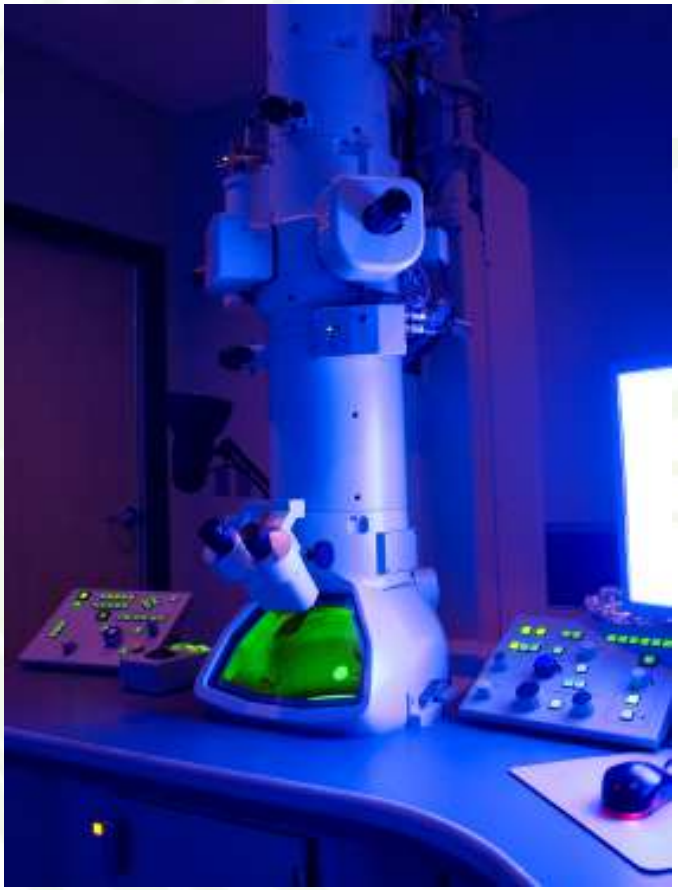
Pitfalls of evidence in wound infection

Keith Harding

Who needs evidence?

- The cornerstone of good medicine
- It should aid and not hinder practice
- That's easier said than done
- Multiple classifications and hierarchies for ranking evidence



Evidence and Changing Practice

Keith Harding

Head of Dept. Wound Healing

Professor of Rehabilitation (Wound Healing)

Clinical Director Wound Healing Cardiff & Vale NHS Trust

Wound Healing Research Unit

Yr Uned Ymchwil Gwella Clwyfau

Cardiff University

Prifysgol Caerdydd

International Wound Infection Institute

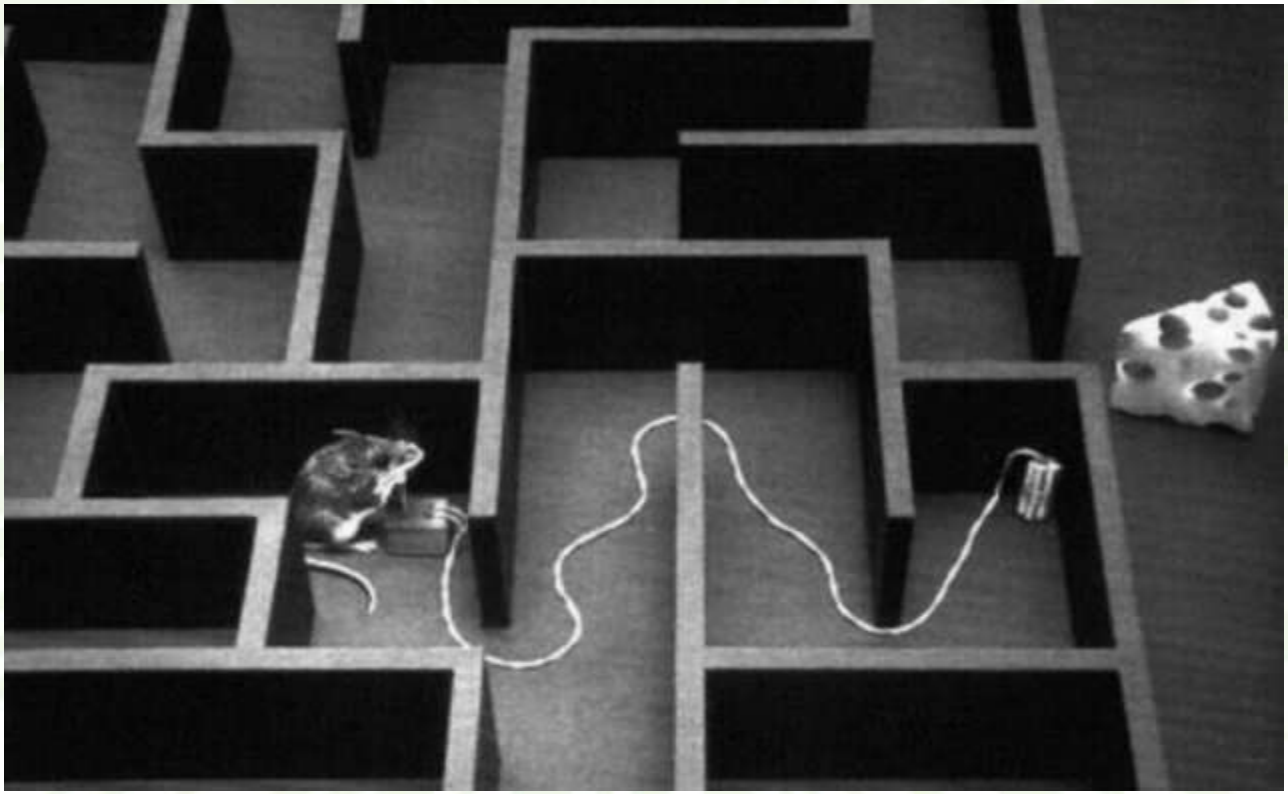
Alternatively:

Evidence v's Experience v's Excuses in changing Practice

Evidence -based medicine

Evidence-based medicine (EBM) requires the integration of the best research evidence with our clinical expertise and our patient's unique values and circumstances" (1)

Strauss et al., 2005

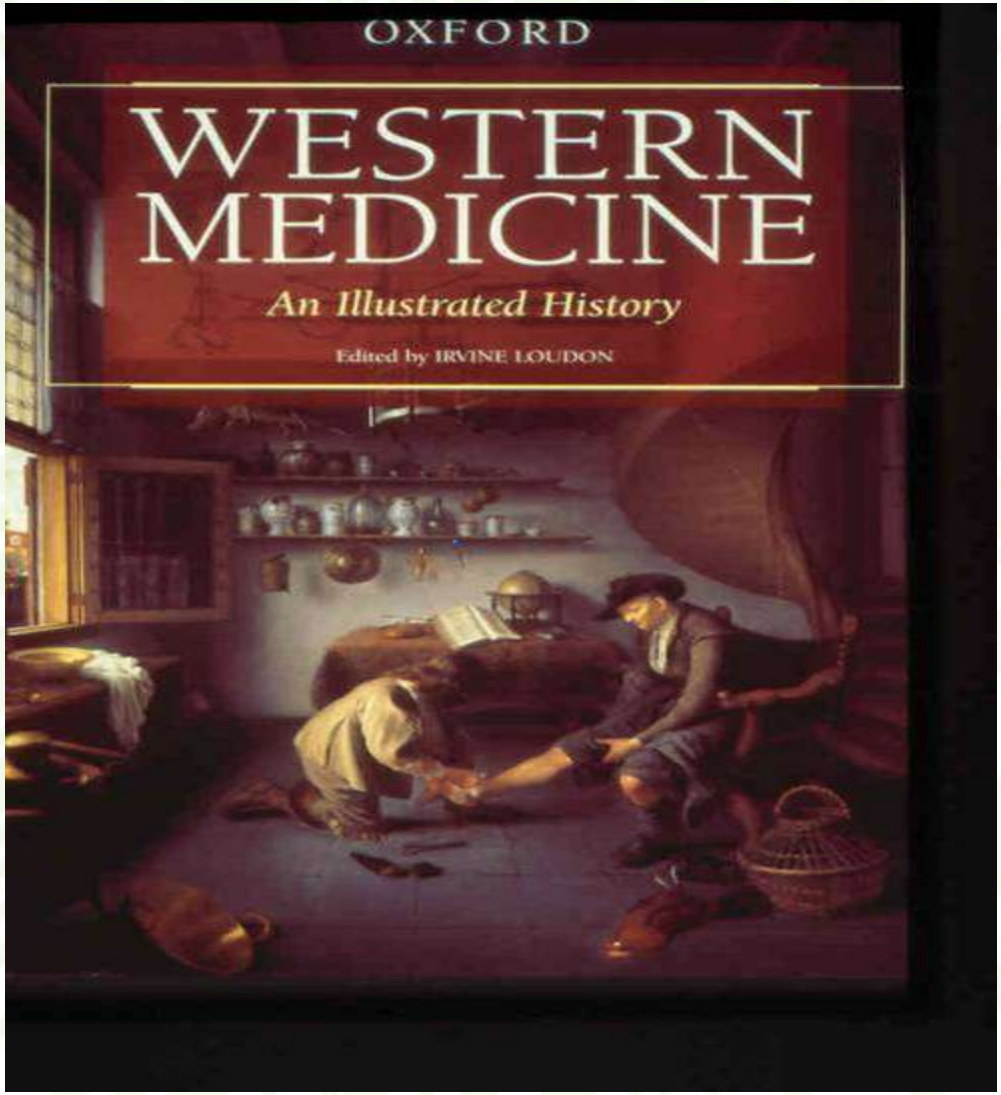


Evidence -based medicine

Clinical Experience and Expertise - **How do you Measure ?**

Patient values (preference, perception, practicability) & Patient circumstances (individual risk, individual clinical state) - **How do you Value ?**

Is This Still the Approach to Wound Healing ?



Attitudes

- Healing wounds – much labour to be bestowed and little glory obtained

-1805

- Diabetic foot disease – extraordinarily complex like fairy godmothers wave antibiotics and dressings over wounds

- 1994

Wound Healing Art or Science ?

Evidence v's Experience

Educational Paradigm

Knowledge

+

Skills

+

Attitudes

=

Behaviour change

Evidence v's Experience

Maturity

Conception

Birth

Child

Teenager

Young Adult

Mature adult

Old Age

Retirement

Evidence v's Experience

Maturity

Conception

Birth

Child

Teenager

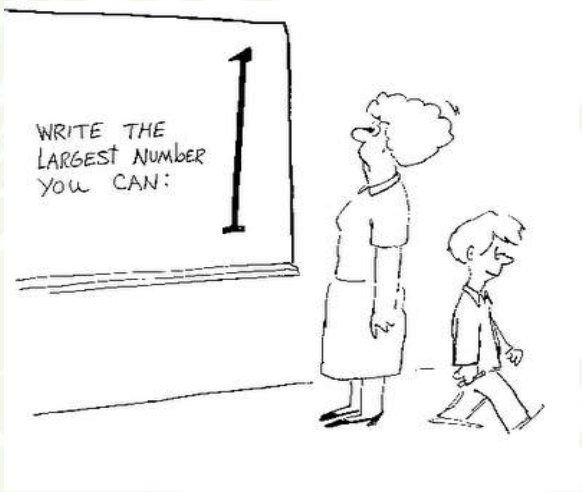
Young Adult

Mature adult

Old Age

Retirement

Wound Care 2010



Evidence v's Experience

<u>Experienced Clinician</u>

Self evaluation

Inquiry path

Hypotheses

Data interpretation

Problem formulation

Diagnostic decisions

Therapeutic decisions

Sequential or continuing management

Efficiency

Patient

Problem

↓

Help

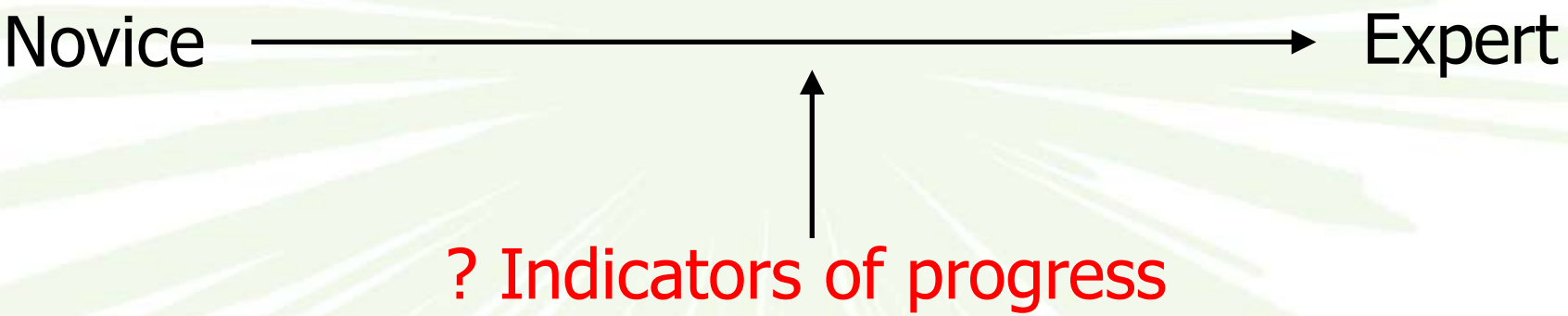
↓

Solution

Evidence v's Experience

Experience

Managing Patients with Wounds



Infected ?

Infected ?

Optimal Treatment ?

Evidence v's Experience

Change Theory

Innovators

Early Converters

Late adopters

Laggards

Which one are you ?

WHS guidelines for VLU-2006

- Assess patient
- Measure vascular status
- Check bloods
- Undertake biopsy if not healing
- Consider inflammatory disease
- Compression is key
- IPC is useful intervention
- Debride ulcer if necrotic tissue present
- Non migrating edge may be sign of infection
- Biopsy and high levels of bacteria /gm tissue diagnose infection
- Reduce bacterial load prior to grafting
- Consider systemic disease, drugs and nutrition affecting healing

WHS guidelines for VLU-2006

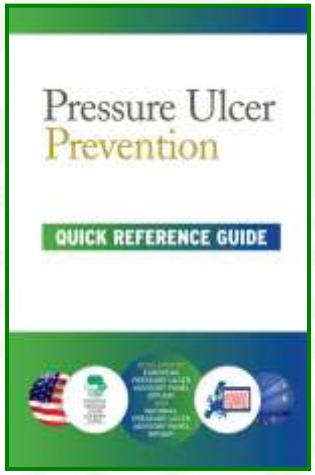
- Use dressings that maintain moist environment
- Protect peri ulcer skin
- Select dressings that stay in place
- Cost effective dressings should be used
- Change local treatment only if not healing
- Skin grafting is not an intervention for long term success
- Compression and surgery may influence recurrence
- Free flaps may help
- Cytokines and growth factors still not proven
- Topical free radical scavengers and fibrinolytics not effective
- Bilayered allografts are helpful
- Cultured epithelial autografts not proven

WHS guidelines for VLU-2006

- Electrical stimulation may help
- NPT is useful prior to skin grafting
- Systemic Pentoxifyline will assist healing
- Systemic prostaglandins and prostaglandin antagonists are not helpful
- Systemic flavinoid fractions may be helpful
- Systemic fibrinolytics may be helpful
- Oral Zinc has no benefit
- Stockings for life
- Calf muscle exercises are helpful in preventing recurrence

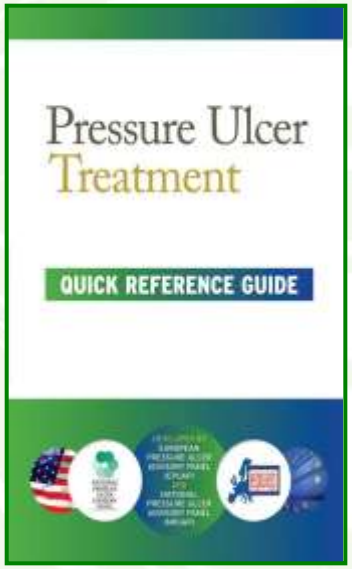
Pressure Ulcer Guidelines 2010
A Level Evidence

- 6 Recommendations only
- Nutrition
- Repositioning
- Mattresses-High Spec Foam/No diff. Low air loss and Alternating



EPUAP / NPUAP

- 1 Recommendation only
- Electrical Stimulation



NPUAP / EPUAP

Evidence v's Experience

Evidence for best practice

- No evidence Yes/No
- Some evidence Yes/No
- Adequate evidence Yes/No

Neuropathy or Ischaemia ?

Infection or Maceration ?

Surgical or Autoamputation ?

Wet or Dry ?

Osteomyelitis or Not ?

Hot Spot due to OM or Reactive ?

Evidence v's Experience

Evidence

Of what?

Efficacy	Efficiency	Effectiveness
↓	↓	↓
Healing	Frequency of visits	Cost
recurrence	Days in hospital	QoL

Price 1999

Who knows what a P value is ?

Who knows what a P value is ?

Who believes in P values ?

Who knows what a P value is ?

Who believes in P values ?

Who changes practice because of P values

Technologies

Biologically Based Therapy

Growth Factors

Animal models number of growth factors increase granulation tissue 150 – 200%

PDGF

	Pts	Placebo	30 µcgm	100 µcgm	Good Care
1	118	25%	48% (*)		
2	382	35%	36%	50% (*)	
3	172	36%		44%	22%
4	250			36%	32%

Centre 1 15% debridement – 20% healed
Centre 2 81% debridement – 83% healed

Steed 1996

Technologies

Biologically Based Therapy

Tissue Engineered Allografts

Apligraf

VLU - at 6 months

63% - test

49% - control

(p=0.02)

Better for larger, deeper, older ulcers

Arch Derm 1998

DFU - at 12 weeks

56% - test

38% - control

(p=0.004)

Veves 2001

Technologies

Biologically Based Therapy

Tissue Engineered Allografts

Dermagraft

DFU - at 12 weeks

51% - test

32% - control

(p=0.006)

Wounds 1997

Evidence based Practice

"That hurts, does it ?"

- Statistically Significant **or**
- Clinically Impressive ?

Where do you get your information from ?

Evidence v's Experience

Sources of Information in UK

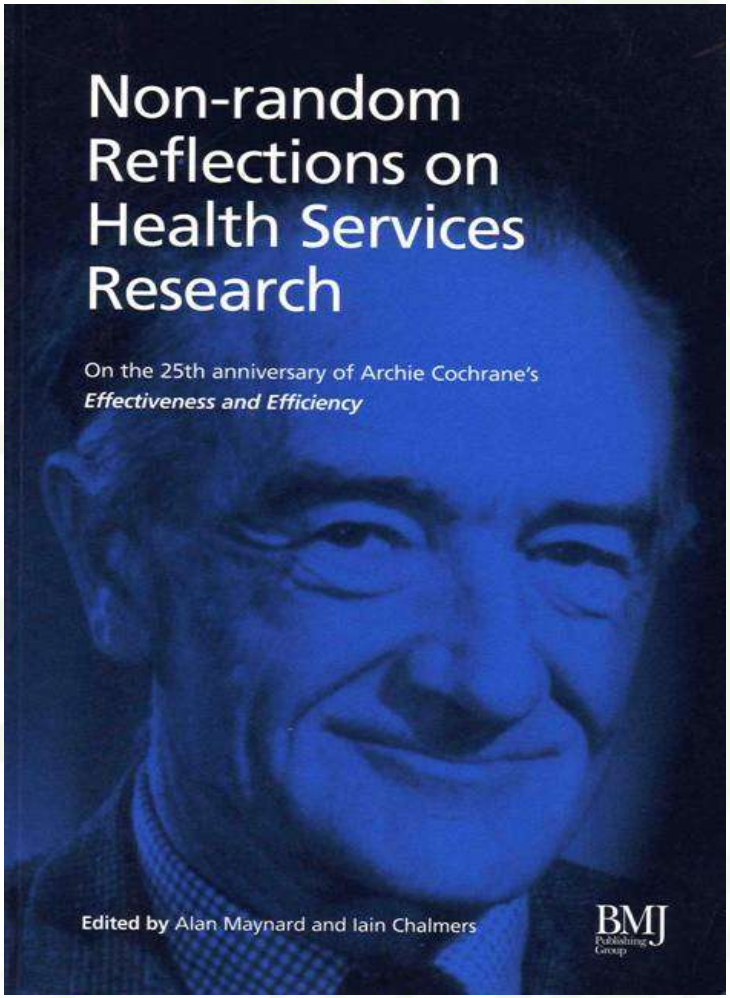
H T A

NICE guidelines / appraisals

Local guidelines – SIGN, CREST

Cochrane library

Evidence based Practice



- Clinicians for the Restoration of Autonomous
- Practice writing group

  BMJ 2002

International Wound Infection Institute

Evidence v's Experience

Experience - VLU

Use of:

Ultrasound	Yes/No/Don't Know
Pentoxifylline	Yes/No/Don't Know
Skin grafting	Yes/No/Don't Know
Lasers	Yes/No/Don't Know
Zinc	Yes/No/Don't Know
Compression - healing	Yes/No/Don't Know
- recurrence	Yes/No/Don't Know

Evidence v's Experience

Cochrane Library

Chronic Wounds - VLU

	Year	Trials	Patients	Problems	
Ultrasound	**2008**	**8**	**?**	sham, standard	poss benefit
Pentoxifylline	**2007**	**12**	**864**	variable	effective
Skin grafting	**2007**	**15**	**768**	diff types skin	artificial skin
Compress for recurrence	**2000**	**2**	**466**	no compression not studied	weak
Compression for healing	**2001**	**22**	**?**	diff types compared	high/low some/none multi/single
Electromagnetic Therapy	**2006**	**3**	**?**	different comparators	no evidence
Zinc for healing	**1998**	**6**	**?**	need to measure levels	weak if zinc low

Evidence v's Experience

Cochrane Library

Chronic Wounds - PU

	Year	Trials	Patients	Problems	
Ultrasound	**2006**	**3**	**146**	sham	no benefit
Electromagnetic	**2006**	**2**	**60**	standardisation	no benefit
Nutrition	**2003**	**8**	**?**	Small poor quality	Not clear
Beds, mattress	**2004**	**41**	**?**	prevention- high quality foam treatment- air fluidized + low air loss	impossible to determine most effective

Evidence v's Experience

Cochrane Library

Chronic Wounds - DFU

	Year	Trials	Patients	Problems	
Education for prevention	**2004**	**9**	**?**	conflicting	unknown
Debridement	**2007**	**6**	**?**	comparators	hydrogels work surgical + larval don't
Silver	**2006**	**0**		No studies reported	no
TNP	**2007**	**1**	**162**	DF Amputations	Acute-Yes Chronic-?

Treatment Options for Diabetic Foot Ulcers

Other Interventions

	Pts	Outcome	
Iloprost	109	↑ healing 4/52	2
Phenytoin	50	↑ healing	2
Collagen	10	↑ healing	2
Ketanserin	69	↑ healing 12/52	2
	19	↑ healing rate	2
LMWH	10	↓ size	2
HBO	17	↑ healing	2
	35	↓ amputation	2
	8	↓ size	2
	14	↑ healing	2
Electrical stim	32	↓ size	2

1 –Accepted, 2 – RCT, 3 - Unproven

Diabetic Med 2004

Treatment Options for Diabetic Foot Disease

HBO

6 studies met criteria - all ulcers

5 studies pooled data - DFU

118 patients

↓ risk major amputation

RR 0.31 CI 0.13 - 0.71

NNT 4 CI 3 - 11

Ulcer healing and rate of minor amputation not affected

Br J Surgery 2005

The myth of the RCT

No allowance for our ability to execute these designs in the real world!!

From http://servers.medlib.hscbklyn.edu/ebm/2100.htm

Evidence Based Practice

Latest Developments……

Grade System-Quality of Evidence

- High
- Moderate
- Low
- Very low

Strong recommendation for/against

Weak recommendation for/against

BMJ May 2008

Grade System

Factors Influencing Quality of Evidence

- Study limitations
- Inconsistency of results
- Indirectness of evidence
- Imprecision
- Publication bias
- Large magnitude of effect
- Plausible confounding factors
- Dose – response gradient

BMJ May 2008

Cost Effectiveness of Modern Wound Care Products

- 15 Studies on 519 Patients with PU
- 12 Studies on 843 Patients with LU
- HCD 1 £422 / Healed Wound
- HCD 2 £643 / Healed Wound
- Gauze £2548 / Healed Wound in PU
- Gauze £541 / Healed Wound in LU
- *(Harding et. al. 2000)*

Dressings & DFU- HTA Study 2008

ITT analysis	Ongoing/ withdrawn	Healed	Total
Inadine	60 (55.6%)	48 (44.4%)	108
Aquacel	57 (55.3%)	46 (44.7%)	103
N-A	65 (61.3%)	41 (38.7%)	106
Total	182 (57.4%)	135 (42.6%)	317

Chi square = 0.995, df = 2, p=0.61

Modern Dressings in Practice

- Do you use these products in your management of patients with Diabetic Foot Ulcers and other Chronic wound situations?

- P.S. I Do!!!!!

Honey dressings in VLU

- RCT 368 patients
- Adequate power
- In combination with compression
- No effect on healing of ulcers at 12 weeks

BJSurg 2008

Do you use these products in your practice?

Dressings for Leg Ulcers

- Systematic Review
- Dressings under Compression have no effect on healing of VLU
- Dressing choice- base on cost and Patient/care giver preference

BMJ 2007

Do you choose Products based solely on Cost?

NPT in Chronic Wounds

- 162 Patients Partial foot Amputation
- Healing at 16 weeks
- 56% NPT 39% Moist Healing (p=0.40)
- Rate of Healing and Granulation tissue Faster

Lancet 2005

- Use in chronic wounds restrict to research settings

DTB 2007

Do you agree with this Statement ?

NPT in Acute and Chronic Wounds

- 15 Publications on 13 RCTs
- Chronic and diabetic wounds no effect on healing but reduction in time (1-10 days) to secondary closure
- In acute wounds 17% increase in number healed but at 11% increased complication rate
- Conclusion – there is little evidence to support use and claims for reimbursement of TNP in treatment of wounds

Ubbink, Nelson BJS 2008

Why do we mainly focus on evaluation of new products ?

Dressings and other materials

Nurse time

Hospitalisation

Typically 10%-15% of total cost

Typically 25%-30% of total cost

Typically 50%+ of total cost

How to Measure Success in Treating Leg Ulcers

- RCT – larvae
  - no diff healing
  - big diff debridement
- RCT – compression
  - 4LB better healing
  - SSB helpful in mobile patients
- Unrealistic to use complete healing as primary outcome measure ….. more appropriate to adopt broader based approach

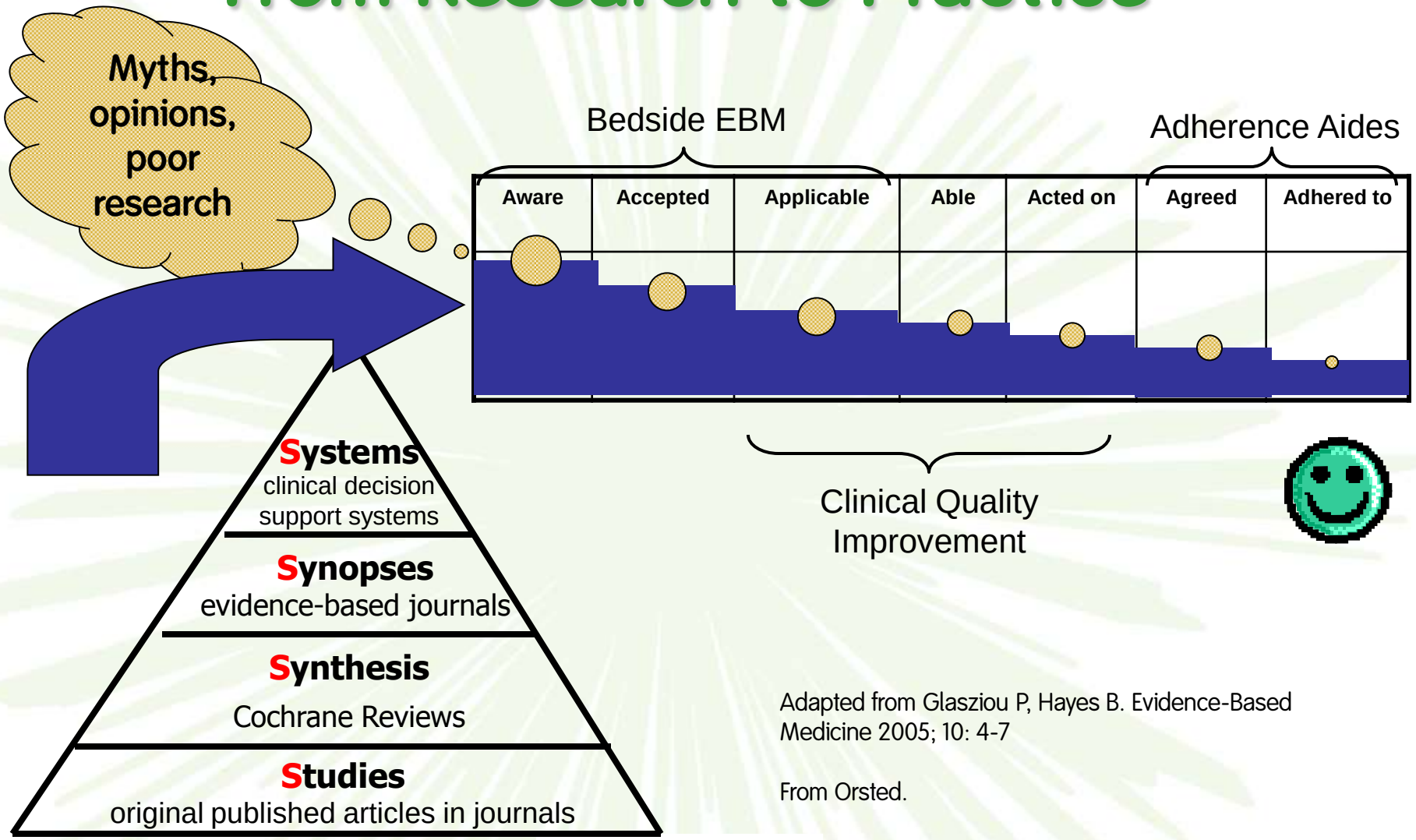
Grey, Leaper, Harding

Editorial BMJ 24 April 2009

How do you measure success?

- Wounds healed?
- ‘Wound free days’?
- Decrease in pain, odour or exudate?
- Eradication of infection?
- Increase in patients quality of life?
- Changes in Patients/ Care givers Experience ?
- Improved Cost Effectiveness ?

From Research to Practice

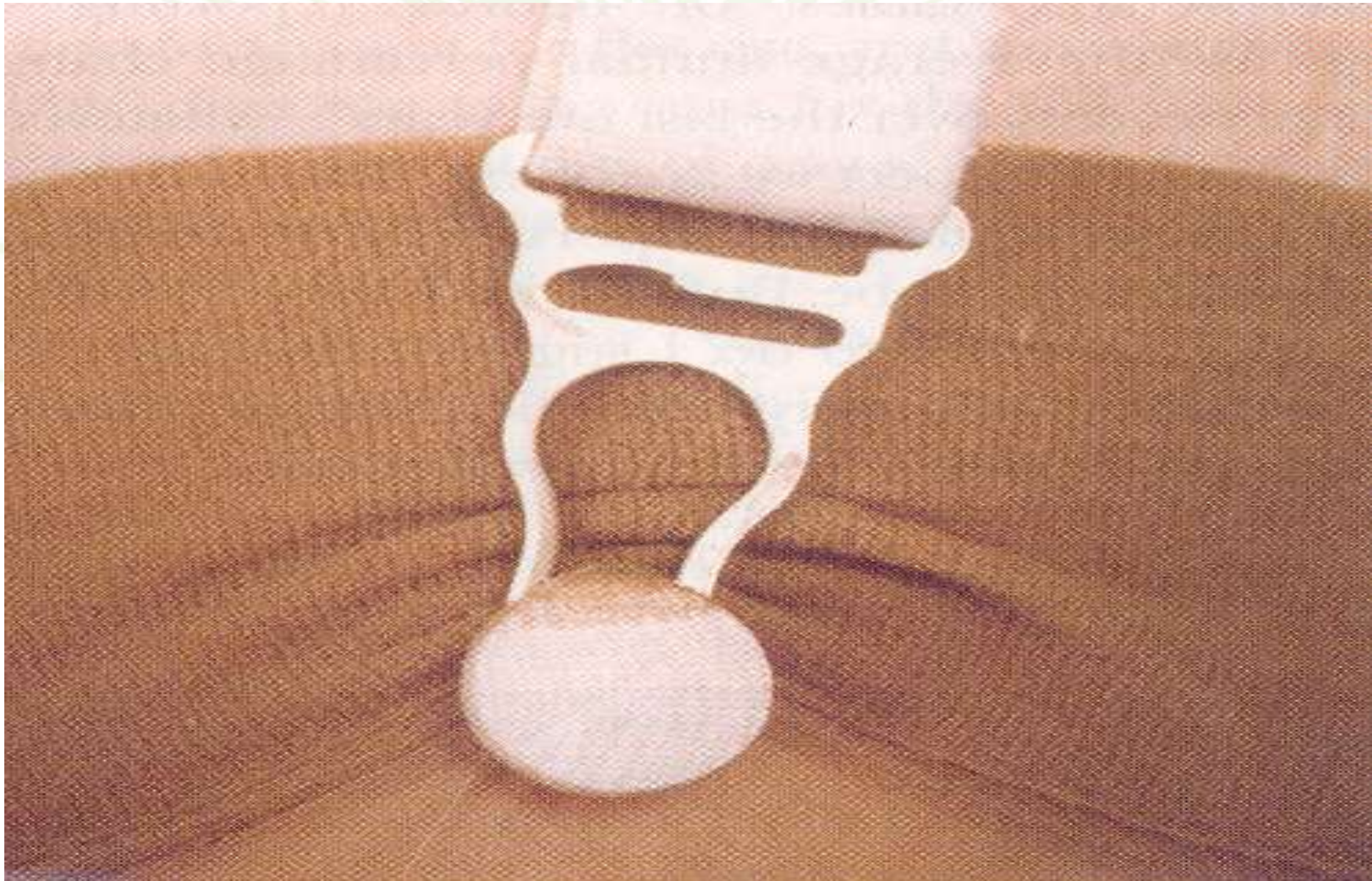


4 S Levels of Organization of Evidence from Research

Adapted from Glasziou P, Hayes B. Evidence-Based Medicine 2005; 10: 4-7

From Orsted.

What is the Relevance of this ?



The Real World

- A 92 year old lady attended the elderly care day unit and was prescribed diuretic tablets for heart failure. On her next visit we were pleased to see that the tablets had been put to excellent use in holding up her stockings This unusual route of administration had no apparent ill effects.

BMJ 2002: 325; 1489

Evidence v's Experience

Conclusions

- Excuses often used
- Behaviour change is essential
- Measures of experience needed
- Awareness of interpretation variability
- More evidence required
- Patients need consistency of approach

How committed are we to Change ?

Evidence Pyramid

Typical rating system

1. Meta analysis and systematic reviews
2. Randomised controlled trials
3. Non randomised controlled trials, case control studies, prospective cohort studies (2 groups followed over time), observational studies, evidence summaries or evidence guidelines
4. Case reports, case series
5. Expert opinion, other literature reviews

Pitfalls of evidence in wound infection 1

- Where does wound infection begin and where does it end?
- Consistency of definitions
- Lack of double blind placebo controlled trials/low patient numbers
- Commercial interest
- Where should we go to find our evidence?

Pitfalls of evidence in wound infection 2

- Wounds have multiple causes
- So do wound infections
- Patients with wounds can have several co-morbidities
- If assessing evidence for treatments, are we clear on what they are meant to do?

Silver dressings and chronic wounds

- many silver products available
- evidence still not entirely clear
- confusion over toxicity exists
- all provide silver release

Leaper IWJ 2006

Systematic Review Cochrane wounds group

– no evidence effect on healing *WRR 2007*

The evidence we found in wound infection

- 81 papers were studied and abstracted
- No meta analyses this time last year
- 7 randomised controlled trials
- 49 other studies/evidence reviews
- Remainder are case reports, case series, expert opinion or literature reviews
- The 9 most influential papers were Grade 3 or below!

New Level 1 study

- Randomised contolled trial and cost effectiveness analysis of silver-donating antimicrobial dressings for venous leg ulcers (VULCAN trial)

British Journal of Surgery 2009;96:1147-1156

Summary

- 213 patients with venous leg ulcers with were randomised between 2 types of dressing (silver-donating versus non-silver low adherence dressings in the treatment of venous leg ulcers)
- The primary outcome measure was complete ulcer healing at 12 weeks. Secondary outcomes included time to healing, quality of life and cost effectiveness
- **Conclusion: “No significant differences were found in either primary or secondary end points. There is no evidence to support the routine use of silver-donating dressings beneath compression for venous ulceration”**

Does that fit with your experience?

But……..

- Range of Silver products included
- Variable time of use
- Variable frequency of dressing change
- Healing was primary outcome measure
- No difference in HRQoL in healed patients
- Added Cost Effective argument to a RCT
- Led to editorial saying don’t waste money on dressings in VLU
- Now leading to article in Drug & Therapeutics Bulletin

Some issues

- Is it right to measure wound healing with a dressing designed to treat wound infection?
- Does this take into account the varying co-morbidities of the 213 patients? Would this have been possible in any case?
- Are most patients with wounds too complex for large scale RCTs in any case?
- Would it be preferable (or possible) to pool several individual clinicians and publish real live data on wound healing (or infection control)

Some comments

- It is of course quite right to question the routine use of costly wound infection treatments
- It is of course quite right to be circumspect about the claims made by industry on new agents designed for all aspects of wound management
- There are clearly not enough high levels of published evidence in several areas of wound infection. We need them, but they need to be optimally designed. Is this an insurmountable problem?