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

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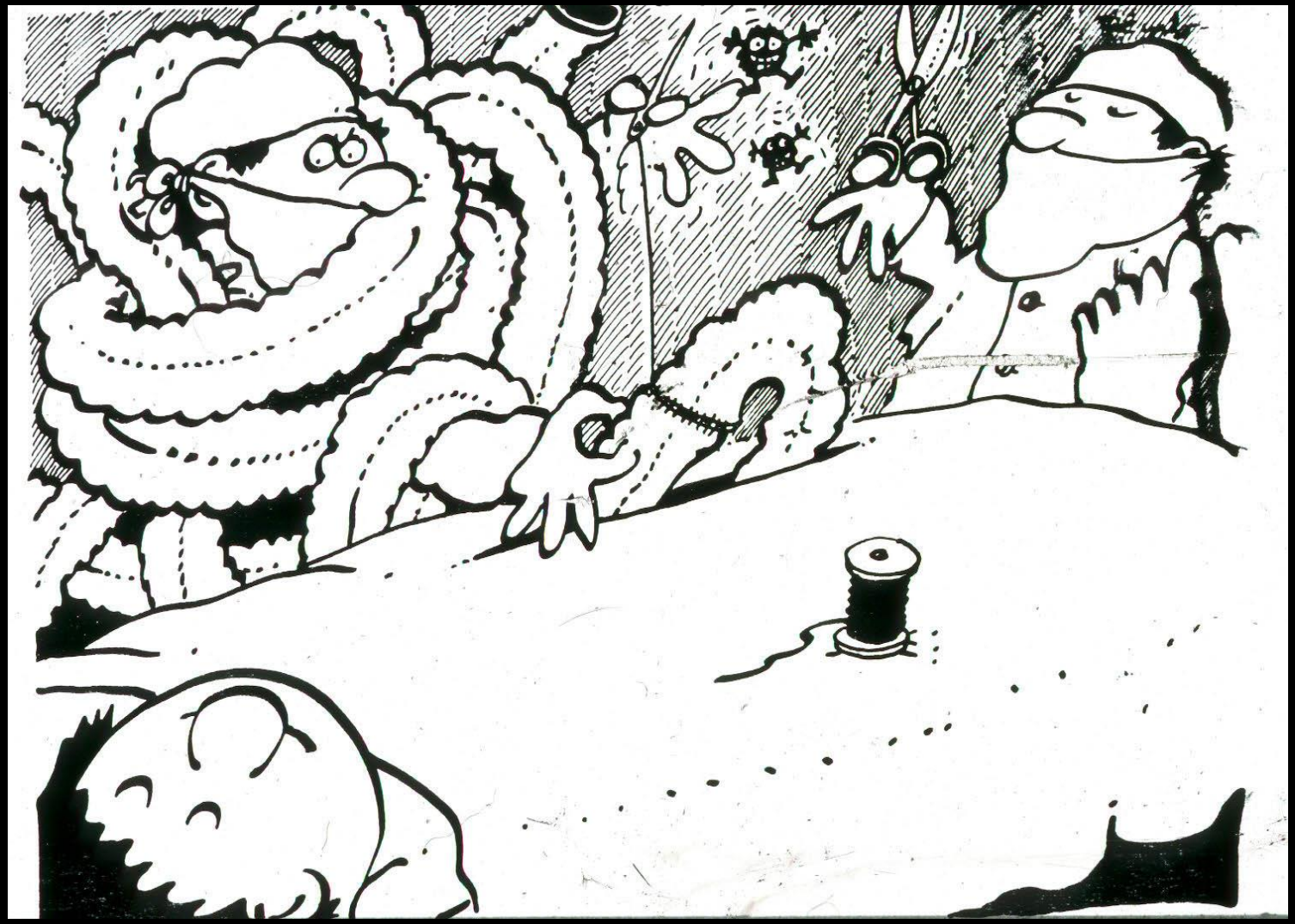
Copenhagen Wound Healing Center, F. Gottrup



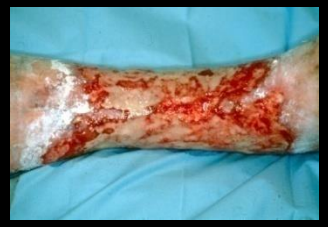
Content

- 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

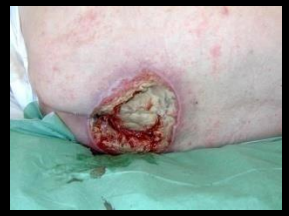
Burden of Wounds

Types of Non-Healing Wounds

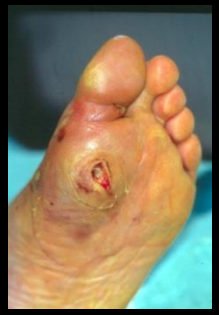
Leg Ulcers



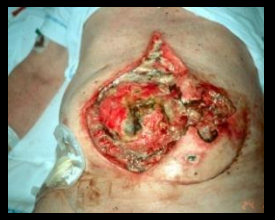
Pressure Ulcers



Diabetic Foot Ulcers



Complicated Acute Wounds



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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+
- **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

F. Gottrup

Copenhagen Wound Healing Center (CWHC)

Depart. of Dermatology, Bispebjerg University Hospital

In Patient Department (15 Beds)

Out Patient Clinic (Total 7 Rooms)

Education Auditoriums

Research

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

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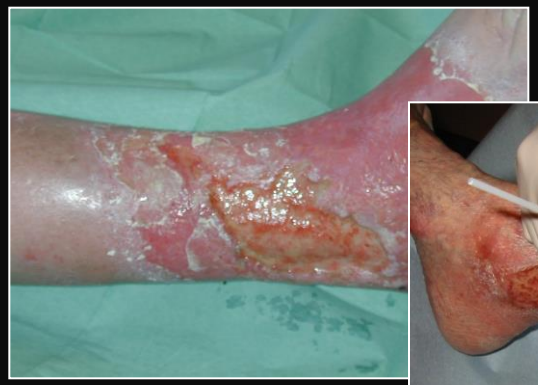
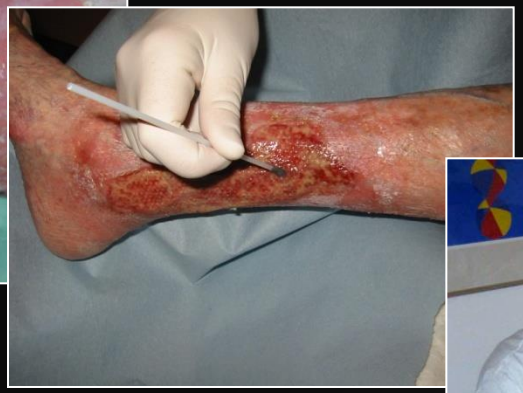
Collaborating Departments

(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.

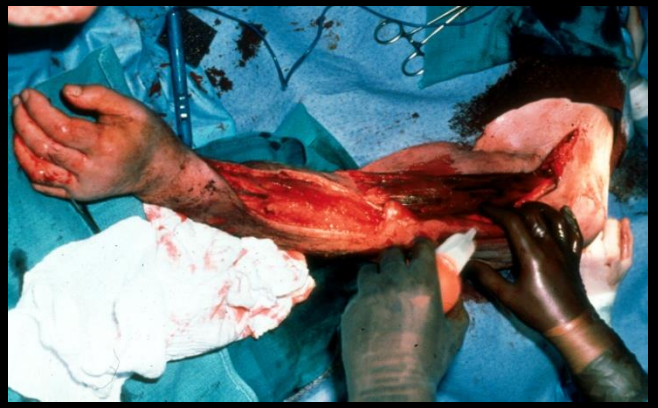
e.g. at least Visit once a Week

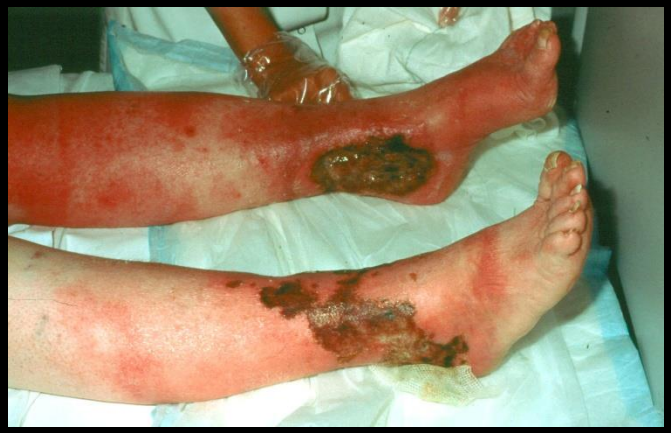
Antimicrobial Document

Barriers for Healing Bacteria, Infection

Barriers for Healing

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



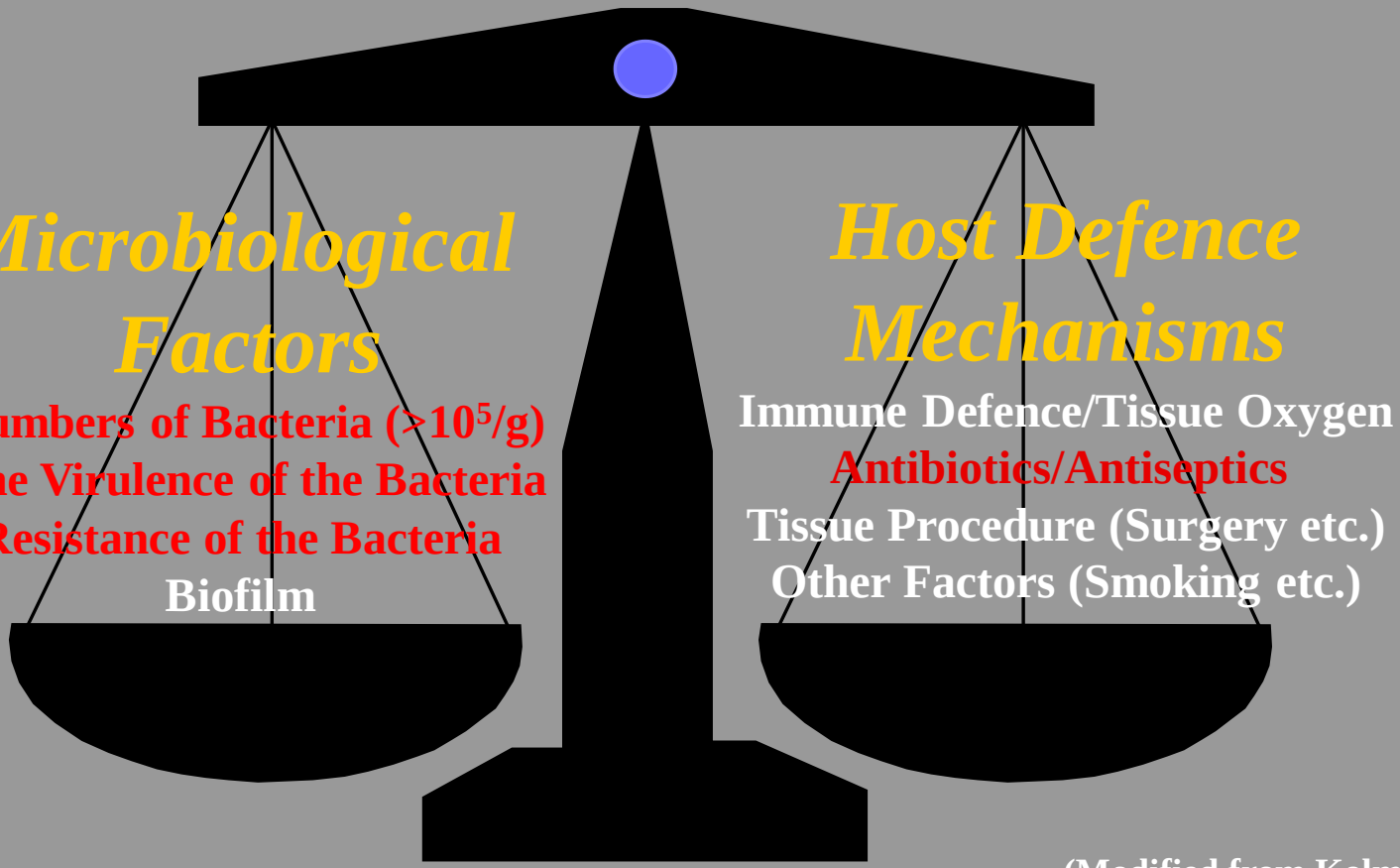


Accellerated Healing: $10^1 – 10^2$ Bacteria/g Tissue
Delayed/stopped Healing: $10^5 – 10^8$ Bacteria/g Tissue
(Tenorio et al. 1976
Levenson et al. 1983)

Copenhagen Wound Healing Center, F. Gottrup

+/- Infection

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



Microbiological Factors

Numbers of Bacteria (>10^5/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.)

(Modified from Kolmos 2002)

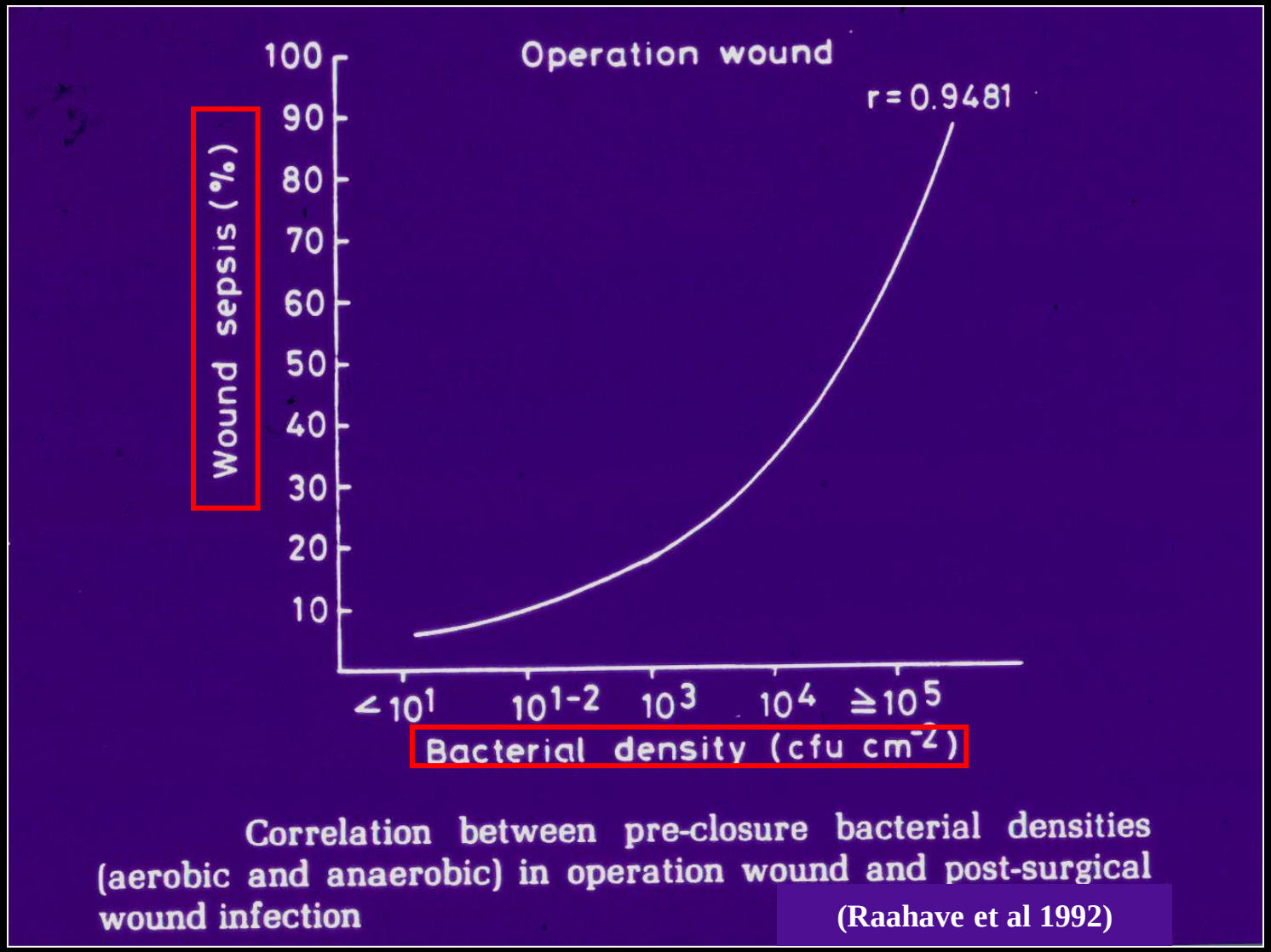
Antimicrobial Document

Copenhagen Wound Healing Center, F. Gottrup

Microbiological Factors

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

Numbers of Bacteria



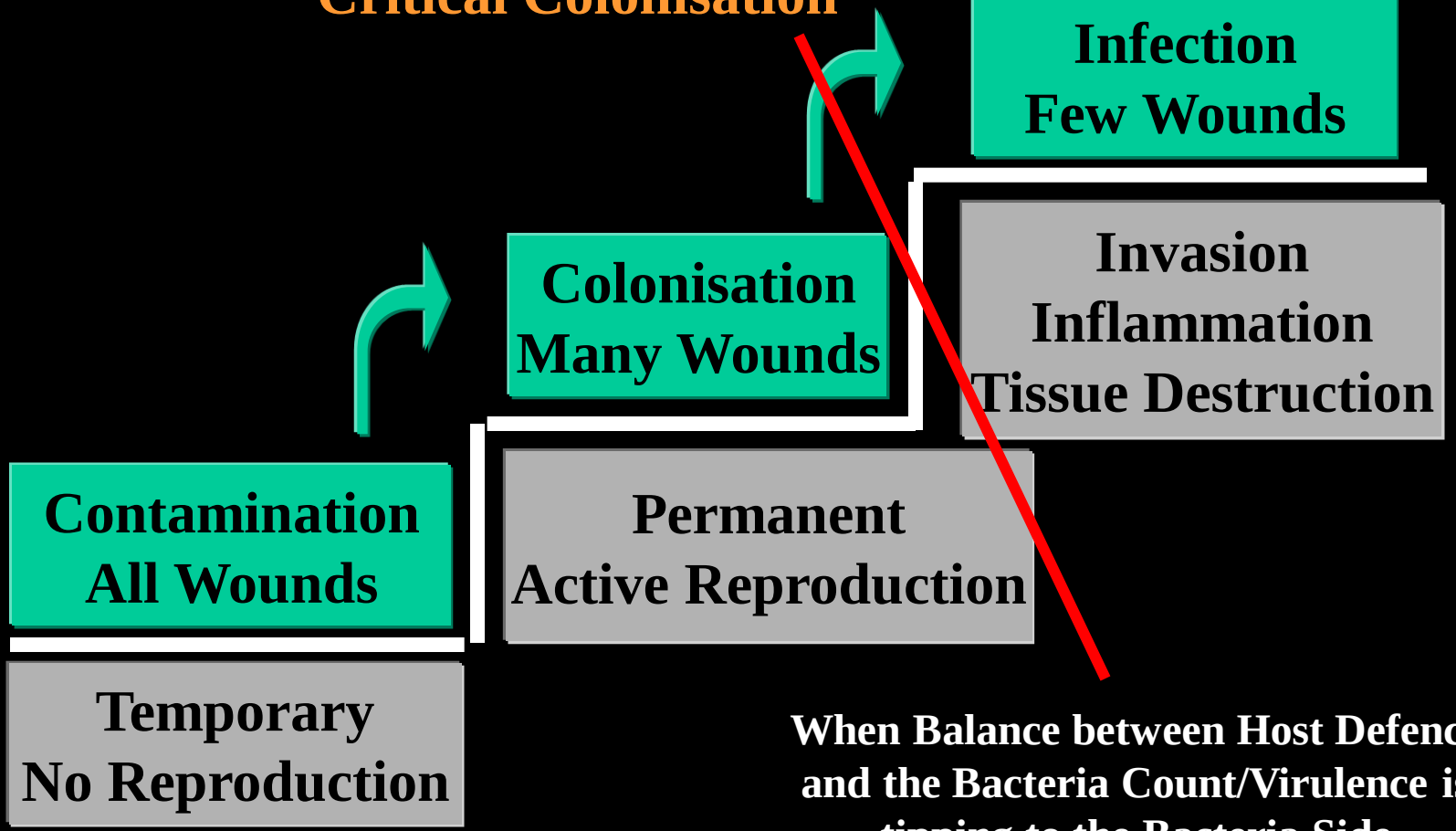
Correlation between pre-closure bacterial densities (aerobic and anaerobic) in operation wound and post-surgical wound infection

(Raahave et al 1992)

Numbers of Bacteria

From Contamination to Infection

(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

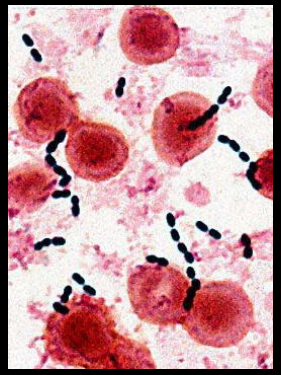
- **Haemolytic streptococcus, group A, C, G (GAS)**
- **Other Haemolytic streptococci**
- **Staphylococcus aureus**
- **Clostridium perfringens**
- **Vibrio vulnificus**

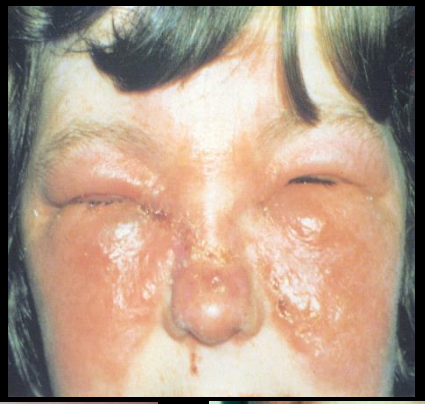
Infection

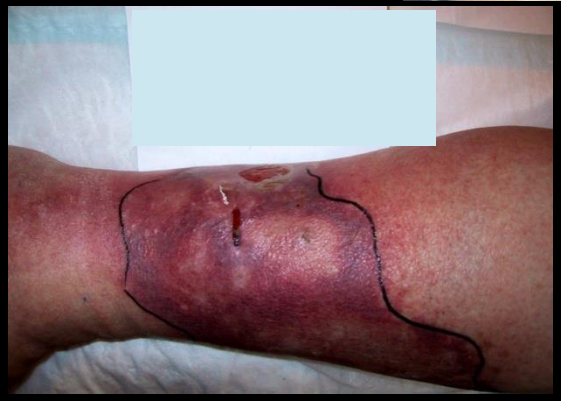
Erysipelas and Group A Streptococcus

Virulens Factors:

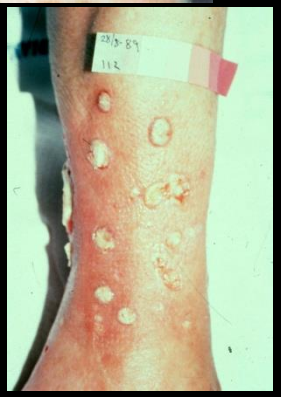
- Pyrogene exotoksines
- Streptolysins
- Streptokinases
- Deoxyribonukleases
- C5a peptidases
- Hyaluronidases
- DPNases







(Erysipelas Leg)



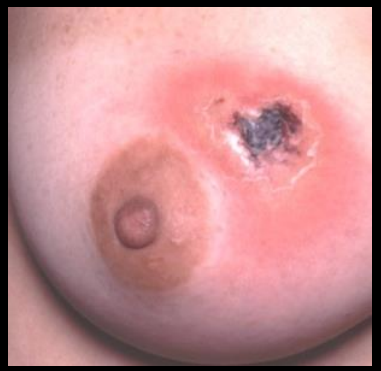
(HJ Kolmos)

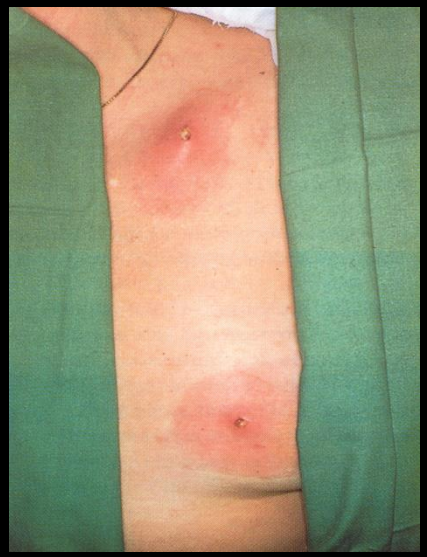
Infection

Skin Abscesses (Furuncles) and Staphylococcus Aureus

Virulens Factors:

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





(HJ Kolmos)

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

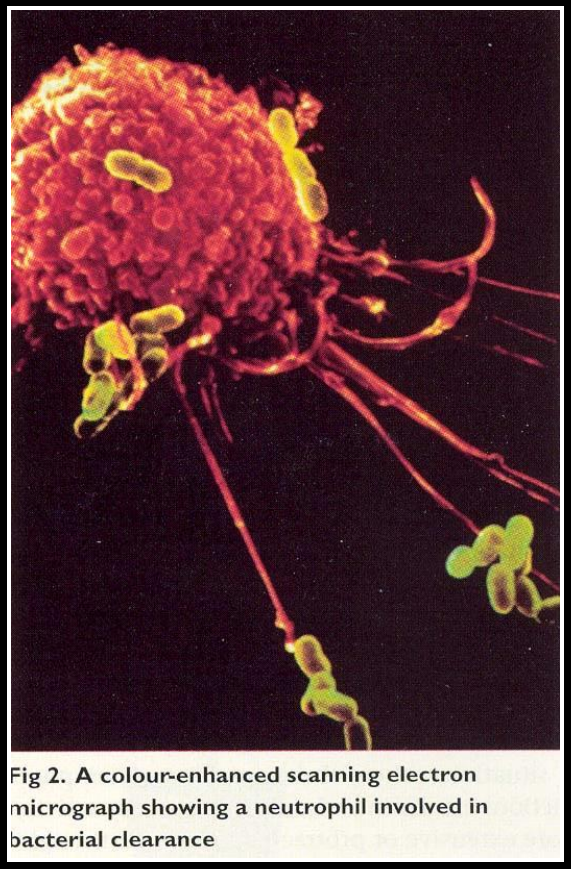


Fig 2. A colour-enhanced scanning electron micrograph showing a neutrophil involved in bacterial clearance

Risk of Osteomyelitisin the DFU: Increased by a factor 4

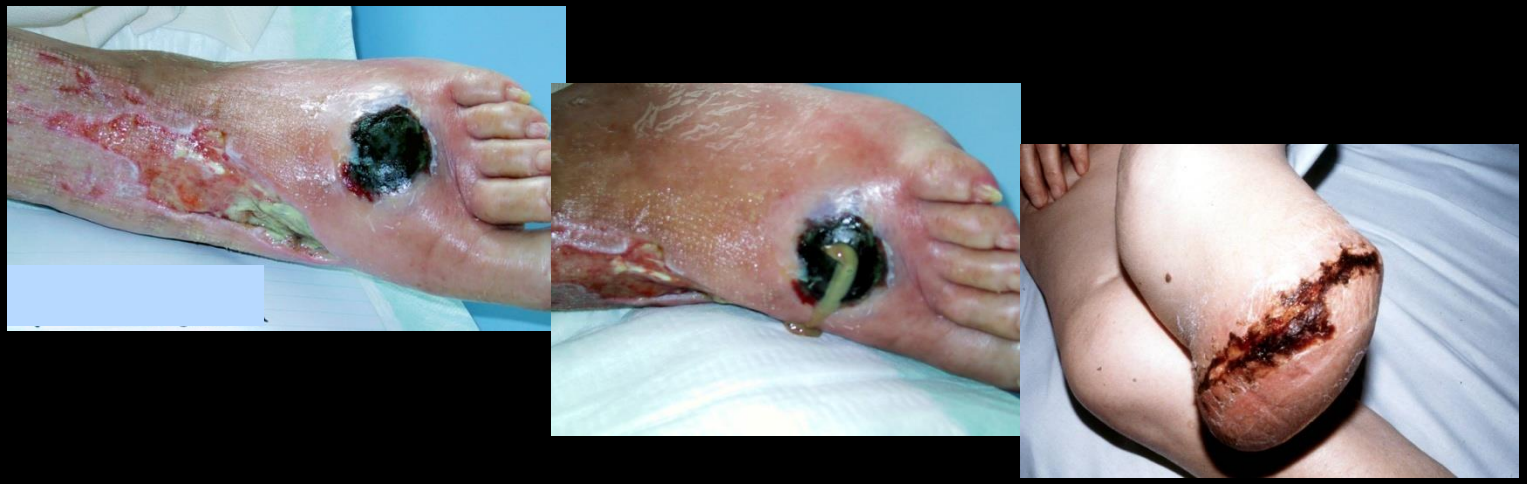
(Shah, Hux, 2003)

- 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

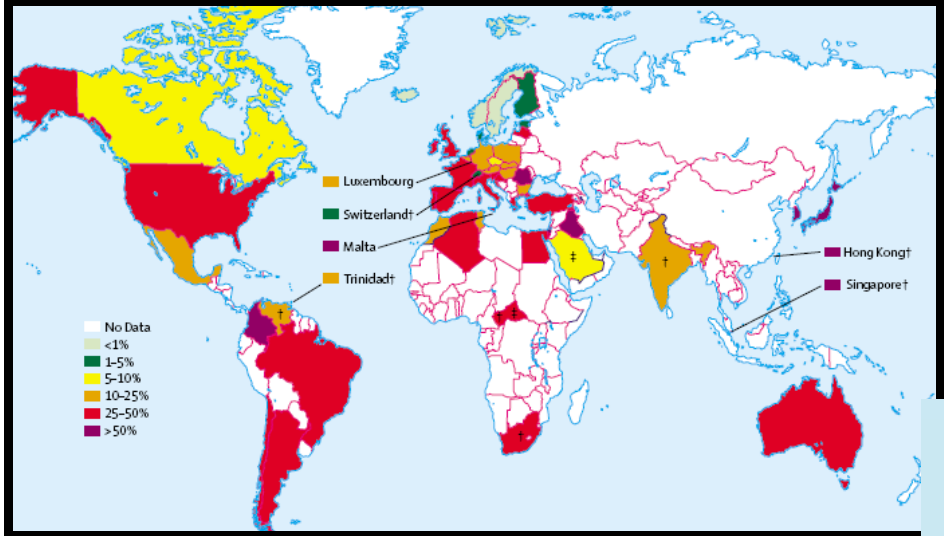
Clostridium difficile

Salmonella and E. coli

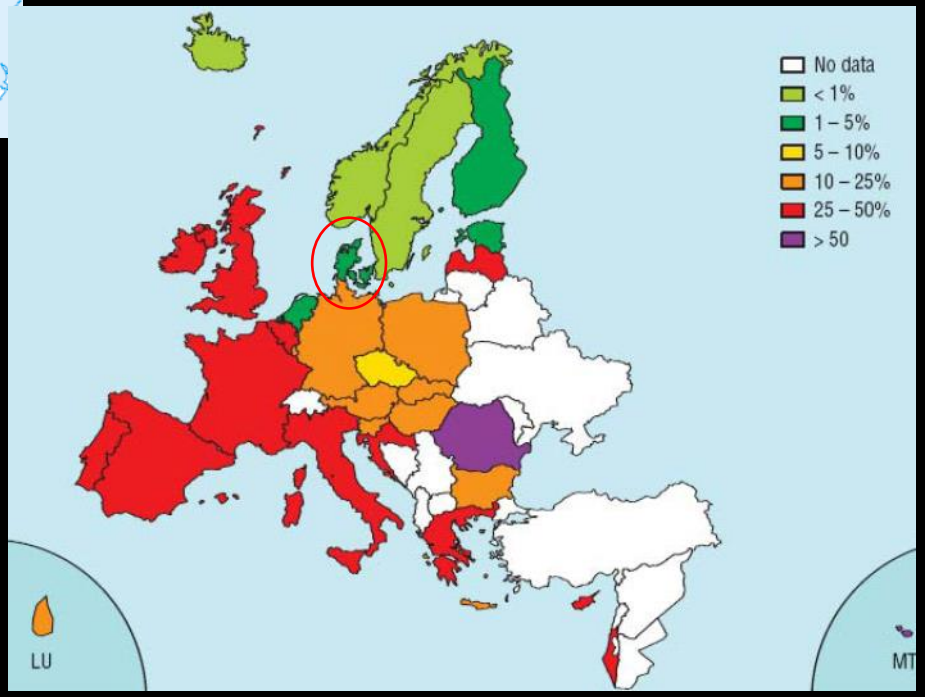
Acinetobacter baumannii

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. Published online
June, 2006 DOI:10.1016/S0140-6736(06)68853-3

Fra European Antimicrobial Resistence Surveillance System (EARSS), Annual report 2004, September 2005

Antimicrobial Document

EU-Initiativs

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.[1-3]

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)[3]

1. Danish Presidency of the Council of the European Union 2012. Combating Antimicrobial Resistance - Time for Joint Action. 2012
2. European Commision - 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

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 Postion Statement Document

BSAC The British Society for Antimicrobial Chemotherapy

Joint symposium with Veterinary Wound Healing Association (VWHA)
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EWMA Document:

Antimicrobials and Non-healing Wounds

Evidence, controversies and suggestions

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EUROPEAN · WOUND · MANAGEMENT · ASSOCIATION
EWMA

JWC
journal of wound care

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.

Copenhagen Wound Healing Center, F. Gottrup

Focus Area

Primary Focus:

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

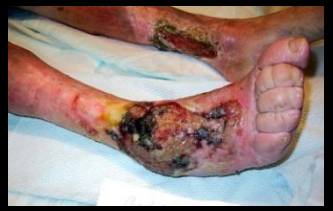
Not focused on:

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)

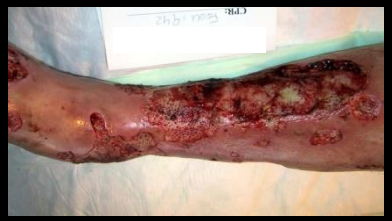


Practical Treatment:

Clean the Wound:

Debridement Techniques

Other cleaning Techniques



The next Question then is:

Local Antiseptic and/or Antibiotics?

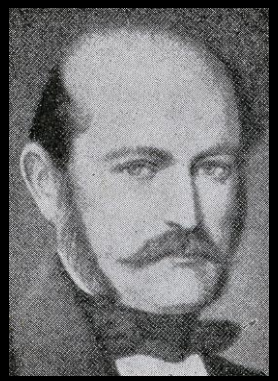
Infection: Treatment (Denmark)

Local Antibiotics:

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

Local Antiseptics:

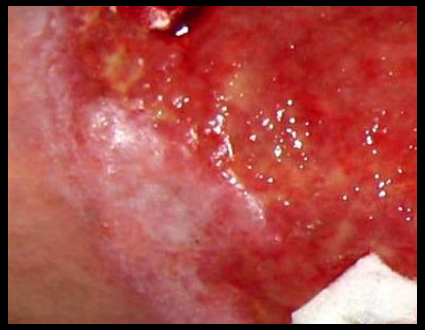
- Hypochlorite Solutions (Many Adverse Effects)
- *Chlorhexidine (Few Adverse Effects)
- *Hydrogen Peroxide
- *Proflavine
- Iodine Solutions (Iodosorb ® (Cadexome iodine), Povidine)
- Silver Sulphadiazine (Flammazine®)
- Silver Ionised (New type of Dressings)
- Other antiseptics (e.g PHMB)?



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

Projects related to Antiseptic and/or Antibiotics

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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**

EWMA'S Antimicrobial Stewardship (AMS) Programme

Copenhagen Wound Healing Center, F. Gottrup

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

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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

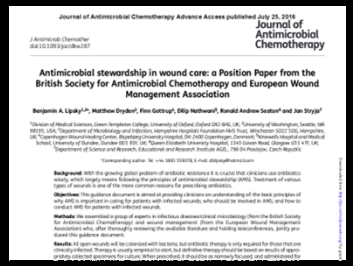
EWMA

BSAC The British Society for Antimicrobial Chemotherapy

JAC The Journal of Antimicrobial Chemotherapy

EWMA'S Antimicrobial Stewardship (AMS) Programme

Copenhagen Wound Healing Center, F. Gottrup



Journal of Antimicrobial Chemotherapy Advance Access published July 25, 2016

Journal of Antimicrobial Chemotherapy

J Antimicrob Chemother
doi:10.1093/jac/dkw287

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

Benjamin A. Lipsky[1,2*], Matthew Dryden[3], Finn Gottrup[4], Dilip Nathwani[5], Ronald Andrew Seaton[6] and Jan Stryja[7]

[1]Division of Medical Sciences, Green Templeton College, University of Oxford, Oxford OX2 6HG, UK; [2]University of Washington, Seattle, WA 98195, USA; [3]Department of Microbiology and Infection, Hampshire Hospitals Foundation NHS Trust, Winchester SO22 5DG, Hampshire, UK; [4]Copenhagen Wound Healing Center, Bispebjerg University Hospital, DK-2400 Copenhagen, Denmark; [5]Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, UK; [6]Queen Elizabeth University Hospital, 1345 Govan Road, Glasgow G51 4TF, UK; [7]Department of Science and Research, Educational and Research Institute AGEL, 756 04 Prostejov, Czech Republic

*Corresponding author. Tel: +44-1865-310478; E-mail: dilippa@hotmail.com

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

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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 administrated 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.

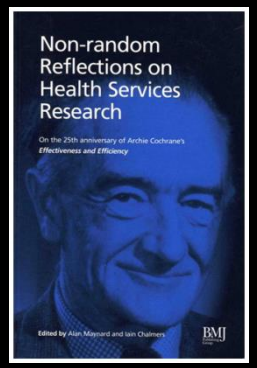
Conclusions: Available evidence is limited, but suggests that applying principles of AMS to the care of patients with wounds should help to reduce the unnecessary use of systemic or topical antibiotic therapy and ensure the safest and most clinically effective therapy for infected wounds.

Evidence Based Medicine

Evidence in the Wound Area

Evidence in Wound Healing

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

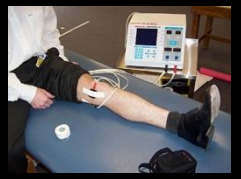


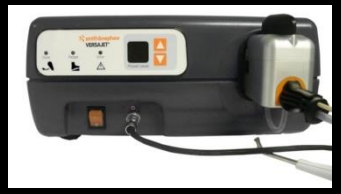
Type of Publication	Evidence	Strength
Meta-analysis, Systemic reviews	Ia	A
Randomised clinical trials (at least one)	Ib	
Controlled, Non-randomised trials (at least one)	IIa	
Cohort studies (at least one)	IIb	B
Diagnostic tests (Direct Diagnostic Method)		
Case-control studies	III	C
Diagnostic tests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

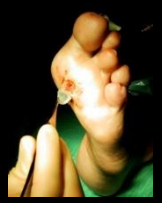
(Modified from Eccles et al. BMJ, 1998)

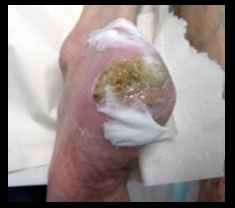
Copenhagen Wound Healing Center, F. Gottrup

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

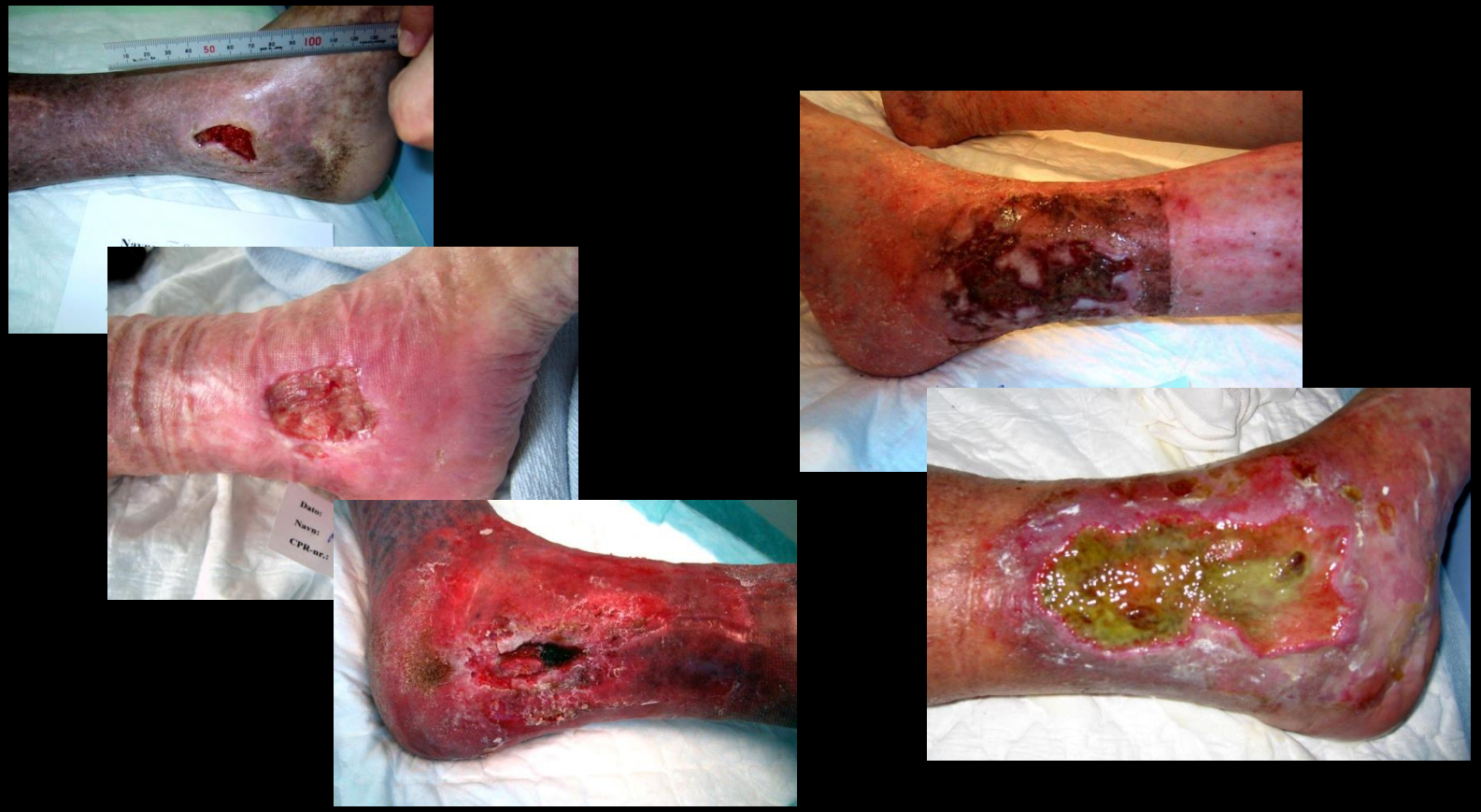
Evidence Problems in the Wound Area

Main Challenges using RCTs in Wound Healing

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

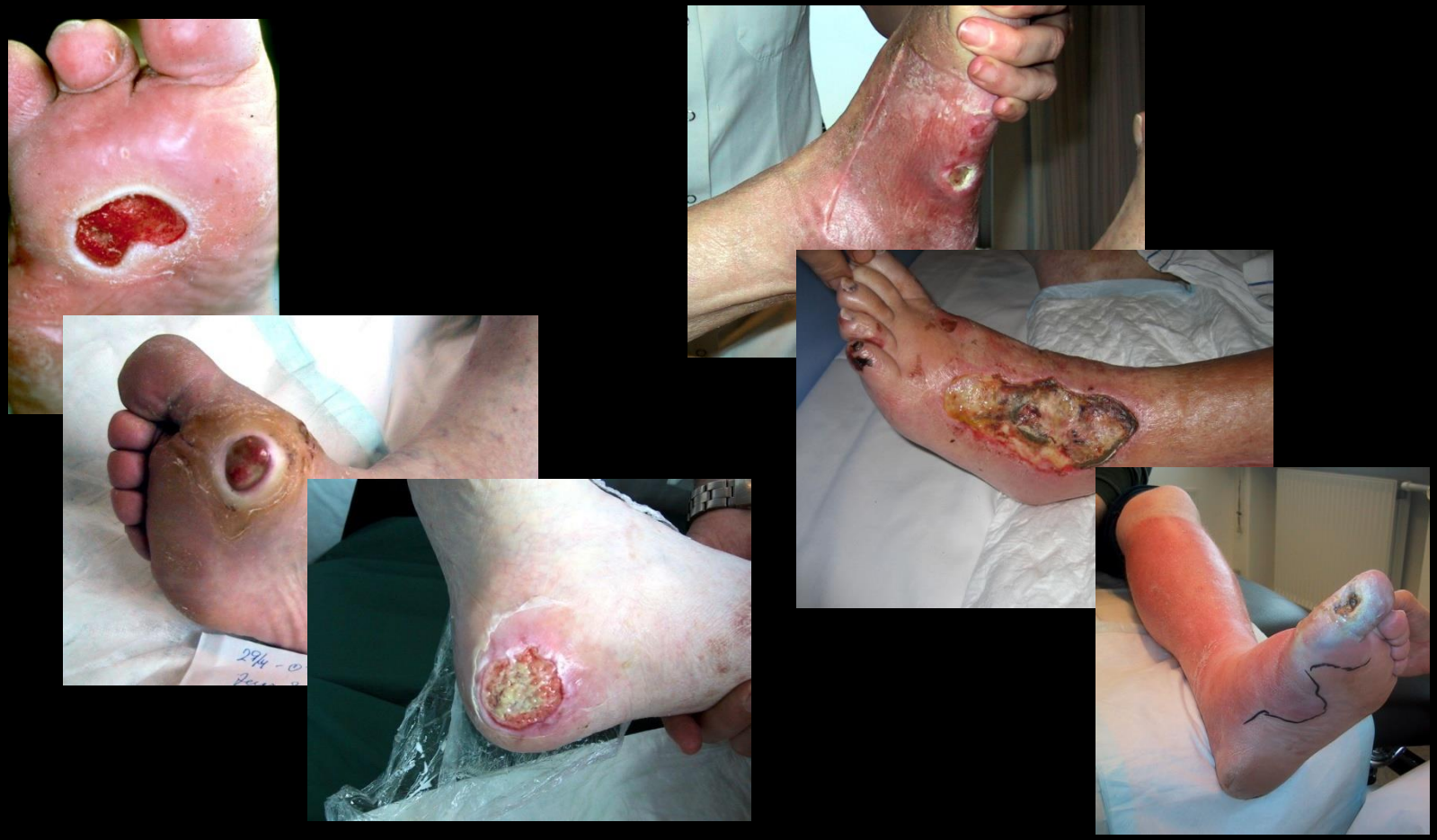
Evidence Based Medicine

1. How to standardise Venous Leg Ulcers?



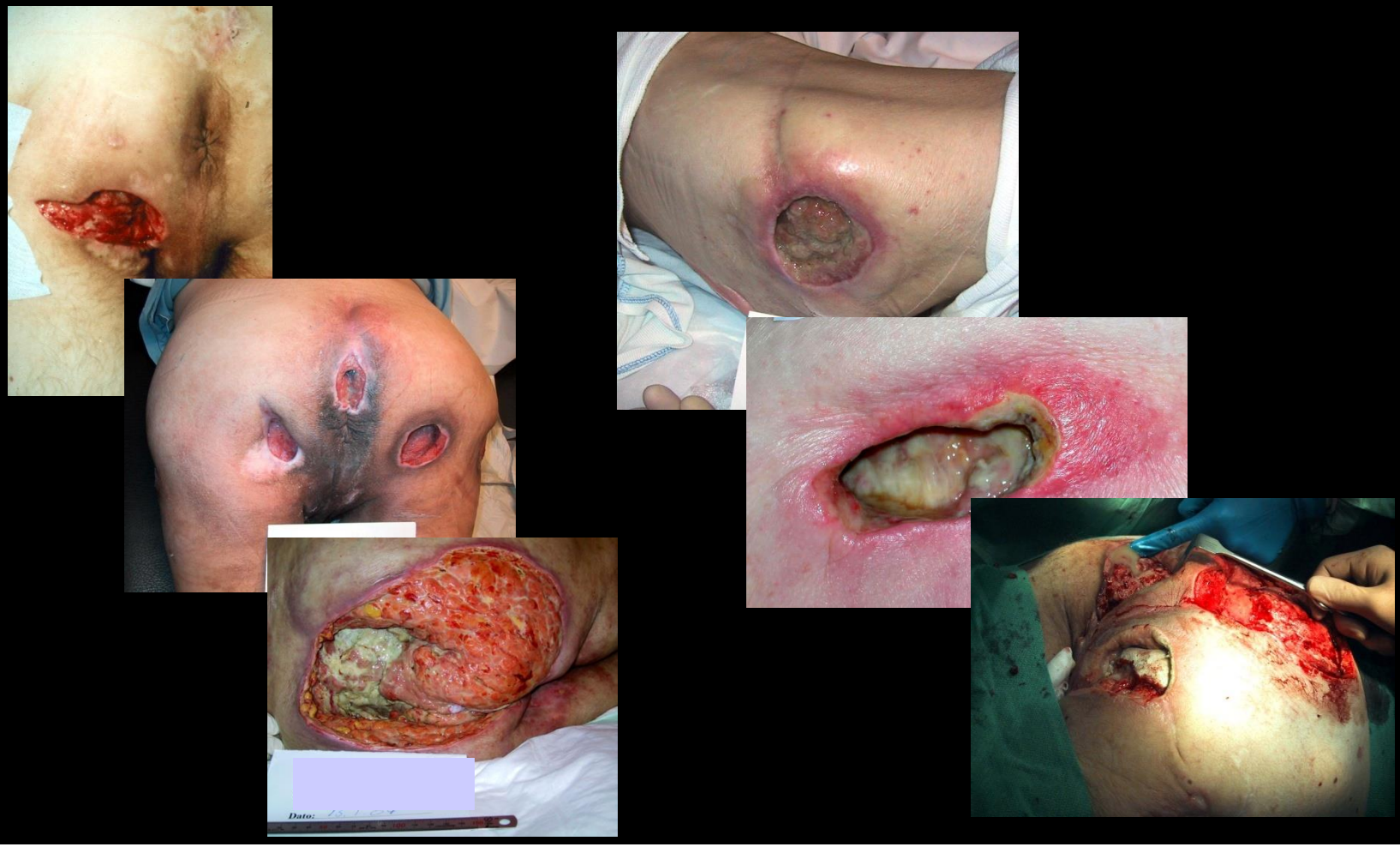
Evidence Based Medicine

1. How to standardise Diabetic Foot Ulcers?



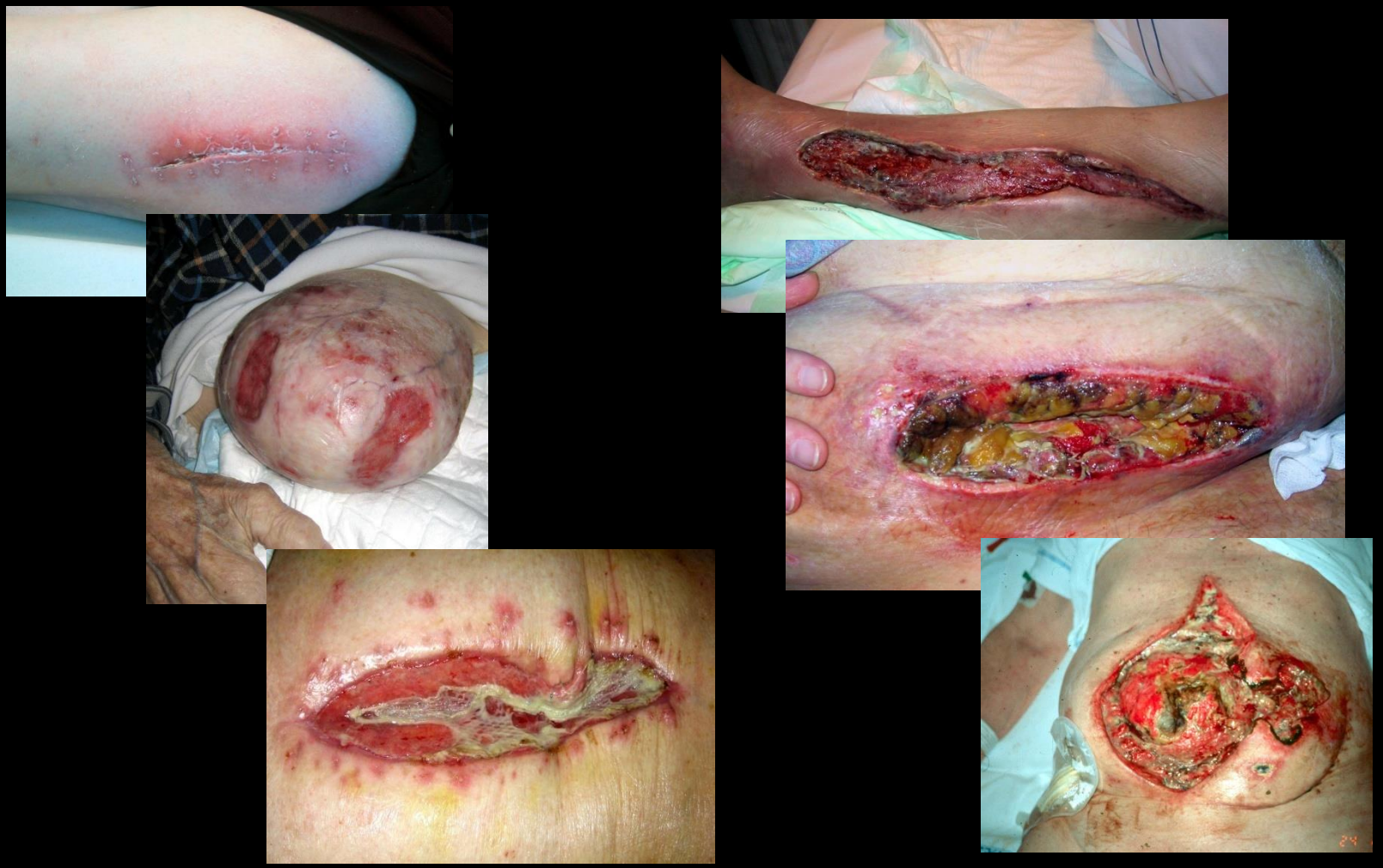
Evidence Based Medicine

1. How to standardise Pressure Ulcers/Sores?



Evidence Based Medicine

1. How to standardise Acute Problem Wounds?



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?

P. Price, Cardiff, England

Evidence of What?

(Outcomes/Endpoints)

(3 E´s)

Efficacy	Efficiency	Effectiveness
↓	↓	↓
Healing	Frequency of Visits	Cost
Recurrence	Days in hospital	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

Copenhagen Wound Healing Center, F. Gottrup

Outcomes/Endpoints in the Wound Area

Copenhagen Wound Healing Center, F. Gottrup

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

Guest Editorial

Evidence Is a Challenge in Wound Management

Nonhealing wounds are significant problems to 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 counts for more than 2% to 4% of the health care budgets.[1,2] If patients 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.[3,4] The question then 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 technologies. According to the Cochrane Wounds Group, a large number of these procedures and technologies 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.[5] 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 those RCTs that come within the defined zones. This approach helps to minimize bias inherent in comparisons.

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. Currently, economical resources to clinical and research work also have been based on the ability of the involved area to fulfill the concept of EBM.

Does this practice fit into the wound area? Most procedures, methods, materials, and technologies used in wound management may not fulfill the above-mentioned criteria. A great deal of clinical research suffers from inadequate sample sizes, short follow-ups, nonuniform allocation to treatment arms, nonblinded assessment of outcomes, poor description of control and concurrent intervention, and so on.[6]

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 deemed safe for use after successful investigations of safety based on Phase 1 and 2 trials yield satisfactory outcomes. Thus the motivation for designing 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 modern dressings in the treatment of leg ulcers.[7] In 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 evidence of the used products. Consequently, traditional products such as gauze and other dry wound-healing dressings may be reinforced, whereas no reimbursement is achieved 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 appropriated strategy. The

Correspondence should be sent to Finn Gottrup, MD, DMSci, The University Center of Wound Healing, Odense University Hospital, DK-5000 Odense C, Denmark; e-mail: finn.gottrup@ouh.fyns.amt.dk.

Conflict of Interest: None.
DOI: 10.1177/154479150600200412
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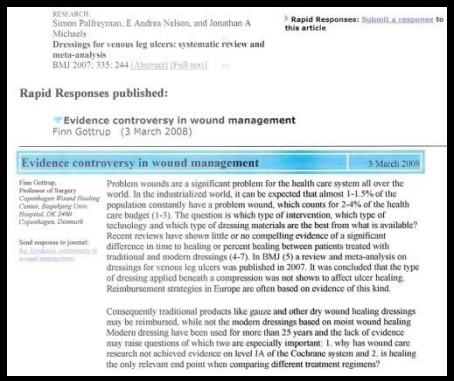
F. Gottrup:
Editorial,
Lower Extremity
Wounds 5; 2006: 74-75



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 Univ. Hospital, DK 2400 Copenhagen, Denmark

Send response to journal:
Re: Evidence controversy in wound management

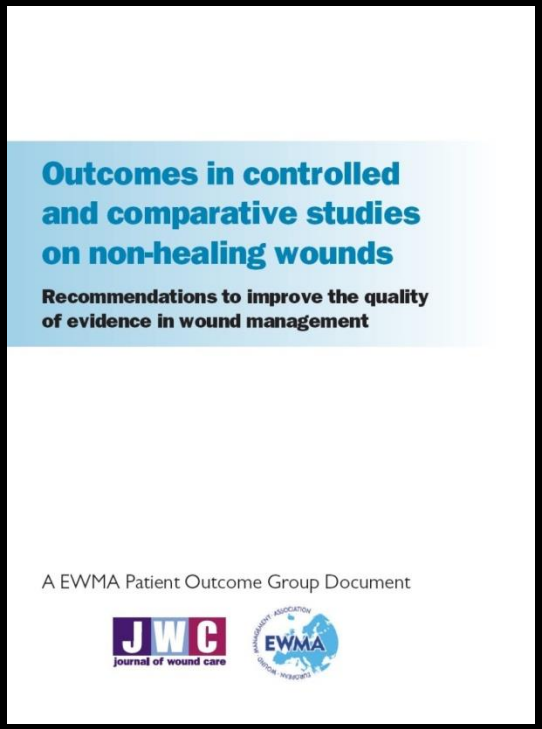
Problem wounds are a significant problem for the health care system all over the world. In the industrialized world, it can be expected that almost 1-1.5% of the population constantly have a problem wound, which counts for 2-4% of the health care budget (1-3). The question is which type of intervention, 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 1A of the Cochrane system and 2. is healing the only relevant end point when comparing different treatment regimens?

F. Gottrup:
Rapid Respose
BMJ, 3 March 2008

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

The EWMA Patient Outcome Group (POG)



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

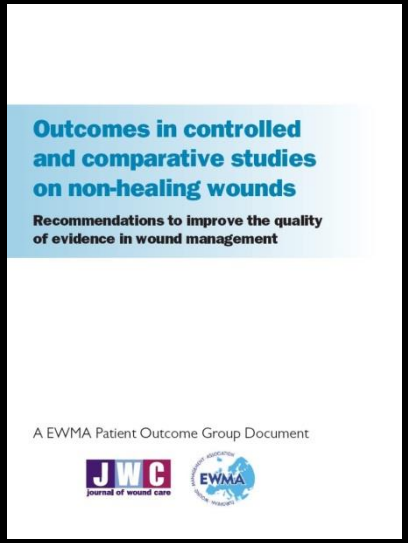
Aim of the Document

- 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

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

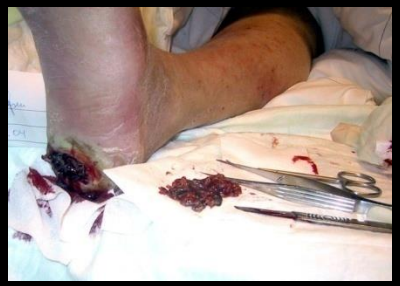
Copenhagen Wound Healing Center, F. Gottrup

No or Little Evidence

(Primarily Topics related to FDA Meeting)

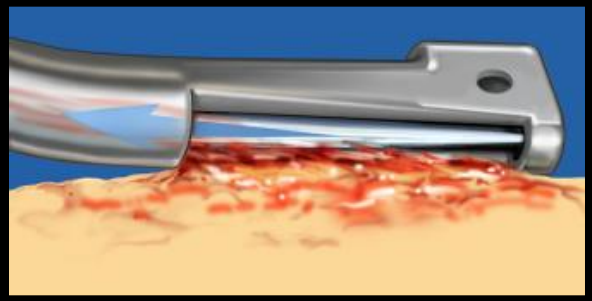
Copenhagen Wound Healing Center, F. Gottrup

Debridement



Sharp

Maggots (Larvae)



Versajet®

Conclusion

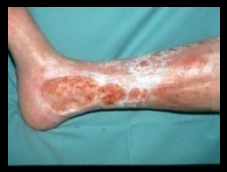
Despite the widespread and vital use in clinical practice, there is little evidence on the highest level for sharp and maggot debridement has any effect. In a Cochrane review* it was evidence to suggest that hydrogel dressing increases healing rate of DFU compared to gauze.

(* 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 (RTCs)

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

Copenhagen Wound Healing Center, F. Gottrup

Use of Dressings

Hydrocolloid
Hydrogel

Foam

Algenates
Hydrofiber

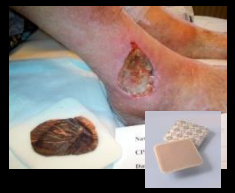
Other Types

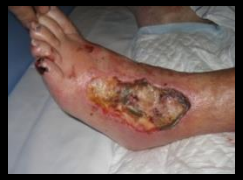
Conclusion

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 (RTCs) 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.

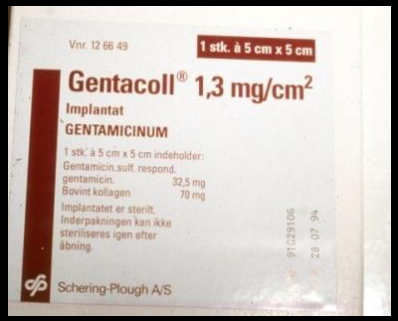
Topical Silver for preventing Wound Infections

(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

Copenhagen Wound Healing Center, F. Gottrup

Use of Antimicrobials and Dressings



Antiseptics **Antibiotics**

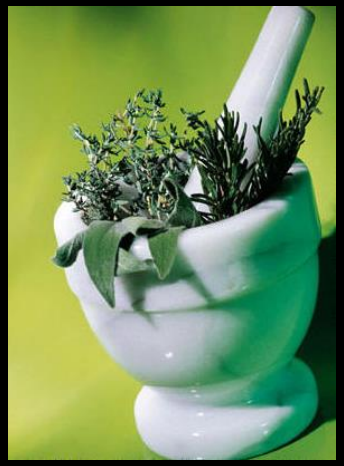
Conclusion

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.

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

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

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

Copenhagen Wound Healing Center, F. Gottrup

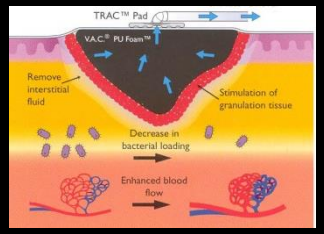
Perhaps/Probably some Evidence

(Primarily Topics related to this Meeting)

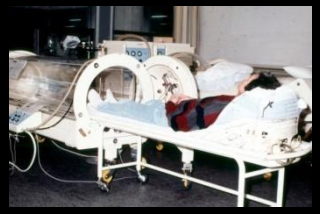
Evidence in Wound Healing

Copenhagen Wound Healing Center, F. Gottrup

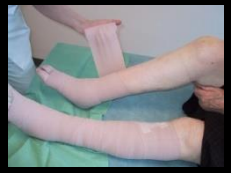
Topical Negative Pressure (TNP)



Hyperbaric Oxygen Therapy (HBOT)



Use of Compression (Bandages/Stockings)



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

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)

What can be done?

New Outcome Measures

Efficacy

Healing
Recurrence

Efficiency

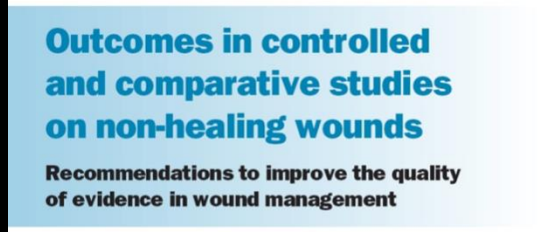
Frequency of Visits
Days in Hospital
Others

Effectiveness

Cost
QoL
Others

Evidence in Wound Healing

Patient Outcome Group (POG)



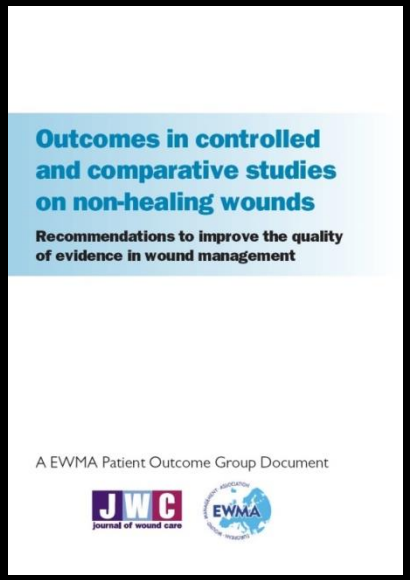
Recommendations on Endpoints/Outcome Parameters

- 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 an 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

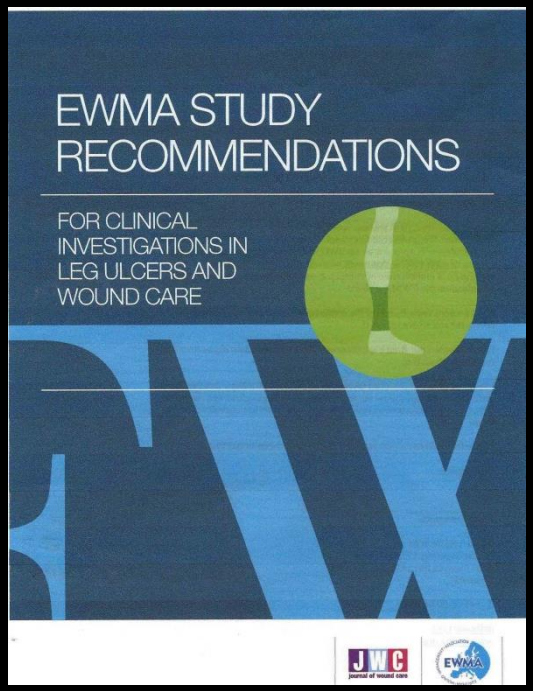
Some important Questions to agree on in the Future

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



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



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

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.**

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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