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

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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
Impact of Wounds

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

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

Started in 1996
Personnel only for Wound Management

University Center of Wound Healing (UCWH)
Department of Plastic Surgery, Odense University Hospital

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
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)
Microbiological Balance

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.)

(Copenhagen Wound Healing Center, F. Gottrup)

(Modified from Kolmos 2002)
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**
- **Infection**
- **Few Wounds**
- **Invasion**
- **Inflammation**
- **Tissue Destruction**

**Contamination**
- All Wounds
- Temporary
- No Reproduction

**Colonisation**
- Many Wounds

**Permanent Active Reproduction**

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

(Local → Systemic) (Cutting et al 1994)

(Kingsley 2001)
The Virulence of the Bacteria: Groups of Wound Bacteria

- Invasive Wound Bacteria
- Local Wound Bacteria
- Opportunistic Wound Bacteria
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
Erysipelas and Group A Streptococcus

Virulence Factors:
- Pyrogene exotoxins
- Streptolysins
- Streptokinases
- Deoxyribonucleases
- C5a peptidases
- Hyaluronidases
- DPNases

(Erysipelas Leg)  (HJ Kolmos)
Skin Abscesses (Furuncles) and Staphylococcus Aureus

Virulence Factors:

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

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

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
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

Fra European Antimicrobial Resistance Surveillance System (EARSS), Annual report 2004, September 2005
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.\textsuperscript{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 “\textit{Combating Antimicrobial resistance – Time for Joint Action}” (March 2012)\textsuperscript{3}

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.
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)
Projects related to Antiseptic and/or Antibiotics

**Antimicrobials & Non-healing Wounds Evidence, Controversies and Suggestions.**
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2015: Development of *clinical Decision support Tool* facilitating appropriate use of Antimicrobials

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Joint BSAC/EWMA Policy Statement in Wound Management
Produce a Postion Statement Document

**Joint symposium with Veterinary Wound Healing Association (VWHA)**
(EWMA Conference 2014, 2015)
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)?

(* Rarely used for wound 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
Projects related to Antiseptic and/or Antibiotics


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

Antimicrobial Stewardship in Wound Management
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Joint symposium with Veterinary Wound Healing Association (VWHA)
(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

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 the shortest possible time.
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 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 in the Wound Area

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

<table>
<thead>
<tr>
<th>Type of Publication</th>
<th>Evidence</th>
<th>Strength</th>
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<tbody>
<tr>
<td>Meta-analysis, Systemic reviews</td>
<td>Ia</td>
<td>A</td>
</tr>
<tr>
<td><strong>Randomised clinical trials (at least one)</strong></td>
<td>Ib</td>
<td></td>
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<tr>
<td>Controlled, Non-randomised trials (at least one)</td>
<td>IIa</td>
<td></td>
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<tr>
<td>Cohort studies (at least one)</td>
<td>IIb</td>
<td>B</td>
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<tr>
<td><strong>Diagnostic tests (Direct Diagnostic Method)</strong></td>
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<tr>
<td>Diagnostic tests (Indirect Nosographic Method)</td>
<td>III</td>
<td>C</td>
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<td>Case-control studies</td>
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<td><strong>Descriptive investigations</strong></td>
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<tr>
<td>Small-scale evaluation, Casuistic cases</td>
<td>IV</td>
<td>D</td>
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<tr>
<td>Tradition textbook and review articles</td>
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<tr>
<td>Expert evaluation, Editorialials</td>
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(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
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
1. How to standardise Venous Leg Ulcers?
1. How to standardise Diabetic Foot Ulcers?
Evidence Based Medicine

1. How to standardise Pressure Ulcers/Sores?
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)
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
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.

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?

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

F. Gottrup:
Rapid Respose BMJ, 3 March 2008
The EWMA Patient Outcome Group (POG)

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

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%)
- 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%).
Present Status of Wound Evidence on the highest Level

(Primarily Topics related to FDA Meeting)

No or Little Evidence
Perhaps/Probably some Evidence
No or Little Evidence

(Primarily Topics related to FDA Meeting)
Evaluation of present Evidence

Debridement

**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.


(Gottrup F. Apelqvist J. *Diabetes Metab Res Rev* 2012; 28 (Suppl 1): 64-71)
Efficacy of Modern Dressings in the Treatment of Leg ulcers: A systematic Review


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.
Use of Dressings

**Evaluation of present Evidence**

**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.

Evaluation of present Evidence

Silver Treatments of Leg Ulcers: A systematic Review

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
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)
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)
Perhaps/Probably some Evidence

(Primarily Topics related to this Meeting)
Evidence in Wound Healing

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?

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.

(Copenhagen Wound Healing Center, F. Gottrup)

(Gottrup F, Apelqvist J, Price P)
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?
**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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