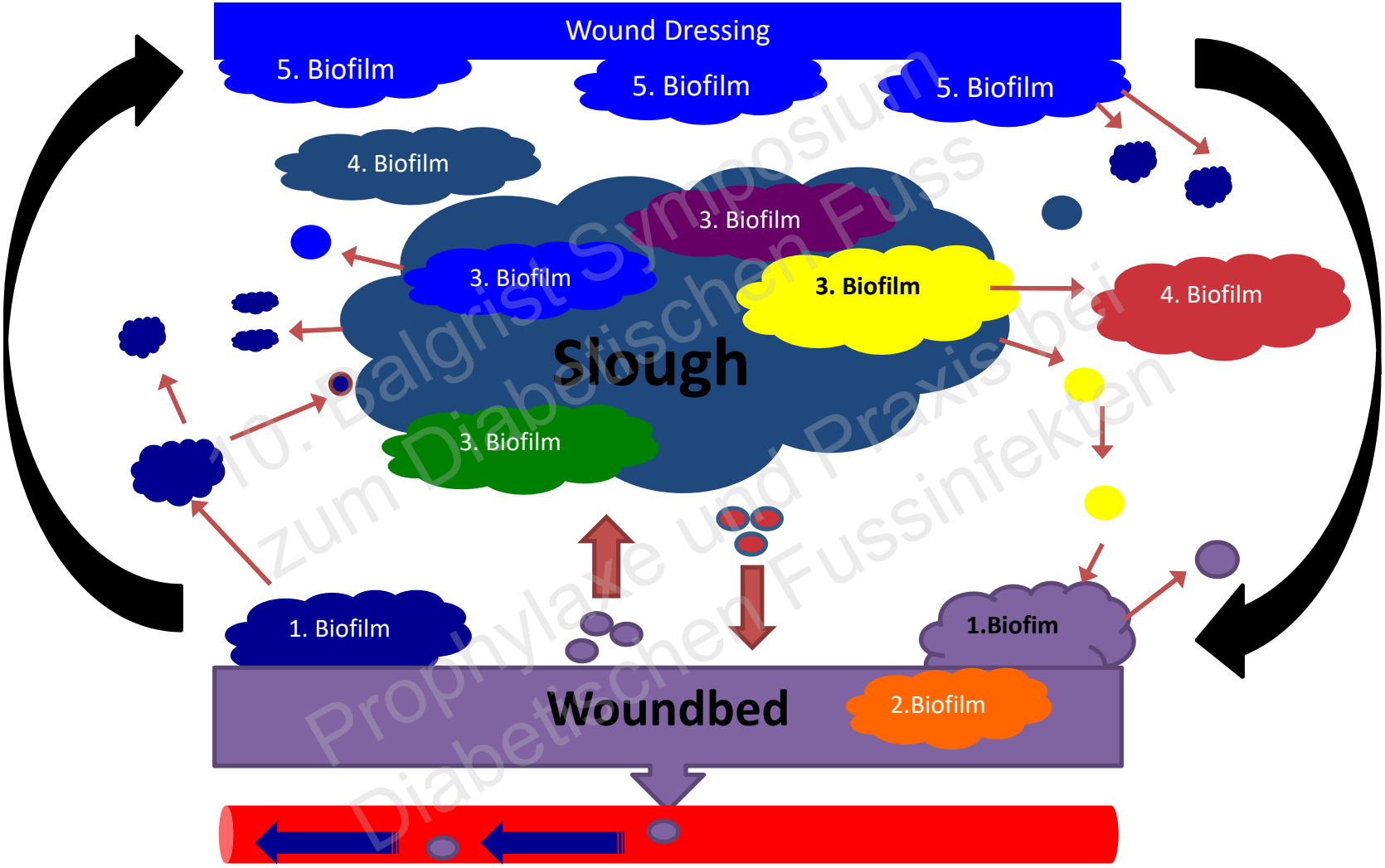
Bakaletz, L. Nat Rev Microbiol 2, 552–568 (2004)

Stage 3:
Biofilm Development and Dissemination



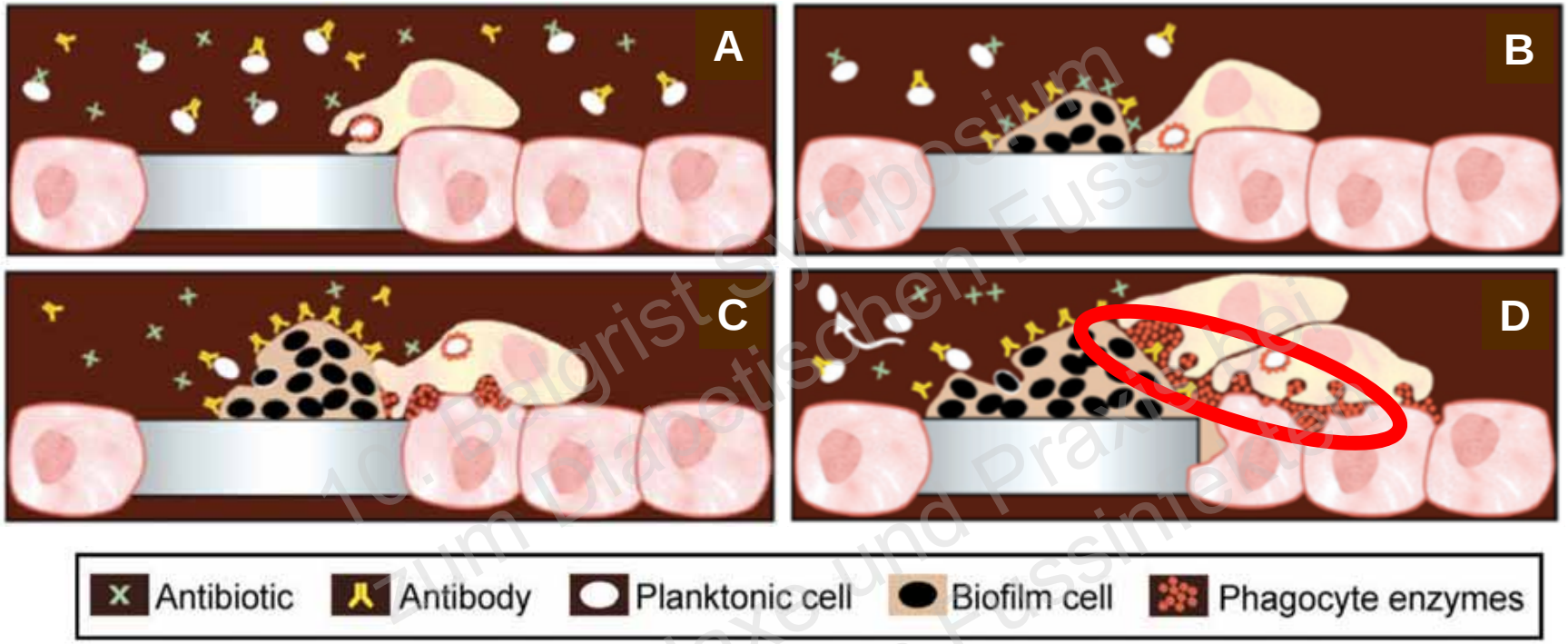
British Journal of Surgery, Volume: 104, Issue: 2, Pages: e85-e94, First published: 25 January 2017, DOI: (10.1002/bjs.10433)

There is more than one!!!



Percival SL, Suleman L. Slough and biofilm: removal of barriers to wound healing by desloughing. J Wound Care. 2015 Nov;24(11):498, 500-3, 506-10.

How Does The Immunological Response to Biofilms Cause Tissue Damage and Impair Healing?



In Panel A, planktonic bacteria can be cleared by antibodies, phagocytosis, and are susceptible to antibiotics. Adherent bacterial cells (Panel B) form biofilms preferentially on inert surfaces or devitalized tissue, and these sessile communities are resistant to antibodies, phagocytosis and antibiotics. Neutrophils (Panel C) are attracted to the biofilms, but cannot engulf biofilm. Neutrophils still release proteases and reactive oxygen species. Phagocytic enzymes (Panel D) damage tissue around the biofilm, and planktonic bacteria are released from the biofilm, causing dissemination and acute infection in neighboring tissue. Costerton, Stewart, Greenberg, Science 284, 1999

Courtesy G Schultz

Clinical Relevance

- Debridement at regular intervals
- "Antibiofilm" antiseptic dressings
- Dressing changes at suitable intervals

Diagnostics of DFI

Senneville É, Albalawi Z, van Asten SA, et al. IWGDF/IDSA Guidelines on the Diagnosis and Treatment of Diabetes-related Foot Infections (IWGDF/IDSA 2023). Clinical Infectious Diseases 2023. DOI: 10.1093/cid/ciad527.

Recommendation 1

(a) Diagnose a soft tissue diabetes-related infection clinically based on the presence of local or systemic signs and symptoms of inflammation. GRADE recommendation: Strong; Certainty of evidence: Low)

(b) Asses the severity of any Diabetes-related foot infection (DFI) using the International Working Group on the Diabetic Foot (IWGDF)/Infectious Diseases Society of America (IDSA) classification scheme. (Strong; Low).

Table 1. The classification system for defining the presence and severity of foot infection in a person with diabetes.[a]

Clinical classification of infection, definitions	IWGDF/IDSA classification
No systemic or local symptoms or signs of infection	1/Uninfected
Infected: At least two of these items are present: • Local swelling or induration • Erythema >0.5 but <2 cm[b] around the wound • Local tenderness or pain • Local increased warmth • Purulent discharge	2/Mild
And, no other cause of an inflammatory response of the skin (e.g., trauma, gout, acute charcot neuro-arthropathy, fracture, thrombosis, or venous stasis)	
Infection with no systemic manifestations and involving: • Erythema extending ≥2 cm[b] from the wound margin, *and/or* • Tissue deeper than skin and subcutaneous tissues (e.g., tendon, muscle, joint, and bone)[c]	3/Moderate
Infection involving bone (osteomyelitis)	Add "(O)"
Any foot infection with associated systemic manifestations (of the systemic inflammatory response syndrome [SIRS]), as manifested by ≥2 of the following: • Temperature, > 38°C or <36°C • Heart rate, > 90 beats/min • Respiratory rate, > 20 breaths/min, *or* PaCO2 < 4.3 kPa (32 mmHg) • White blood cell count >12,000/mm^3, *or* < 4G/L, *or* >10% immature (band) forms	4/Severe
- Infection involving bone (osteomyelitis)	Add "(O)"

The presence of clinically significant foot ischaemia makes both diagnosis and treatment of infection considerably more difficult.

[a]infection refers to any part of the foot.

[b]in any direction, from the rim of the wound.

[c]if osteomyelitis is demonstrated in the absence of ≥2 signs/symptoms of local or systemic inflammation, classify the foot as either grade 3(O) (if <2 SIRS criteria) or grade 4(O) if ≥2 SIRS criteria) (see text).

Diagnostics of DFI

Senneville É, Albalawi Z, van Asten SA, et al. IWGDF/IDSA Guidelines on the Diagnosis and Treatment of Diabetes-related Foot Infections (IWGDF/IDSA 2023). Clinical Infectious Diseases 2023. DOI: 10.1093/cid/ciad527.

Recommendation 4

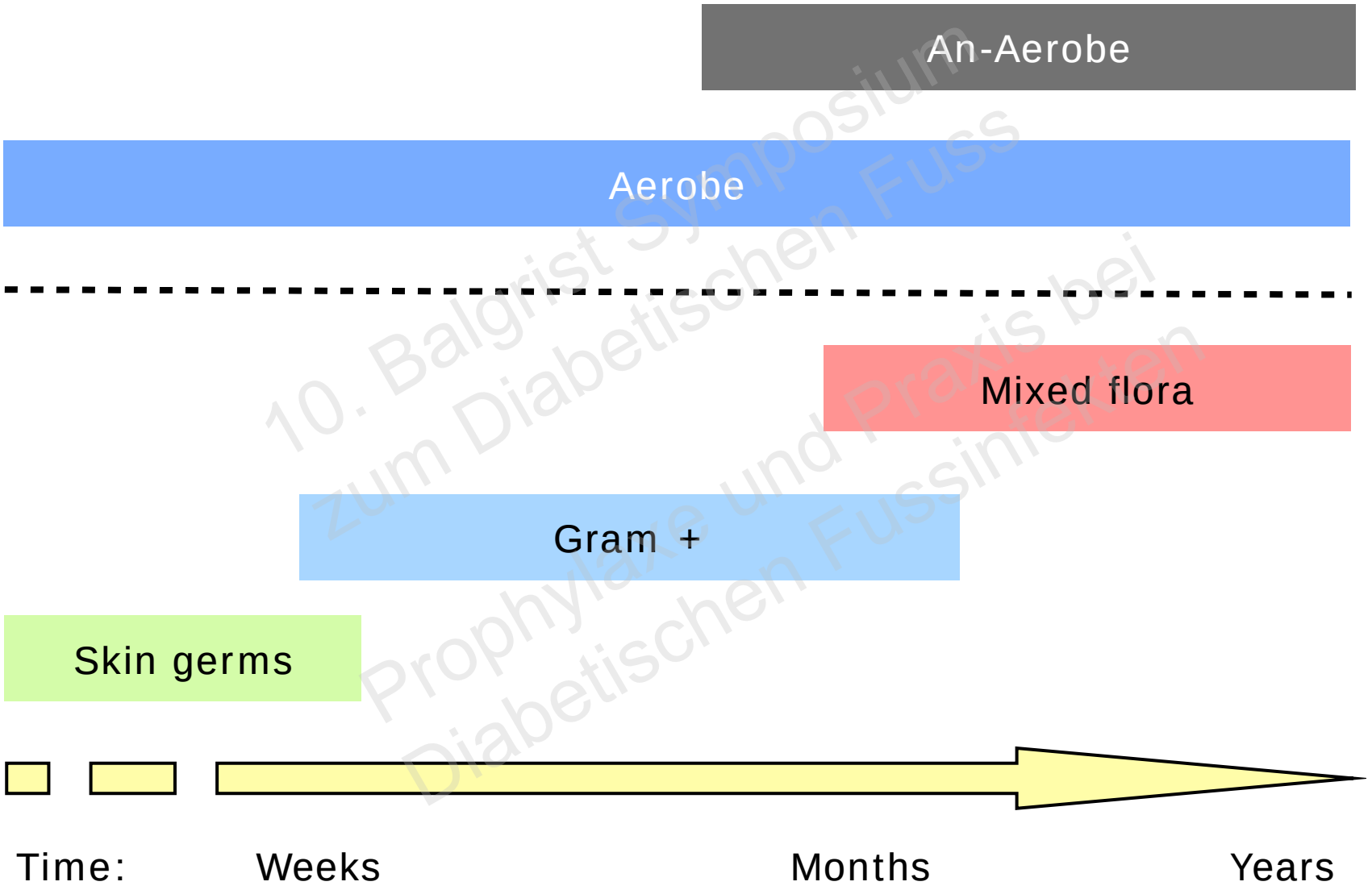
For diagnosing diabetes-related foot soft-tissue infection, we suggest not using foot temperature (however measured) or quantitative microbial analysis. (Conditional; Low).

Table 3. Odds ratios, sensitivity, and specificity for presence of clinical assessment variables by semi-quantitative culture results (scant/light or moderate to heavy bacterial growth)

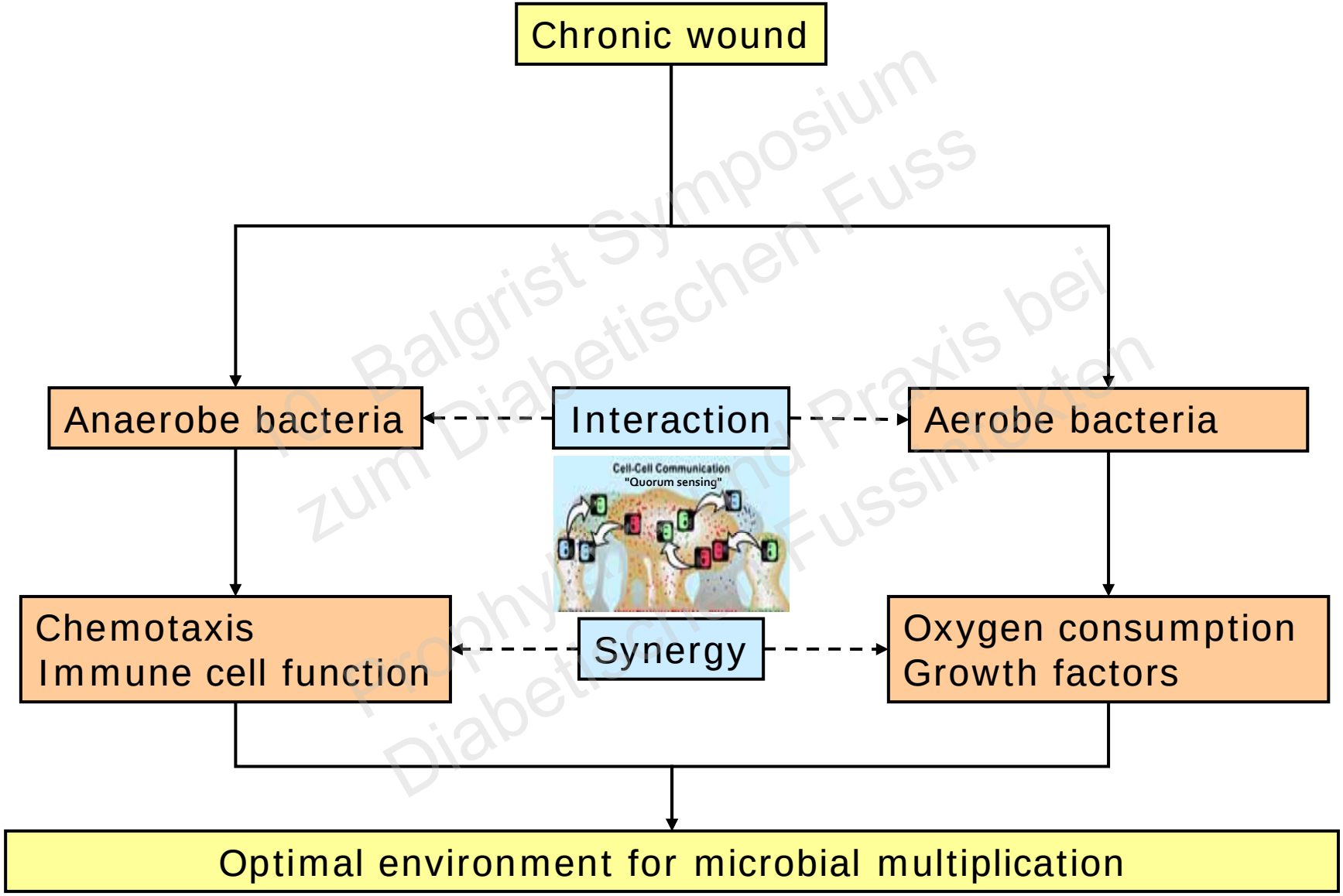
	Signs and symptoms	Odds ratio (95% CI)	Sensitivity (%)	Specificity (%)
	Scant / light bacterial growth			
N	Nonhealing	0.42 (0.18–0.97)	32	47
E	Exudate	5.36 (0.54–53.66)	70	64
R	Red friable tissue	5.07 (1.7–14.83)	45	86
D	Debris	5.63 (2.19–14.45)	62	78
S	Smell	3.59 (1.22–10.58)	37	86
	Moderate / heavy bacterial growth			
S	Size increasing	5.00 (1.82–13.76)	50	83
T	Temperature	8.05 (2.90–22.38)	76	71
O	O (probes to bone)	2.76 (1.04–7.31)	40	81
N	New breakdown	5.71 (1.79–18.21)	37	89
E	Edema/erythema	4.88 (1.79–13.27)	87	44
E	Exudate	4.13 (1.72–9.91)	70	64
S	Smell	3.59 (1.22–10.58)	37	86

Woo KY, Sibbald RG. Ostomy Wound Manage 2009;55(8):40-8.

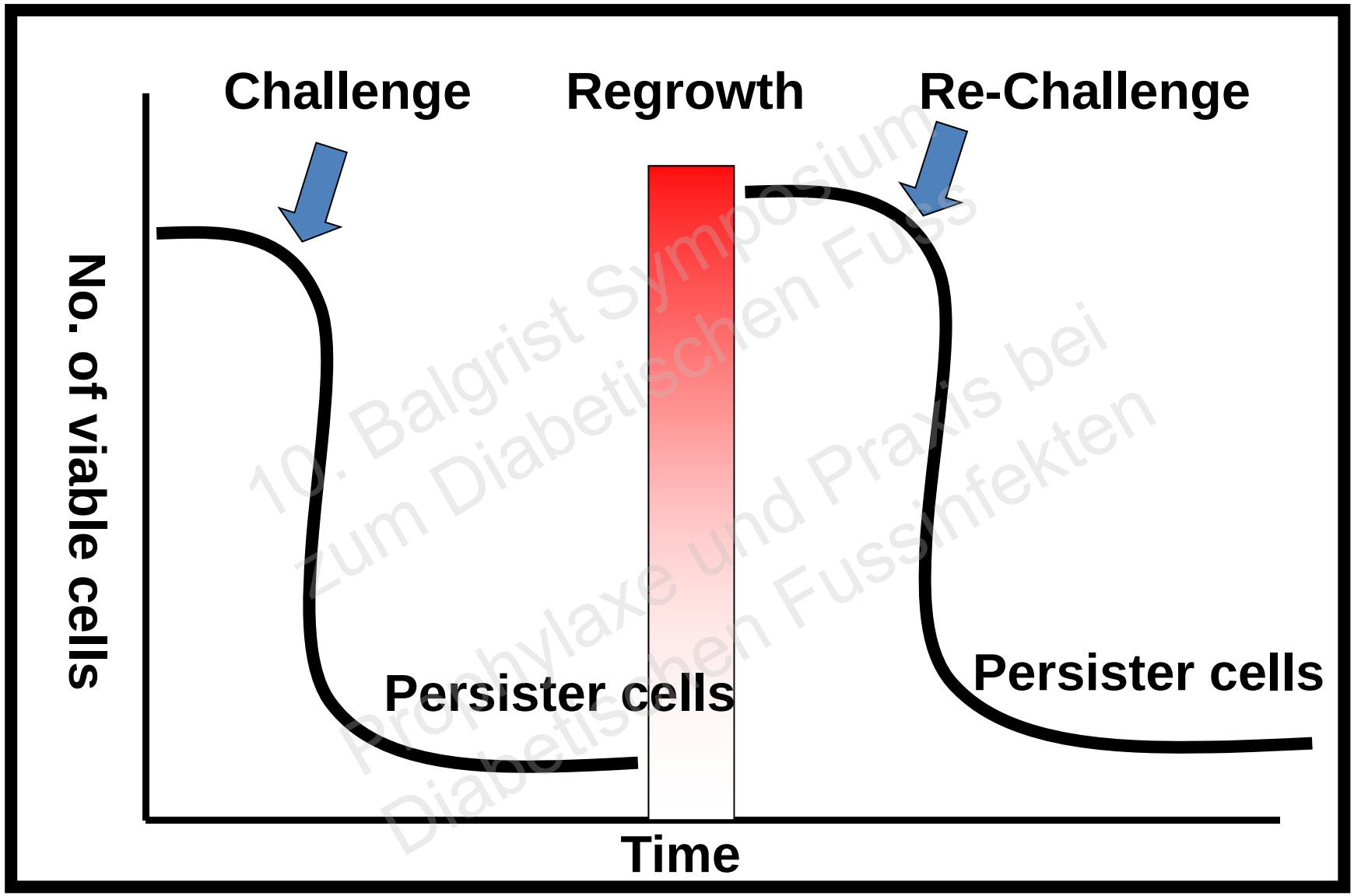
Microbial shift in wounds



Microbial interaction („quorum sensing“)



Persister Cells



Clinical Relevance

Early Diagnosis of DFI is key to outcome

Clinical expression of DFI not always clear

Guidelines not always helpful in daily life

Treatment of DFI

Senneville É, Albalawi Z, van Asten SA, et al. IWGDF/IDSA Guidelines on the Diagnosis and Treatment of Diabetes-related Foot Infections (IWGDF/IDSA 2023). Clinical Infectious Diseases 2023. DOI: 10.1093/cid/ciad527.

Recommendation 23

We suggest not using the following treatments to address DFIs:

(a) adjunctive granulocyte colony-stimulating factor (G-CSF) treatment or

(b) topical antiseptics, silver preparations, honey, bacteriophage therapy, or negative- pressure wound therapy (with or without instillation). (Conditional; Low).

Table V. Antimicrobial dressings for diabetic foot ulcers

Antiseptics/antimicrobials	Bacterial sensitivity	Effect	Adverse effect
Iodine-based Povidone iodine, 10% solution, Cadexomer iodine, and Inadine (available in Europe and Canada, but not in the United States)	• Broad antibacterial effect (Gram-positives more than Gram-negatives) and MRSA • Good penetration of biofilms	• Short-term treatment and reassess every 2-4 wks • Cadexomer iodine releases the iodine slowly to make it less toxic + cadexomer sugar for autolytic debridement + absorbency • Antibacterial effect (0.005% concentration) without tissue toxicity	• Can be toxic to granulation tissue • Antimicrobial action may be neutralized by inorganic and organic agents • Thyroid dysfunction • Can develop an allergy
Chlorhexidine, polyhexamethylene biguanide hydrochloride, a derivative of chlorhexidine—foam and gauze	• Gram-positives more than Gram-negatives, yeast, mold	• 0.02% concentration has been used for wound irrigation • Promotes wound healing[83]	• May damage cartilage/ear toxicity[84,85]
Acetic acid, white vinegar 5%	• Gram-negatives, particularly Pseudomonas	• Compresses 5-10 min • Dilute 1:5 (1%) or 1:10 water (0.5%)	• High concentration and long contact • May have some tissue toxicity and inhibits fibroblast growth
Silver compounds Silver dressings, foams, calcium alginates, hydrofibers, hydrogels, sheets, and powder; silver sulfadiazine cream; silver nitrate sticks	• Antibacterial, including *Escherichia coli*, Klebsiella, *Staphylococcus aureus*, and MRSA • Antifungal • Antiviral	• Must be combined with water to be in the ionized state—Ag +, ++, and +++ • Silver nanoparticles enhanced contact and bactericidal activity • Antiinflammatory effect may relate to the Ag 0 state	• Silver toxicity to reepithelialization process • Toxicity much less with dressings than silver • Sulfadiazine cream with much higher silver release • Sticks plus silver sulfadiazine cream may produce proinflammatory pseudoeschar/delay healing
Honey (medical grade; often Manuka honey), calcium alginate; hydrogel; hydrocolloid	• Antibacterial • Antifungal • Antiviral	• Antiinflammatory • High osmolar concentration contributes to the antibacterial effect	• Potential risk of botulism with food product honey[86]
Sodium hypochlorite (bleach)	• Broad antibacterial effect (Gram-positives more than Gram-negatives)	• Antibacterial effect (0.005%) without lower tissue toxicity	• Irritant with high tissue toxicity • Inhibit fibroblast in 1% concentration • Best used as disinfectant and not for wound care
Benzalkonium chloride	• Gram-positive and -negative, fungi	• Compromised bactericidal activity because of neutralization with organic matter in tissue fluids	• Very high tissue toxicity
Hydrogen peroxide	• Gram-positive bacteria with 3% concentration	• Limited mechanical debridement • Biofilm reduction	• Bulla formation • Risk of air emboli[87] if applied to deep cavities

MRSA, Methicillin-resistant *Staphylococcus aureus*.

J Am Acad Dermatol Volume 70, Number 1

Alavi et al 21.e17

Alavi A, Sibbald RG, Mayer D, et al. Diabetic foot ulcers: Part II. Management. Journal of the American Academy of Dermatology 2014;70(1):21 e1-24; quiz 45-6. DOI: 10.1016/j.jaad.2013.07.048.

„Modern Wound Therapy“

- **All but…**

Semi-occlusive dressings

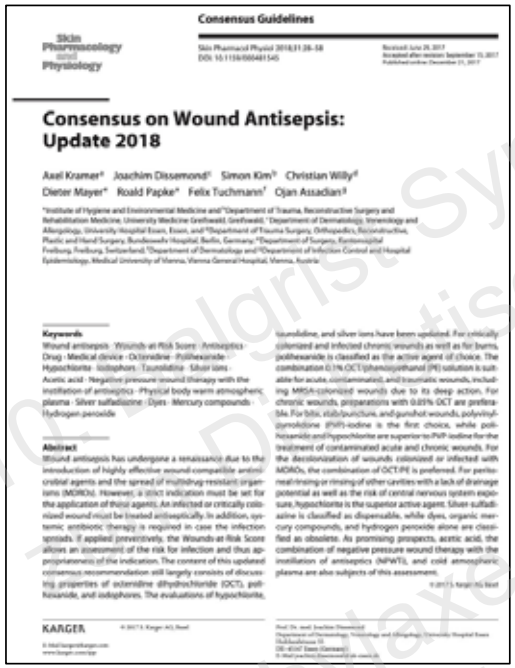
- **Infected wounds**
- **Tumors**
- **Terminal PAD IV**
- **Akrale Nekrosen**
- **(Diabetes)**
- **(Implants)**

Non-occlusive dressings

Which dressing?

Decontamination

Consensus 2018 / Update 2019


Consensus Guidelines

Skin Pharmacology and Physiology

Consensus on Wound Antisepsis: Update 2018

Axel Kramer[a] Joachim Dissemond[b] Simon Kim[b] Christian Willy[d] Dieter Mayer[e] Roald Papke[a] Felix Tuchmann[f] Ojan Assadian[g]

KARGER

The consensus was reviewed and formally approved by the boards of the following scientific associations:

- Dachorganisation deutschsprachiger Vereine und Gruppen im Bereich Wundmanagement (Wund-D.A.CH.)
- Österreichische Gesellschaft für Krankenhaushygiene (ÖGKH)
- Deutsche Gesellschaft für Krankenhaushygiene (DGKH)
- Initiative Chronische Wunden e. V. (ICW)
- Working Group Antiseptics of the International Society of Chemotherapy for Infection and Cancer (ISC)

What, when, how to use (frequency, duration)

Indications for the antiseptic treatment of wounds	**Preparation for debridement or wound cleansing of chronic wounds**
	Treatment of local wound infection
	Prevention of infection of traumatic wounds
	Prevention of postoperative surgical site infections (SSI)
	Decolonisation in case of MSSA, MRSA & other MRB…

In case of therapeutic failure of an antiseptic after 2 weeks of treatment, review the therapeutic regimen and perform further diagnostics!

What, when, how to use (frequency, duration)

Criteria for the selection of active ingredients

Acute wounds

- In acute wounds, the focus is on the **rapid onset of efficacy** of the antiseptic, possibly with required **depth effect** (bite, puncture, gunshot wound).

Chronic wounds

- For chronic wounds, a **longer exposure time** is desirable for achieving the antiseptic effect due to repeated application and/or remanent effect on the wound; ideally, wound healing should be promoted.

Efficacy (≥ 3 log¹⁰) and (local / systemic)tolerance!

What, when, how to use (frequency, duration)

Important characteristics of antimicrobial agents used on wounds

Compound	Antimicrobial onset time	Depth effect[2]	Resistance development	Wound healing	Cartilage tolerability	Sensitization	Systemic risks
Ag^+	>24 h[1]	3	Yes	Inhibition	?	Yes (very rare)	Cannot be excluded
CHD gel (0,05%)	3-10 h[1]	1	Yes	No inhibition	No	Yes (rare), anaphylaxis (n>200)	?[5]
Acetic acid	5 min-3 h	2	No	At 0,15% supportive	?	No	No
OCl^-	30 s-5 min[1,3]	2	No	Supportive	< 0,00004%	No	No
OCT gel (0,05%)	5 min-10 h[1]	1[4]	No	No inhibition	No	No	No
PHMB gel (0,04%)	30 min-3 h[1]	2	No	Supportive	< 0,005%	Yes (rare), anaphylaxis (n=3)	No
PVP-I (10%)	5-30 min[1]	3	No	Partial inhibition	Yes (0,5%)	Yes	Yes

[1] Test-carrier (TC) with organic load; [2] Due to a lack of experimental data, theoretical extrapolation based on physicochemical properties or demonstrated absorption: 1= superficial effect due to high protein binding, 2= shallow penetration depth, 3= larger than 2; [3] Without load; [4] In combination with phenoxyethanol 2 or 3; [5] Possibility of separation of 4-chloraniline from the chlorhexidine molecule .

Skin Pharmacol Physiol 2018; 31(1): 28-58

What, when, how to use (frequency, duration)

Conclusions of the analyzed clinical studies				
Feature	**NaOCl/HOCl**	**OCT**	**PHMB**	**PVP-I**
Antiseptic efficacy	Yes	Yes	Yes	Yes
Stimulation of wound healing	Yes**	No inhibition	Yes	Partial inhibition
Peritoneal irrigation in case of septic peritonitis	Possible	Contraindicated	Contraindicated	Contraindicated
Exposed CNS	Possible	Contraindicated	Contraindicated	Toxic
Exposed cartilage	< 0,00004%*	Contraindicated	Only at ≤ 0,005%	Yes
Better than Ag+ PVP-I CHD	 Tend. better Sign. better No studies	 Sign. better Tend. better No studies	 Sign. better Sign. better Sign. better	 Tend. better - No studies

What, when, how to use (frequency, duration)

Orientating recommendation for the indication-based selection of wound antiseptics

Indication	**Antiseptic compound**	
	1st choice	2nd choice
Critically colonized wounds Wounds at risk of infection	PHMB	Hypochlorite, ionic silver, OCT/PE
Burns	PHMB	Hypochlorite
Byte, stab, and gunshot wounds	PVP-I	OCT/PE*
MDRO-colonized or infected wounds	OCT/PE	OCT, PHMB, ionic silver
Decontamination of acute and chronic wounds	Hypochlorite, PHMB, OCT	OCT/PE
Peritoneal lavage	Hypochlorite	-
Risque of CNS tissue exposure	Hypochlorite	-
Wounds with lack of drainage	Hypochlorite	-

* The prerequisite is good drainage without the risk of retention of OCT in the tissues!

After decontamination

"BEST PRACTICE" for non-infected (diabetic) wounds

Inflammation

Local reactive changes in tissues following Injury or Irritation

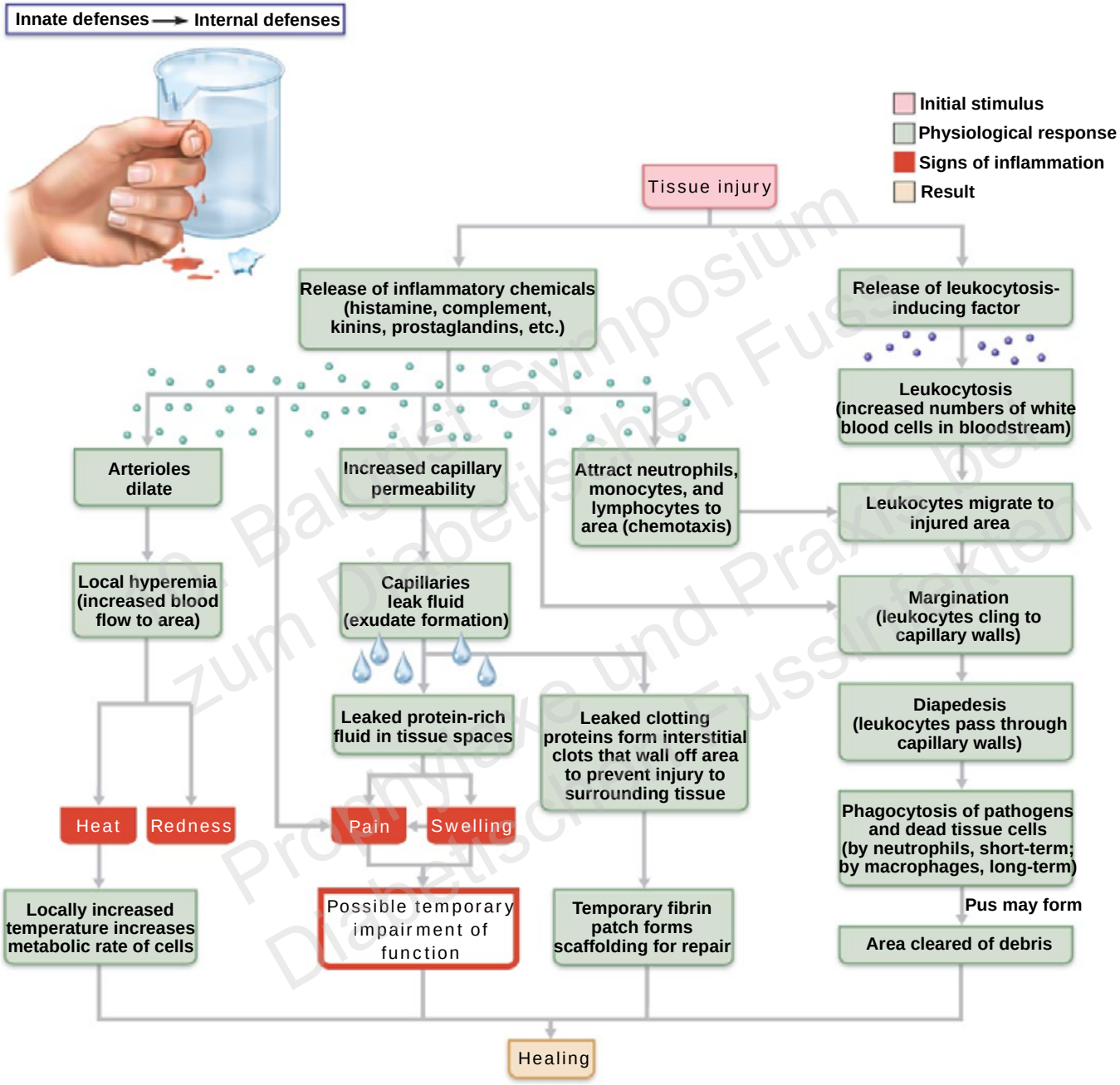
Infection

Invasion and spread of pathogenic bacteria

The vicious circle of inflammation, high protease activity levels and delayed wound healing

Sibbald RG, Orsted H, Schultz GS, et al. Preparing the wound bed: focus on infection and inflammation. *Ostomy Wound Manage*. 2003;49:23-51.

Figure 21.3 Inflammation: flowchart of events.

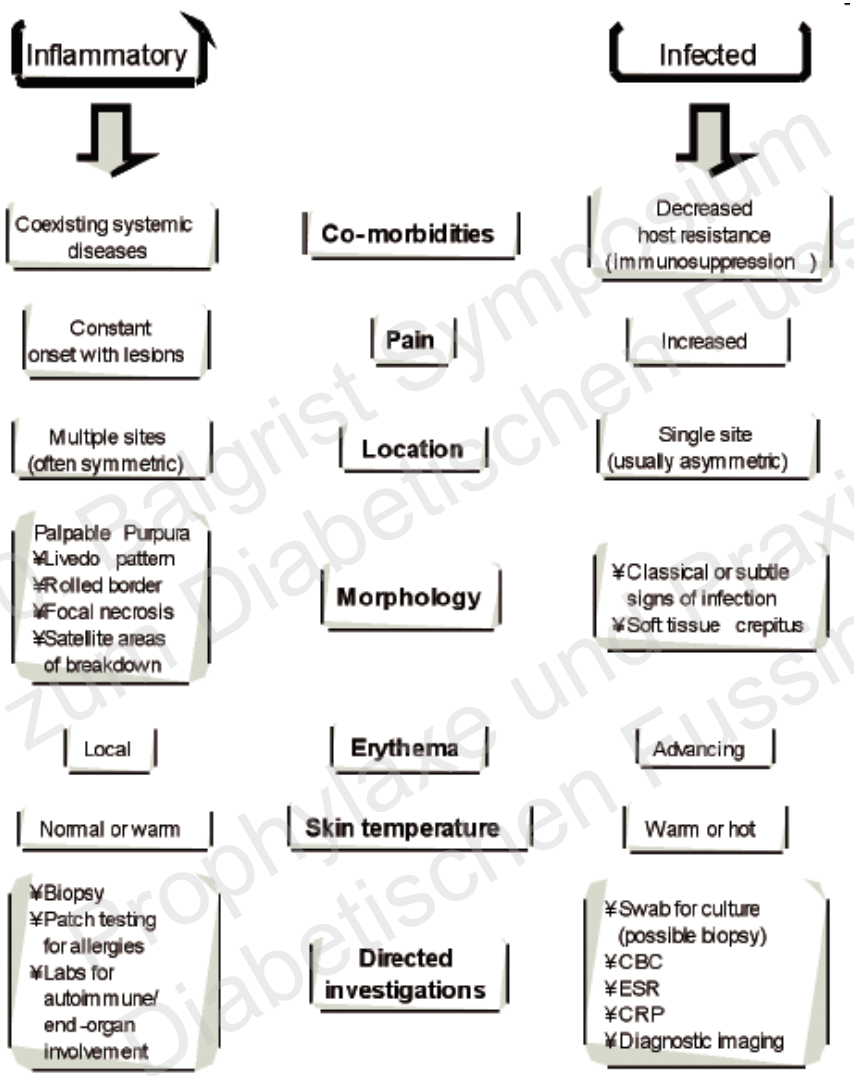


The difference

Table 2. Local signs of inflammation and infection (Cutting and Harding, 1994; Dowsett and Newton, 2005; Wound Source, 2016; WUWHS, 2019)	
Inflammation	**Infection**
Local swelling that decreases over time	Persistent swelling
Redness that decreases over time	Redness around the wound that continues to expand or worsen
Pain worsens with stimuli (e.g. touching or dressing change) and decreases over time; may increase and become continual in stalled/hard-to-heal wounds	Increasing or continual wound pain
Increased skin temperature near the wound	Increased skin temperature near the wound and possibly spreading from the wound
Loss of function and movement in the wounded area	Loss of function and movement in the wounded area
Exudate more likely to be: ■ Thin, watery or slightly thicker than water ■ Clear ■ Amber, straw-coloured or pink	Exudate more likely to be: ■ Thick ■ Cloudy, milky or opaque ■ Green, yellow, tan, brown or red ■ Malodourous
	Friable granulation tissue that bleeds easily
	Pocketing/bridging at the base of the wound
	Wound breakdown/enlargement
	Cellulitis/redness

Wounds UK (2019) Identifying and managing inflammation Made Easy. London: Wounds UK. Available from: www.wounds-uk.com/made-easy

The difference



CBC, Complete blood count; CRP, C -reactive protein; ESR, Erythrocyte sedimentation rate

Sibbald RG et al, Ostomy/Wound Management 2003;49(11):24-51

Clinical Relevance

How to treat?

INFLAMMATION

- MMP Scavengers (e.g. ORC/cellulose)
- Surfactant 68 / PMM Gel
- Anti-inflammatory drugs (NSAID, Corticosteroids, anti-TNF-alpha)
- NPWT
- Debridement

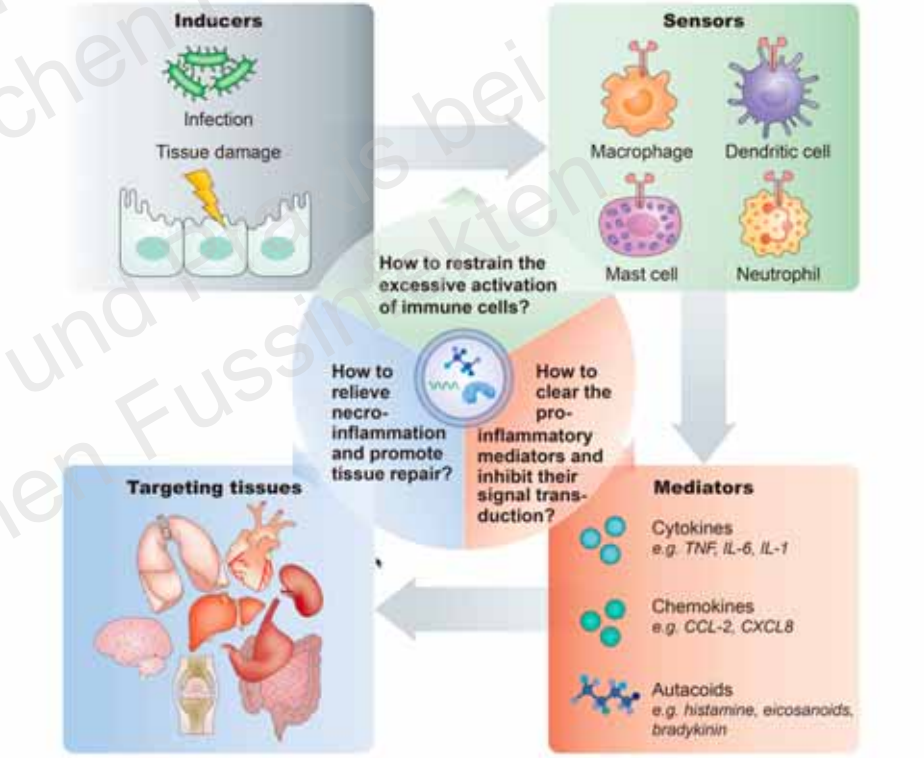
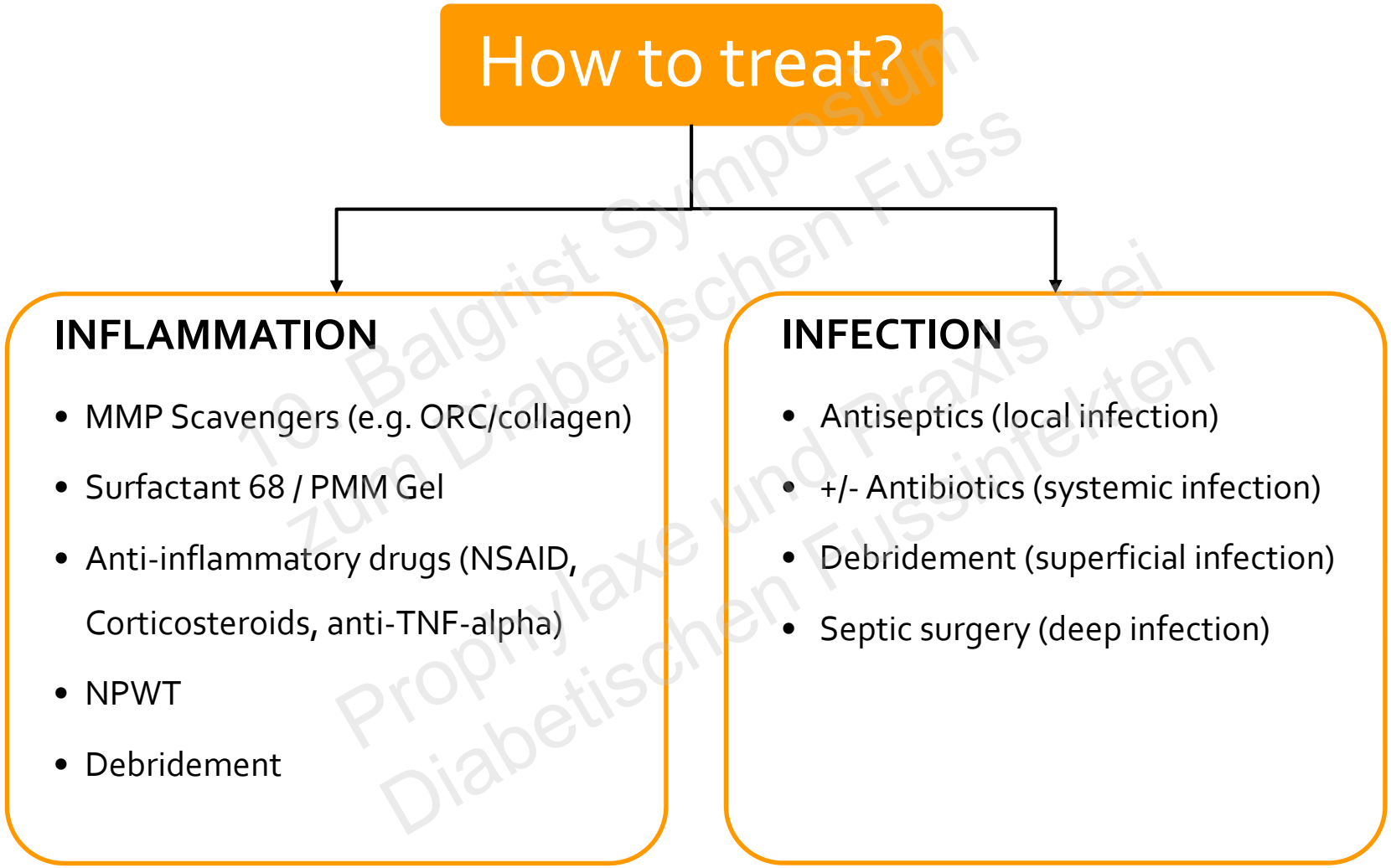


Figure 5. Inflammatory pathway components and key considerations of anti-inflammatory treatment. A typical inflammatory pathway consists of inducers, sensors, mediators and effectors. For the anti-inflammatory therapy, important questions are: How to restrain the excessive activation of immune cells? How to clear the pro-inflammatory mediators and inhibit their signal transduction? How to inhibit necroinflammation and promote tissue repair?

Theranostics 2020; 10(18): 8111-8129

Clinical Relevance



Take Home DFI

- IWGDF Guidelines difficult to apply in real practice
- Dressings alone don't make the real difference
- Targeting the real barriers to wound healing does
  - Biofilm removal
  - Infection control
  - Inflammation therapy