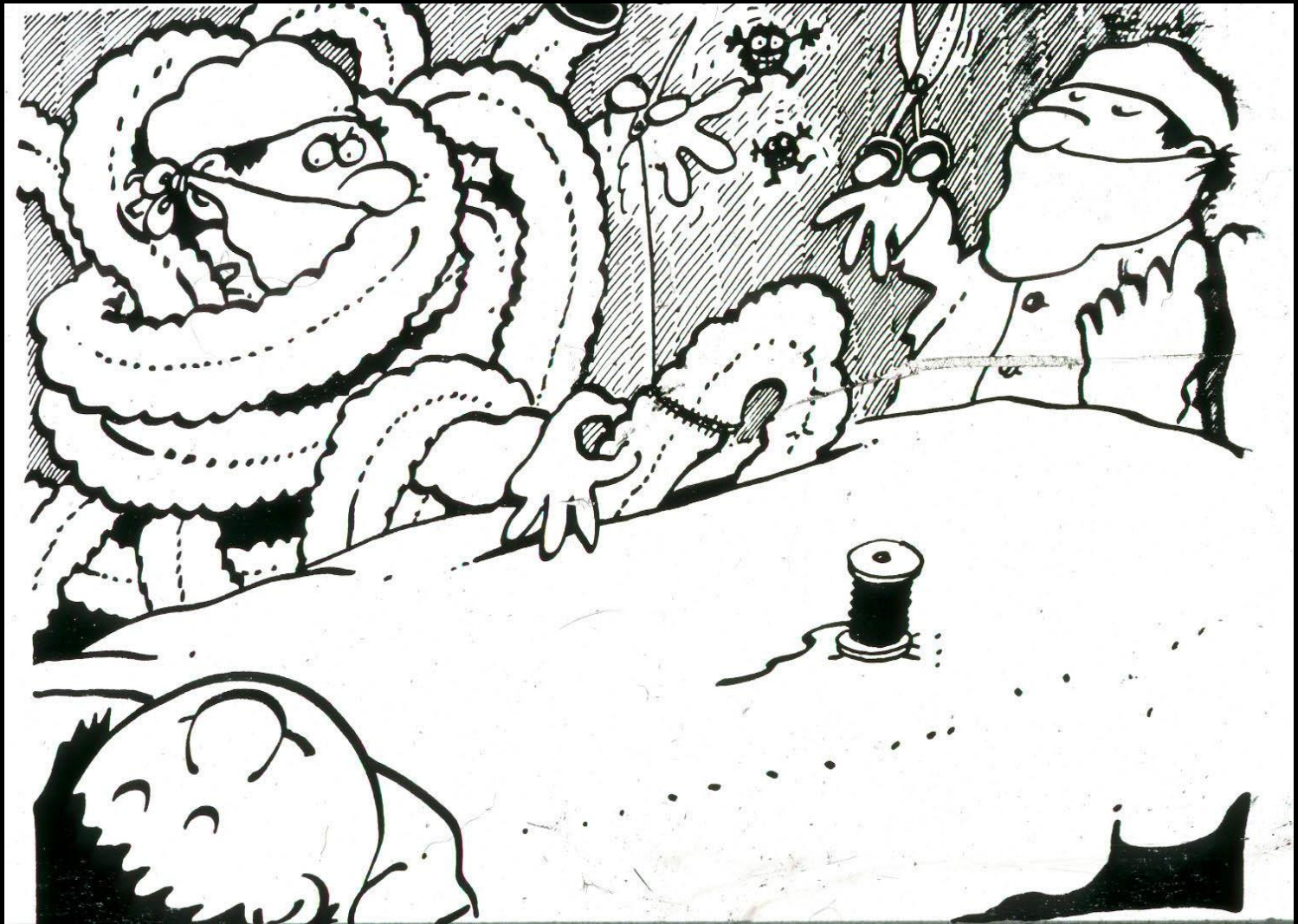


**Clinical Wound Management with espc.  
Focus on Infection, Development of AMR,  
Evidence and Study Outcome/Endpoints.**

**Finn Gottrup MD, DMSci.  
Professor of Surgery  
University of Southern Denmark**

**Copenhagen Wound Healing Center  
Department of Dermatology  
Bispebjerg University Hospital  
Copenhagen, Denmark**





# Content

- **Burden of Wounds**
- **Optimum Clinical Organization**
  - A Multidisciplinary Wound Centre
- **Barriers for Healing, Infection**
  - Microbiological Factors
  - Treatment of Infection
- **Evidence in the Wound Area**
  - Evidence of What in the Wound Area?
  - Evidence Problems in the Wound Area
  - Outcomes/Endpoints in the Wound Area
  - Present Status of Wound Evidence
  - What can be done?
- **Conclusion**

# **Burden of Wounds**

**Impact of Wounds**

# Types of Non-Healing Wounds

**Leg Ulcers**



**Pressure Ulcers**



**Diabetic Foot Ulcers**



**Complicated Acute Wounds**



# Burden of Chronic Wounds in European Union

(Posnett, Gottrup, Lundgren, Saal, J Wound Care 2009)

(Review on Prevalence, Incidence or Costs of Chronic Wounds  
(SSI, Pressure Ulcers, Leg Ulcers, Foot Ulcers) in European countries)

- **> 1.5 m Patients** with a Wound at any Time
- Wound Care the **most important Call on Community Nurse Time**
- In Acute Care:
  - **25%- 50% of Inpatients have a Wound**
  - The Prevalence of Pressure Ulcers is **20%-25%**
  - The majority of PU are Hospital-acquired
  - **3%-4% of Surgical Wounds become infected leading to extended Hospitalisation and Risk of Reoperation.**
  - The excess Mortality Rate in Patients with SSI is **4%-5%**.
- The **Cost** of healing Patients with **Foot Ulcers and Venous Leg Ulcers** alone is likely to be **> €10 Billion annually.**

# Burden of Chronic Wounds in USA

(Sen, Gordillo, Roy, Kirsner, Lambert, Hunt, Gottrup, Gurtner, Longaker,  
Wound Rep Reg, 2009)

(Review on Prevalence, Incidence or Costs of Chronic Wounds in USA)

- **> 6.5 million patients** with a wound at any time
- The **cost** of healing patients with non-healing wounds is likely to be **> US\$ 25 billion annually**.
- These expenses are **rapidly growing**
- The **wound treat** is rising because of increasing problems with **diabetes, aging, obesity**
- Scar and fibrosis problems is counting for **US\$ 12 annually**
- Development of **educational programs** are vital importance

# Problem Wounds (Denmark)

- **No. Wounds:** **>1 % of Population**
- **Expenses:** **2-4 % of Total Health Care Expenses \***
- **Nursing Time:** **25-30 % in the Prim. Health Care Sector<sup>+</sup>**
- **Future:** **In 30 Years 25 % of Population > 65 Years  
double Incidence of DM next 15-20 Years  
(\*Posnett 2002) (+Posnett et al. 2009)**

The Danish Population is 5.3 Million

Health Care System is **95% Public** and 5% Private.

All Public Treatment is **free for all Patients** and the **Quality is similar** to Private Treatment



# **Optimum Clinical Outcomes**

**Setup with Components for  
A Multidisciplinary Wound Centre**



## Copenhagen Wound Healing Center (CWHC)

Depart. of Dermatology, Bispebjerg University Hospital



Out Patient Clinic  
(Total 7 Rooms)



Education Auditoriums  
Research

In Patient Department  
(15 Beds)

Started in 1996

Personnel only for  
Wound Management

## University Center of Wound Healing (UCWH)

Department of Plastic Surgery, Odense University Hospital



Out Patient Clinic  
(Total 6 Rooms)

In Patient Department  
(13 Beds)

Started in 2003

Personnel only for  
Wound Management

# Components for Optimum Clinical Outcomes

## Wound Management Setup

### *Facilities:*

Diagnostic and Treatment

Out- and Inpatients Services

Standardisation of Procedures (e.g. Referrals, Guidelines)

Contact between Health Care Sectors (e.g. Telemedicine)

Research

Administration

### *Employees:*

Multidisciplinary Arrangement

Sufficient Number

Sufficient Education

## Organisation

### *Collaboration*

Between Health Care Sectors

Primary: Between Employees

Secondary: Between Employees and Specialties

### *Implementation*

In National Health Care System

# Collaborating Departments

## (Management of underlying Medical Conditions)

- **Surgery**
  - Plastic Surgery
  - Orthopedic Surgery (close Collaboration)
  - Vascular Surgery (close Collaboration)
  - Gastrointestinal Surgery
- **Internal Medicine** (5 and 3 times a Week)
- **Microbiology** (a weekly round)
- **Dermatology** (by Contact)
- **Clinical Physiology** (Toe Pressure, Duplex Scanning)
- **Radiology** (X-Ray, Scanning, etc.)
- **Others**

# Microbiologist: Antimicrobial Policy



**Optimal Cooperation  
with the Microbiologist.  
e.g. at least Visit once a Week**

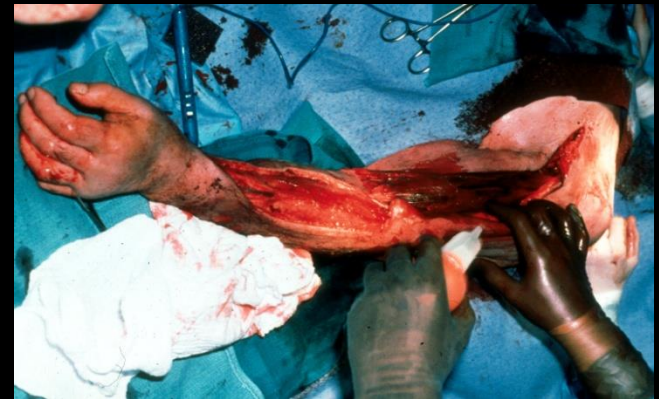


**Antimicrobial Document**

**Barriers for Healing  
Bacteria, Infection**

# Barriers for Healing

- **Bacteria, Infection**
- **Necrotic Tissue**
- **Exudate**
- **Molecular Environment**
- **Cellular Dysfunction**  
(Senescent, aged and nonmigrating)



**Accelerated Healing:  $10^1 - 10^2$  Bacteria/g Tissue**

**Delayed/stopped Healing:  $10^5 - 10^8$  Bacteria/g Tissue**

(Tenorio et al. 1976

Levenson et al. 1983)

# +/- Infection

$$\text{Infection} = \frac{\text{Bacterial load} \times \text{virulence}}{\text{Host resistance}}$$

## *Microbiological Factors*

**Numbers of Bacteria (>10<sup>5</sup>/g)**  
**The Virulence of the Bacteria**  
**Resistance of the Bacteria**  
Biofilm

## *Host Defence Mechanisms*

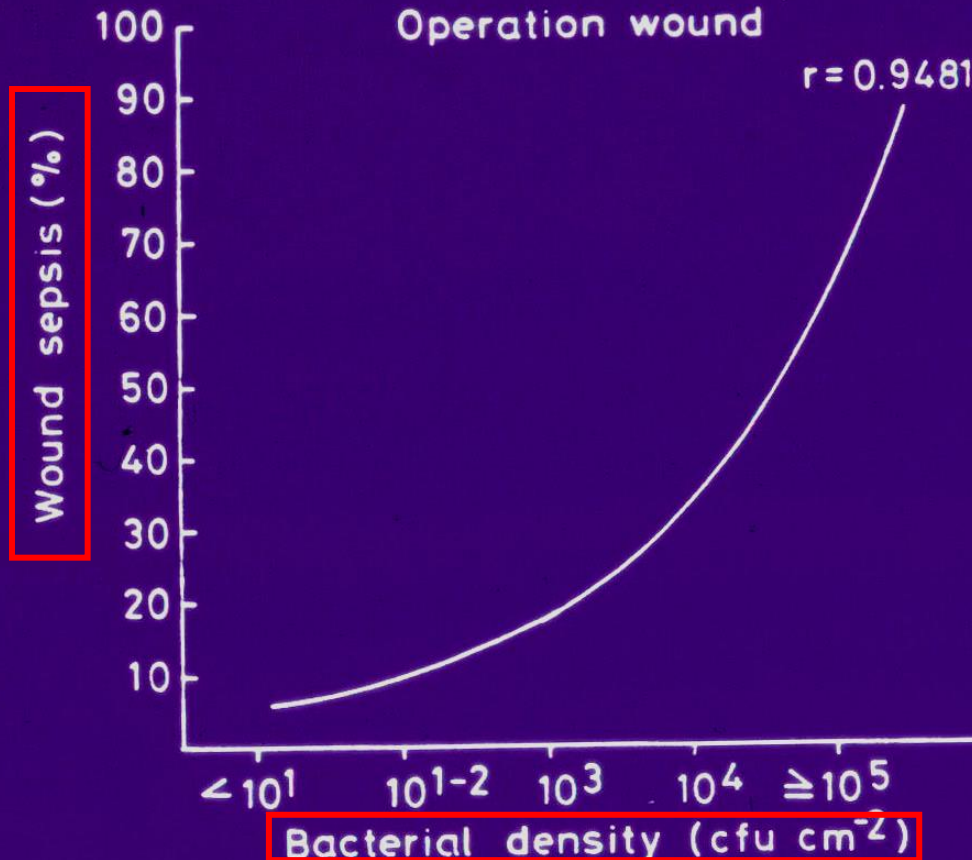
Immune Defence/Tissue Oxygen  
**Antibiotics/Antiseptics**  
Tissue Procedure (Surgery etc.)  
Other Factors (Smoking etc.)



# **Microbiological Factors**

**Numbers of Bacteria**  
**The Virulence of the Bacteria**  
**Resistance of the Bacteria**  
**(Biofilm)**

# Numbers of Bacteria

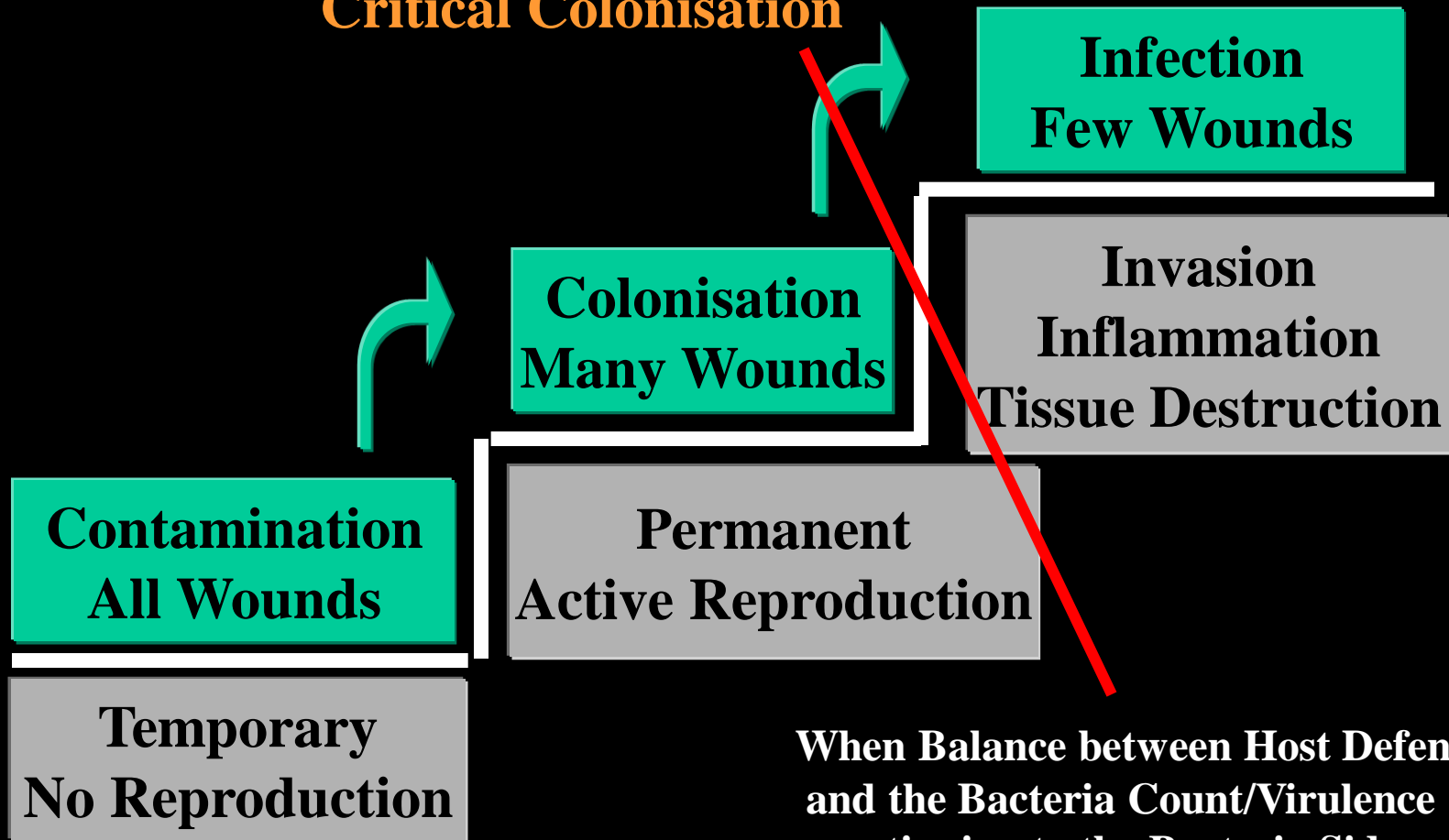


Correlation between pre-closure bacterial densities (aerobic and anaerobic) in operation wound and post-surgical wound infection (Raahave et al 1992)

## From Contamination to Infection

**Critical Colonisation**

(Local → Systemic) (Cutting et al 1994)



When Balance between Host Defence and the Bacteria Count/Virulence is tipping to the Bacteria Side

(Kingsley 2001)

## **Microbiological Factors**

# **The Virulence of the Bacteria: Groups of Wound Bacteria**

- **Invasive Wound Bacteria**
- **Local Wound Bacteria**
- **Opportunistic Wound Bacteria**

## Infection

*Examples of :*

# Invasive Wound Bacteria

*Normal Vital Tissue can be attacked and infected*

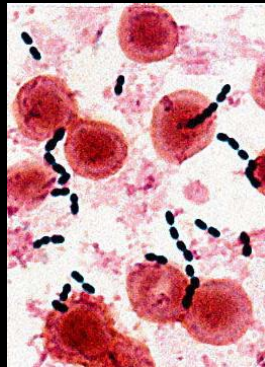
- **Haemolytic streptococcus, group A, C, G (GAS)**
- **Other Haemolytic streptococci**
- **Staphylococcus aureus**
- **Clostridium perfringens**
- **Vibrio vulnificus**

## Infection

# Erysipelas and Group A Streptococcus

### *Virulens Factors:*

- Pyrogene exotoksines
- **Streptolysins**
- **Streptokinases**
- Deoxyribonukleases
- C5a peptidases
- Hyaluronidases
- DPNases



(Erysipelas Leg)



(HJ Kolmos)

## Infection

# Skin Abscesses (Furuncles) and Staphylococcus Aureus

### *Virulens Factors:*

- **Coagulase**
- **Catalase**
- **Hyaluronidase**
- **Fibrinolysin**
- **Lipases**
- **Nukleases**
- **Cytotoksiner etc.**



# Increased Risk of Infection in Patients with **Diabetic Foot Ulcers (DFU)**



Fig 2. A colour-enhanced scanning electron micrograph showing a neutrophil involved in bacterial clearance

## Risk of Osteomyelitis in the DFU: **Increased by a factor 4**

(Shah, Hux, 2003)

- **Failure of Immune system**
- **Bad Regulation of blood-sugar:  
Decreased Function of  
Leucocytes**



## Diabetic Foot Ulcers (DFU)

# Increased Risk of Infection

*(Development of Infection in 24-36 Hours)*



**5-15 % of Diabetic Patients will develop a Foot Ulcer**

Lower Extremity Amputation (LEA) will be required in **up to 25 % of DFU Pts.**  
After First Leg Amputation:

**9-20 % had a Second Leg Amputation in 1 Year**

**28-51 % had a Second Leg Amputation in 5 Years**

**Five Years Mortality: 39-68 %**

## Microbiological Factors

# Resistance of the Bacteria

## Staphylococcus Aureus

**Methicillin Resistant Staphylococcus Aureus (MRSA)**

Vancomycin-resistant Staphylococcus aureus (VRSA)

## Streptococcus and Enterococcus

**Pseudomonas aeruginosa**

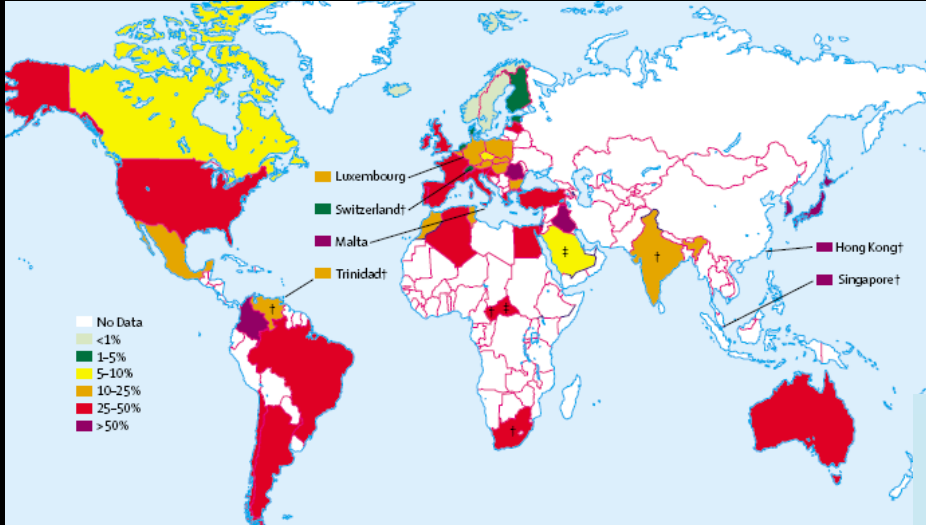
**Clostridium difficile**

**Salmonella and E. coli**

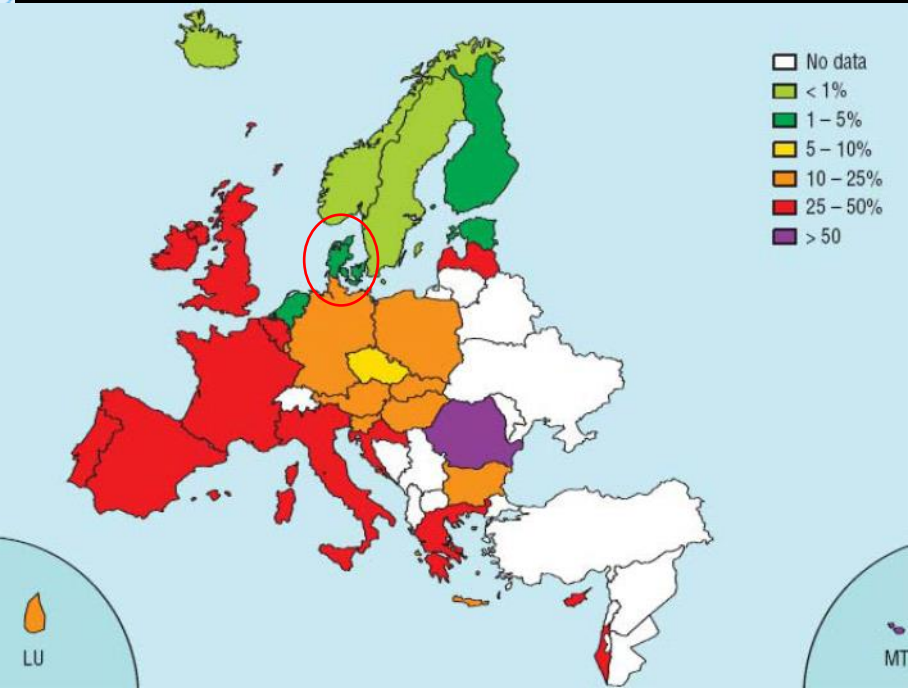
**Acinetobacter baumannii**

**Mycobacterium tuberculosis**

# Microbiological Factors



# MRSA Incidence



Emergence and resurgence of meticillin-resistant *Staphylococcus aureus* as a public-health threat  
 Hajo Grundmann et al. [www.thelancet.com](http://www.thelancet.com). Published online  
 June, 2006 DOI:10.1016/S0140-6736(06)68853-3

# Antimicrobial Document

## EU-Initiatives



**Inappropriate use of antimicrobials (especially antibiotics) creates an environment for the selection of resistance against the currently available antimicrobial products and background for an increased political focus.<sup>1-3</sup>**

**In 2009 the EU member states adopted council conclusions concerning innovative incentives for effective antibiotics, followed by several pan-European initiatives such as the conference “*Combating Antimicrobial resistance – Time for Joint Action*” (March 2012)<sup>3</sup>**

1. Danish Presidency of the Council of the European Union 2012. Combating Antimicrobial Resistance - Time for Joint Action. 2012
2. European Commission - Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). Assessment of the Antibiotic Resistance Effects of Biocides. 2009.
3. Mossialos, E., Morel, C.M., Edwards, S. et al. Policies and incentives for promoting innovation in antibiotic research; World Health Organization - on behalf of the European Observatory on Health Systems and Policies; 2010.



# European Wound Management Association

EWMA started in 1991 and is an **Umbrella Organisation**, is **linking around 25,000 European Wound Professionals from 46 Wound Organisations**, as well as **Individuals and Groups with interest in Wound Care**.



One of EWMA's Core Objectives is to contribute to facing the **Challenge of different Important Topics in Wound Healing and Care**



**European Wound  
Management Association**

**Copenhagen Wound Healing Center, F. Gottrup**

# Projects related to Antiseptic and/or Antibiotics

*Antimicrobials & Non-healing Wounds Evidence,  
Controversies and Suggestions.*

Position Document (Gottrup et al. 2013)

2015: Development of *clinical Decision support Tool*  
facilitating appropriate use of Antimicrobials

*Antimicrobial Stewardship in Wound Management*

Joint BSAC/EWMA Policy Statement in Wound  
Management (2015-2016)

Produce a Position Statement Document

*Joint symposium with Veterinary Wound Healing  
Association (VWHA)*

(EWMA Conference 2014, 2015)





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# EWMA Document: Antimicrobials and Non-healing Wounds Evidence, controversies and suggestions

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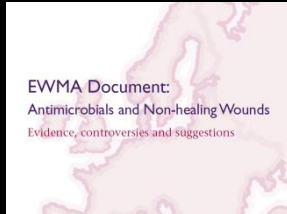






# Objectives

1. Produce an **Update** of each mentioned Topic based on **Evidence at the highest Level**.
2. Show **uncovered Controversies** and Issues related to the use of Antimicrobials in Wound Management.
3. Offer **Perspectives for further Work** and produce **Messages** for the different **Stakeholders** including **Patients, Healthcare Staff, Policy Makers, Politicians, Industry and Hospital Administrators**.



# Focus Area

## *Primary Focus:*

**Local (Topical) Treatment with Antimicrobials (Antibiotics/Antiseptics)**  
**Overall Treatment Strategies, but not judge or compare Treatment Strategies (or Products).**

## *Not focused on:*

**Acute Wounds (Surgical/Trauma Wounds), Burns, Animal Models and Systemic Antibiotics**

**However, if lacking Evidence locally, systemic Evidence may be used.**

## Wound Infection

# Local Treatment (Denmark)



### *Practical Treatment:*

**Clean the Wound:**

**Debridement Techniques**

**Other cleaning Techniques**



**The next Question then is:**

***Local Antiseptic and/or Antibiotics?***

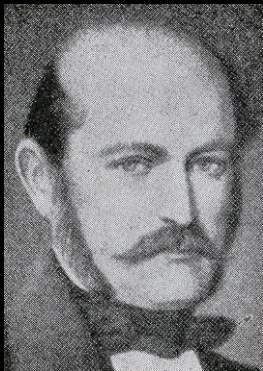
## Infection: Treatment (Denmark)

### *Local Antibiotics:*

- **Cannot be recommended**
- **Flamazine® (Only short time)**
- **Gentacoll?**

### *Local Antiseptics:*

- **Hypochlorite Solutions (Many Adverse Effects)**
- **\* Chlorhexidine (Few Adverse Effects)**
- **\* Hydrogen Peroxide**
- **\* Proflavine**
- **Iodine Solutions (Iodosorb® (Cadexome iodine), Povidine)**
- **Silver Sulphadiazine (Flammazine®)**
- **Silver Ionised (New type of Dressings)**
- **Other antiseptics (e.g PHMB)?**



Semmelweis

( \* Rarely used for wound treatment)

## Infection: Treatment (Own Experience)



# Clinical Experience in the use of Local Antiseptic Treatment

**Iodine** products probably are the **most effective against bacteria** in wounds, however, Iodine also has a **negative effect on the epithelialisation and new granulation tissue.**

**Silver** products may be **lesser effective against bacteria**, but also a smaller effect on the **epithelialisation new granulation tissue**

The practical use of local antiseptics by the presenter for these reasons is in very dirty wounds:

1. Debridement of the wound
2. Iodine products (Iodosorb ® (Cadexome iodine) in 4-5 days))
3. Silver Products then takes over



European Wound  
Management Association

Copenhagen Wound Healing Center, F. Gottrup

## Projects related to Antiseptic and/or Antibiotics

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(EWMA Conference 2014, 2015)





# EWMA'S Antimicrobial Stewardship (AMS) Programme

## *Programme aim*

- **Reduce inappropriate use antimicrobials** in wound care by promoting, facilitating and teaching good antimicrobial practice.

## *Objectives & Programme Plans*

- Development and **Publication of Clinical Treatment Recommendations**
- Development, planning and Execution of **Educational Curriculum and Events**
- Dedicated **Symposia** at upcoming EWMA Conferences
- **Regional Courses** in collaboration with EWMA Cooperating Organisations and International Partner Organisations
- EWMA **EU advocacy Activities**

# Step 1. Development and Publication of Clinical Treatment Recommendations

Journal of Antimicrobial Chemotherapy Advance Access published July 25, 2016

*J Antimicrob Chemother*  
doi:10.1093/jac/dkw287

**Journal of  
Antimicrobial  
Chemotherapy**

## **Antimicrobial stewardship in wound care: a Position Paper from the British Society for Antimicrobial Chemotherapy and European Wound Management Association**

**Benjamin A. Lipsky<sup>1,2\*</sup>, Matthew Dryden<sup>3</sup>, Finn Gottrup<sup>4</sup>, Dilip Nathwani<sup>5</sup>, Ronald Andrew Seaton<sup>6</sup> and Jan Stryja<sup>7</sup>**

<sup>1</sup>Division of Medical Sciences, Green Templeton College, University of Oxford, Oxford OX2 6HG, UK; <sup>2</sup>University of Washington, Seattle, WA 98195, USA; <sup>3</sup>Department of Microbiology and Infection, Hampshire Hospitals Foundation NHS Trust, Winchester SO22 5DG, Hampshire, UK; <sup>4</sup>Copenhagen Wound Healing Center, Bispebjerg University Hospital, DK-2400 Copenhagen, Denmark; <sup>5</sup>Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, UK; <sup>6</sup>Queen Elizabeth University Hospital, 1345 Govan Road, Glasgow G51 4TF, UK; <sup>7</sup>Department of Science and Research, Educational and Research Institute AGEL, 796 04 Prostejov, Czech Republic

\*Corresponding author. Tel: +44 1865 559078; E-mail: dblipsky@hotmail.com

**Background:** With the growing global problem of antibiotic resistance it is crucial that clinicians use antibiotics wisely, which largely means following the principles of antimicrobial stewardship (AMS). Treatment of various types of wounds is one of the more common reasons for prescribing antibiotics.

**Objectives:** This guidance document is aimed at providing clinicians an understanding of: the basic principles of why AMS is important in caring for patients with infected wounds; who should be involved in AMS; and how to conduct AMS for patients with infected wounds.

**Methods:** We assembled a group of experts in infectious diseases/clinical microbiology (from the British Society for Antimicrobial Chemotherapy) and wound management (from the European Wound Management Association) who, after thoroughly reviewing the available literature and holding teleconferences, jointly produced this guidance document.

**Results:** All open wounds will be colonized with bacteria, but antibiotic therapy is only required for those that are clinically infected. Therapy is usually empirical to start, but definitive therapy should be based on results of appropriately collected specimens for culture. When prescribed, it should be as narrowly focused, and administered for



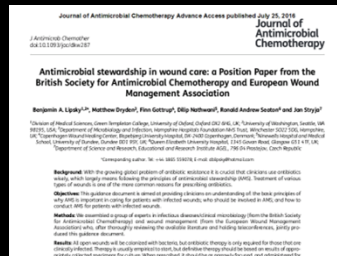
The British Society for  
Antimicrobial Chemotherapy





# EWMA'S Antimicrobial Stewardship (AMS) Programme

Copenhagen Wound Healing Center, F. Gottrup



Lipsky BA, Dryden M, Gottrup F et al.  
J Antimicrob Chemother (July 25, 2016)  
doi:10.1093/jac/dkw287,

**Objectives:** Providing clinicians an understanding of: the basic principles of why AMS is important in caring for patients with infected wounds; who should be involved; and how to conduct AMS.

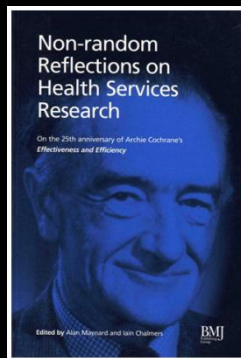
**Results:** All open wounds will be colonized with bacteria, but antibiotic therapy is only required for those that are clinically infected. Therapy is usually empirical to start, but definitive therapy should be based results of appropriately collected specimens for culture. When prescribed, it should be as narrowly focused, and administered for the shorter duration, as possible. AMS teams should be interdisciplinary, especially including specialists in infection and pharmacy, with input from administrative personnel, the treating clinicians and their patients.

**Conclusions:** Available evidence is limited, but suggests that applying principles of AMS to the care of patients with wounds should help to reduce the unnecessary use of systemic or topical antibiotic therapy and ensure the safest and most clinically effective therapy for infected wounds.

**Evidence Based Medicine**

# **Evidence in the Wound Area**

## Classification of Evidence and Strength of Statement According to the Cochrane System



Type of Publication	Evidence	Strength
<b>Meta-analysis, Systemic reviews</b>	<b>Ia</b>	<b>A</b>
<b>Randomised clinical trials (at least one)</b>	<b>Ib</b>	
Controlled, Non-randomised trials (at least one)	IIa	
Cohort studies (at least one)	IIb	B
<b>Diagnostic tests (Direct Diagnostic Method)</b>		
Case-control studies	III	C
Diagnostic tests (Indirect Nosographic Method)		
<b>Descriptive investigations</b>		
Small-scale evaluation, Casuistic cases	IV	D
Tradition textbook and review articles		
<b>Expert evaluation, Editorials</b>		

(Modified from Eccles et al. BMJ, 1998)

# The Main Question in Wound Management related to Evidence is:



**Which Type of Intervention, Technology and Dressing Material to use, and how to use it correctly?**

**This is of vital Interest for the Patient, Therapist, Industry and Society.**

# The Problems with lacking Evidence of Wound Products



- In many Countries **Reimbursement** depend of the **Level of Evidence**
- The Level of **Evidence and Cost-effectiveness** is the Main Reason for using a Product

**Outcome/Endpoint in Trials**

**Evidence Problems  
in the Wound Area**

## Evidence in Wound Healing

# Main Challenges using RCTs in Wound Healing

1. **Sufficient number** of patients with standardised wounds
2. **Is patients comparable** in relation to other diseases

## Evidence Based Medicine

# 1. How to standardise Venous Leg Ulcers?





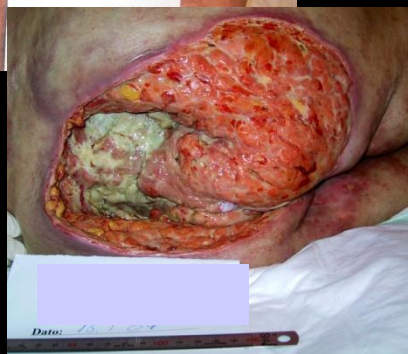
**Evidence Based Medicine**

# 1. How to standardise Diabetic Foot Ulcers?



Evidence Based Medicine

# 1. How to standardise Pressure Ulcers/Sores?



**Evidence Based Medicine**

# 1. How to standardise Acute Problem Wounds?



## Evidence in Wound Healing

# 2. Is the Patients comparable in relation to other Diseases



The risk of development of problem wounds in the patients increases with a factor 2-4 after becoming 65-70 years of age.

Consequently wound patients in most cases are **old and fragile and suffer from several competing diseases.**

*Cochrane Group:*

**“..Breast cancer patients feature similar variability..”**

(Ubbink et al. Correspondence Br J Surg 2010)

## **Evidence Based Medicine**

**Another problem in the Wound Area is:**

**Evidence of What?**

# Evidence of What? (Outcomes/Endpoints)

(3 E's)

**Efficacy**



Healing  
Recurrence

**Efficiency**



Frequency of Visits  
Days in hospital

**Effectiveness**



Cost  
QoL

The **outcome "Healing"** is the reason that almost all studies performed with **DFU** is on **superficial wounds not the severe wounds** risking major amputation

# **Outcomes/Endpoints in the Wound Area**

## Outcome/Endpoint in Trials

# Definition of Clinical Trials Outcomes/Endpoints

**An objective/result of an evaluation/study** A way of measuring the treatment provided to a patient and the patient's responses.

**Primary O/E** Primary objectives provide the **focus of the study** and are critical for the study. If resources are scarce, this takes priority over secondary outcomes. **Secondary O/E** allow **subsidiary questions** that, do not have the same priority of clinical interest

**Clinical O/E** are directly **relates to observational outcomes**, and in wounds most often visible reduction in wound size, particularly intact skin (full healing).

**Surrogate O/E (or marker)** is defined as a **physical sign or a laboratory measurement** that can be used as a substitute for a clinically meaningful endpoint, that measures directly how a patient feels, functions or survives.

(Gottrup F, Apelqvist J, Price P. J Wound Care. 2010;19:237-68)



# Evidence in Wound Healing

# Important Evidence Questions in the Wound Area

# Are Definitions, Classifications, Priorities, End-points/Outcomes in the Wound Healing Area sufficient developed to be tested by a Cochrane Update Evidence Evaluation?

## Evidence Is a Challenge in Wound Management

**N**onhealing wounds are significant problems in health care systems all over the world. The frequency varies and is related to types of population and health care systems, but in the industrialized world, it can be expected that almost 1% to 1.5% of the population constantly have a problem wound, which causes for more than 2% to 4% of the health care budget.<sup>1</sup> If population at risk were identified and aggressive interventions occurred before development of complications or progression of wounds, patient morbidity and health care costs could be significantly decreased.<sup>2,3</sup> The question thus is: Which type of intervention and what dressing materials are the best from what is available?

Evidence-based practice is an accepted way of evaluating the health care procedures and techniques. According to the Cochrane Health Group, a large number of these procedures and techniques used in wound management are not evidence based.

### EVIDENCE-BASED PRACTICE AND REIMBURSEMENT STRATEGIES IN WOUND MANAGEMENT

Evidence-based practice is generally focused on the use of current best evidence in making decisions about care of individual patients.<sup>4</sup> The practice of evidence-based medicine (EBM) means integrating individual clinical expertise with the best available external clinical evidence from systematic research. In the Cochrane system, it is a systematic review of randomized controlled trials (RCTs), which usually leads to a meta-analysis of data from these RCTs that come within the defined issue. This approach helps to minimize bias inherent in comparisons.

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Conflict of interest: None.  
DOI: 10.1177/0898010108316112  
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This type of evidence-based practice has been the gold standard for all types of clinical work and has been the standard that has to be followed if a treatment procedure should be accepted in the medical world. Commonly, randomized research in clinical research work also has been based on the gold standard, the randomized trial to fulfill the concept of EBM.<sup>5</sup> Some time ago, it was the wound area that had a problem. In the wound area, the usual procedures, methods, materials, and technologies used in wound management were to fulfill the above-mentioned criteria. A great deal of clinical research suffers from inadequate sample sizes, short follow-up, nonrandom allocation to treatment arms, unblinded assessment of outcomes, poor description of control and concurrent intervention, and so on.<sup>6</sup> Lack of accepted evidence may also be related to the fact that the majority of products used in wound management are categorized as medical devices, which may be exempted for use after successful investigations of safety based on Phase 1 and 2 trials and satisfactory outcomes. Thus the motivation for adopting and developing Phase 3 studies (RCTs) may be less in the field of wound healing compared to other areas of clinical medicine. The evidence problem has recently been confirmed in a systematic review on the efficacy of occlusive dressings in the treatment of ulcers.<sup>7</sup> A meta-analysis, it was concluded that there is insufficient evidence to determine a difference in healing time between modern and traditional gauze wound products in leg ulcer patients. It was also concluded that well-conducted trials are warranted. This has to be related to the fact that modern wound products were introduced more than 30 years ago.

Reimbursement strategies in Europe are often based on evaluation of the used products. Consequently, traditional products such as gauze and other dry wound-healing dressings may be reimbursed, whereas no reimbursement is allowed for the modern dressings based on moist wound healing.

**FUTURE STEPS**  
The problem is to define a possible and acceptable measure of best evidence in the wound area. RCTs may not be the most appropriate strategy. The

**RESEARCH:**  
Simon Palfreyman, E Andrea Nelson, and Jonathan A Michaels  
**Dressings for venous leg ulcers: systematic review and meta-analysis**  
BMJ 2007; 335: 244 [Abstract] [Full text]

**Rapid Responses:** Submit a response to this article

**Rapid Responses published:**  
Evidence controversy in wound management  
Finn Gottrup (3 March 2008)

**Evidence controversy in wound management** 3 March 2008

Finn Gottrup, Professor of Surgery, Copenhagen Wound Healing Center, Bispebjerg University Hospital, DK-2400 Copenhagen, Denmark

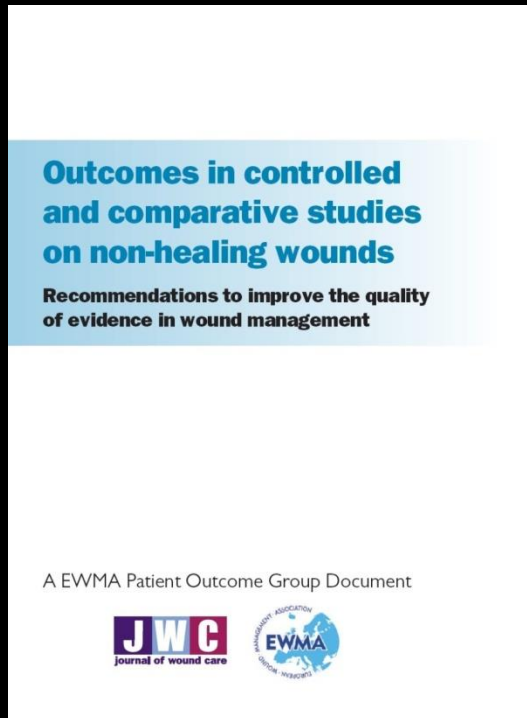
**Send response to journal:**  
See Evidence controversy in wound management

Problem wounds are a significant problem for the health care system all over the world. In the industrialized world, it can be expected that almost 1-1.5% of the population constantly have a problem wound, which counts for 2-4% of the health care budget (1-3). The question is which type of intervention, which type of technology and which type of dressing materials are the best from what is available? Recent reviews have shown little or no compelling evidence of a significant difference in time to healing or percent healing between patients treated with traditional and modern dressings (4-7). In BMJ (5) a review and meta-analysis on dressings for venous leg ulcers was published in 2007. It was concluded that the type of dressing applied beneath a compression was not shown to affect ulcer healing. Reimbursement strategies in Europe are often based on evidence of this kind. Consequently traditional products like gauze and other dry wound healing dressings may be reimbursed, while not the modern dressings based on moist wound healing. Modern dressing have been used for more than 25 years and the lack of evidence may raise questions of which two are especially important: 1. why has wound care research not achieved evidence on level IA of the Cochrane system and 2. is healing the only relevant end point when comparing different treatment regimens?

F. Gottrup:  
Rapid Response  
BMJ, 3 March 2008

F. Gottrup:  
Editorial,  
Lower Extremity  
Wounds 5; 2006: 74-75

## The EWMA Patient Outcome Group (POG)



(Gottrup F, Apelqvist J, Price P.  
J Wound Care. 2010;19:237-68)

# Aim of the Document

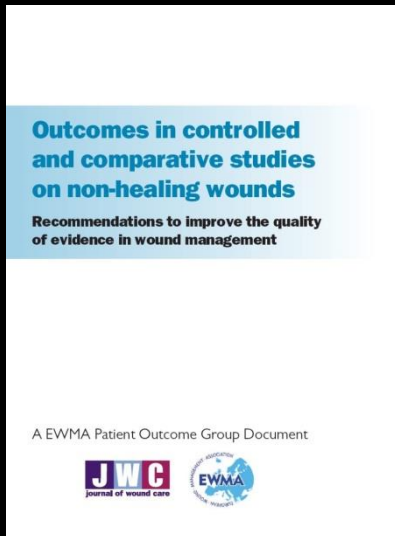
- Providing **recommendations to medical device and/or pharmaceutical companies** to use when planning clinical/economic studies
- Providing a **framework for clinicians** when:
  - a. conducting and evaluating clinical studies
  - b. assessing clinical data, appropriate outcome measures and treatment strategies
- Informing **health technology assessment bodies and decision-makers** about the key features of medical device research

## Outcomes in Wound Healing

# RCTs and Comparative Studies in Non-healing Wounds

(Diabetic Foot, Leg Ulcers & Pressure Ulcers)

From 2003 to September 2009: 371 articles of which 76 articles were selected



(Gottrup F, Apelqvist J, Price P. J Wound Care. 2010;19:237-68)

## Categories of Outcomes

(% represent each category's proportion of the endpoints):

- **Wound reduction rate (24.1%)**
  - **Wound closure (16.9%)**
  - **Healing time (9%)**
  - **Change in wound condition (9%)**
- Almost 60 % relates to Healing
- **Biomarkers and bacteriology (4.5%)**
  - **Circulation (1.9%)**
  - **Infection signs (4.5%)**
  - **Symptoms and signs (13.2%)**
  - **Dressing performance (7.0%)**
  - **Quality of life (5.8%)**
  - **Costs and resources used (4.5%).**

**Evidence Based Medicine**

**Present Status of  
Wound Evidence on the  
highest Level**

*(Primarily Topics related to FDA Meeting)*

**No or Little Evidence**

**Perhaps/Probably some Evidence**

## Evidence in Wound Healing

# No or Little Evidence

*(Primarily Topics related to FDA Meeting)*

## Evaluation of present Evidence

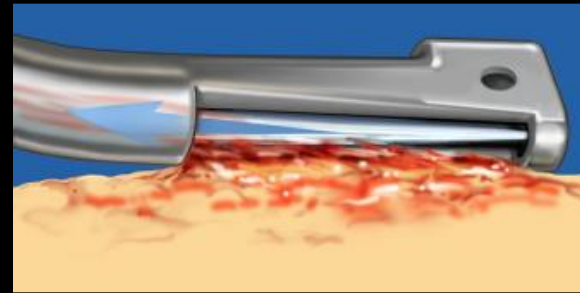
# Debridement



Sharp



Maggots (Larvae)



Versajet®

## Conclusion

Despite the widespread and vital use in clinical practice, there is **little evidence on the highest level for sharp and maggot debridement** has any effect. In a Cochrane review\* it was evidence to suggest that **hydrogel dressing** increases healing rate of DFU compared to gauze.

(\* Edwards J, Stables S. Debridement of diabetic foot ulcers. Cochrane Database of Systemic Reviews 2010)

(Gottrup F, Apelqvist J. *Diabetes Metab Res Rev* 2012; 28 (Suppl 1): 64-71)

## Evaluation of present Evidence

# Efficacy of Modern Dressings in the Treatment of Leg ulcers: A systematic Review

(Bouza C et al. Wound Rep Reg 2005; 13: 218-229)



### Purpose:

Examines the collective evidence on the effectiveness of modern dressings in the treatment of leg ulcers

### Method

Meta-analysis on available randomised clinical trials (RCTs)

### Results

**No significant differences in terms of the proportion of healing ulcers or reduction in wound size for both modern and conventional dressings.**

**No differences between the different modern dressings**

### Conclusion

Insufficient evidence to determine whether the choice of any specific dressing type affects healing course of leg ulcers.

**Well-conducted trials** are warranted

## Evaluation of present Evidence

# Use of Dressings



Hydrocolloid  
Hydrogel



Foam



Algenates  
Hydrofiber



Other Types

## Conclusion

Despite of a **substantial number of studies published**, there is **little evidence** on the highest level, except for **hydrogen dressing** increases healing rate of DFU **compared to gauze**.

(Gottrup F, Apelqvist J. *Diabetes Metab Res Rev* 2012; 28 (Suppl 1): 64-71)



## Evaluation of present Evidence



# Silver Treatments of Leg Ulcers: A systematic Review

(Chambers H, Dumville JC, Cullum N. *Wound Rep Reg* 2007; 15: 2165-173)

- Purpose* Update previous review and establish current evidence to support the increasing use of silver-based products in the treatment of leg ulcers
- Method* Systematic review on available randomised clinical trials (RCTs) up to May 2006
- Results* Nine studies were eligible for inclusion.  
**Inconsistent evidence was provide in regard to effect of the silver products.** The studies generally provided poor evidence due to lack of statistical power, poor study design and incomplete reporting. **Limited evidence for the use of silver products in leg ulcer patients**
- Conclusion* Further research of **well-conducted trials needed before the use of silver-based interventions in routine leg ulcer management.**

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## Topical Silver for preventing Wound Infections

(Storm-Versloot MN, Vos CG, Ubbink DT, Vermeulen H. *Cochrane review* 2010; Issue 3)

- Author's Conclusion:* **Insufficient evidence to establish whether silver-containing dressings or topical agents promote wound healing or prevent wound infections**

# Use of Antimicrobials and Dressings



Antiseptics



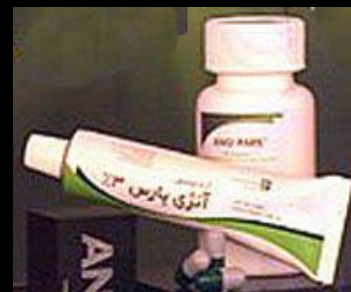
Antibiotics

## Conclusion

Despite the **widespread use** in clinical practice and **several studies** available, there is **little evidence** on the highest level for the use of antimicrobials in wound care.

# Adjuvant therapies

## Herbal Preparations



## *Conclusion*

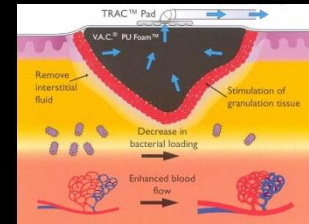
Esp. China and Iran have focused on Herbal products. There is, however, **insufficient evidence** on the highest level to demonstrate that herbal extracts have any effect on the DFU

## Evidence in Wound Healing

# Perhaps/Probably some Evidence

*(Primarily Topics related to this Meeting)*

# Topical Negative Pressure (TNP)



# Hyperbaric Oxygen Therapy (HBOT)



# Use of Compression (Bandages/Stockings)



## Evidence in Wound Healing

# General Summary of the present Status of Evidence :

There is **limited evidence on the highest level** to demonstrate that *Technique/Device X* has effect on the treatment of DFU (and other non-healing wounds)

The **major problem is poor quality** of the papers published

## Evidence in Wound Healing

**What is the  
Consequences?**

## Evidence in Wound Healing

What is the **Consequences for daily clinical Life** in the Wound Area that Cochrane and other Review most often find **“insufficient Evidence”** for Wound Techniques or Devices.

1. **Should not be used** at all before Evidence?
2. **Use in a few Cases** with especially Indications?
3. **Use**, but in the **cheapest** Version of the Product?

*This are Questions to debate!!*



## The following Points also have to be debated

1. Is **insufficient sample size** and use the outcome measure “healing” may result in a **Type II Error** or “**false negative result**” leading to rejection of treatments or products, which actually **may have a positive effect**
2. The best possible methodology and most appropriated design should be used. The **performance of the trial** should also be at the **highest possible level** in order to able to use the results.
3. However, if the **correct optimal trial has weaknesses** in the study performance and **wrong indication**, the results **cannot be accepted** (“Vulcan Study, 2009”\*)
4. Is there situations where it is **unethical to make a RCT for evidence?**

\* (Michaels JA et al. *Br J Surg* 2009; 96: 1147-56.

Gottrup F, Jan Apelqvist, Leading article: *Br J Surg* 2010; 97:303-4)

## **Evidence in Wound Healing**

# **What can be done?**

# **New Outcome Measures**

**Efficacy**



**Healing  
Recurrence**

**Efficiency**



**Frequency of Visits  
Days in Hospital  
Others**

**Effectiveness**



**Cost  
QoL  
Others**

# Evidence in Wound Healing



## Patient Outcome Group (POG)

### Outcomes in controlled and comparative studies on non-healing wounds

Recommendations to improve the quality of evidence in wound management

(Gottrup F, Apelqvist J, Price P)

A EWMA Patient Outcome Group Document



### Recommendations on Endpoints/Outcome Parameters

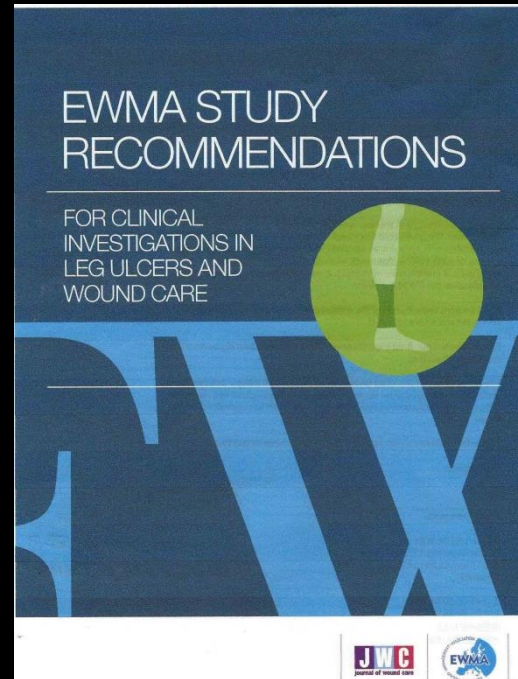
- Wound closure, defined as total epithelialisation without discharge, is the most important endpoint relating to ulcer healing. It must be confirmed by an independent source (photography) and there must be sufficient follow-up to confirm healing
- Wound area reduction is a valid endpoint with regard to wound healing but it must be confirmed by tracing and include a predefined relevant cut-off to ensure that 'reduction rate error' (described in section: 'reduction rate') does not occur
- There is enough evidence to support the use of a 50% reduction in wound surface area over time as a useful outcome, provided that the initial wound size and the measurement technique are taken into consideration. The time interval used in such assessment will vary depending on the wound type. Any reduction of less than 50% cannot be supported by the current literature; in these instances, more objective measures of size reduction must be used
- Time to heal is an important outcome. However, the study protocol must consider the substantial methodological difficulties entailed, particularly confirmation of the exact date of healing for each patient during the specified observation period. To date, the accepted time interval for resource studies is one year
- There is an urgent need for a validated scoring system with regard to wound condition
- When using changes in the wound condition as an outcome parameter, they must be predefined and measured in such a way that they can be validated independently, wherever possible (for instance, by photograph)
- When using biological markers as a primary outcome, they should be clearly predefined, and a clinically relevant unit of change should be specified; reliable and valid quantitative assessment methods should be used
- When using wound infection as a primary outcome marker, it should be clearly predefined. At present, this could be either a binary measure of presence/absence or a composite score focusing on clinical signs and symptoms
- Regardless of the assessment tool used, when using pain as an outcome measure it is important to pre-define the amount of wound pain reduction that is clinically important
- When surrogate parameters such as symptoms and signs, or composite endpoints such as scales, are used as primary endpoints, it is essential that both their basic definition and what is considered to be a clinically relevant difference are predefined. When used as a primary endpoint, it is favourable for it to be verified by an independent evaluator
- When assessing dressing performance in an objective manner, with a focus on a specific aspect of symptom management, a comparative study may not be needed; the relevant data could be better assessed using a cohort study with a standardised, reproducible and validated protocol that includes resource utilisation (when appropriate)
- HRQoL assessments must be based on tools with established psychometrics
- The type of assessment must fit with the purpose of the data collection: if HRQoL data are to be used for health technology assessment reviews, then generic and/or utility methods must be included
- When cost is used as an outcome parameter in wound management, it is essential to measure all the quantities of resources used and then add the value of those resources, according to a predefined protocol. It is recommended that resource use and cost are shown separately

## Evidence in Wound Healing

# Some important Questions to agree on in the Future

1. Should evidence level be different for the separate **wound types** and different **stages** in the **healing process**?
2. Is **controlled, non-randomised trials** or **Cohort studies** acceptable?
3. However, the **performance of trial** should always go for the possible highest level.
4. Should **endpoints/outcomes beside healing** be accepted?

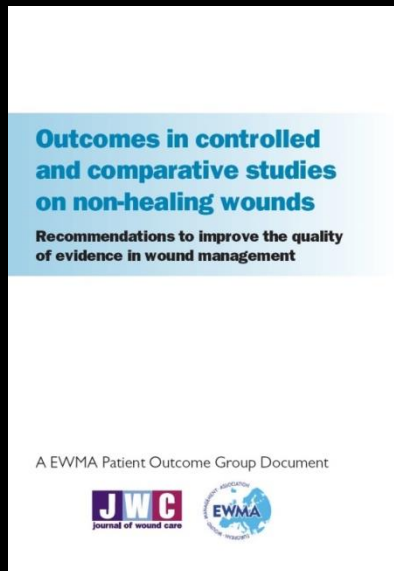
## Evidence in Wound Healing



**Aim:** Highlight key features you will need to think about when **planning, conducting, analysing or reporting** an RCT or cohort study.

**Target Audience:** **Hospital and community clinicians** working collaboratively with other professions or with industry. It is in particular, for the **novice researcher** working within wound care (leg ulcers), but may also be relevant for article reviewers and experienced researcher.

**The format:** A **'step-by-step' instruction** manual to highlight activities to consider and outline frequent mistakes. In some instances, we will provide you with a mark **[!]** to highlight points where **extra attention** is required.



Gottrup F, Price P,  
Apelqvist J:  
J Wound Care 2010;  
19: 237-68

Price P, Gottrup F, Abel M:  
J Wound Care 2014; 23: 5,  
S1-S36.

# Conclusions

## Infection:

Infection is probably the **most critical complication** of non-healing wounds.

Tight **collaboration** between involved health care providers, microbiologists, administrators and the patients is needed in order to **avoid development of resistant bacteria**

## Evidence:

In the wound area is **Evidence** on the highest level a **problem**. **Important questions (wound types, type of trials accepted, endpoints used etc.)** have to be agreed on before we reach a reasonable level of Evidence.



**Thank You for Your Attention  
Time for Discussion**

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