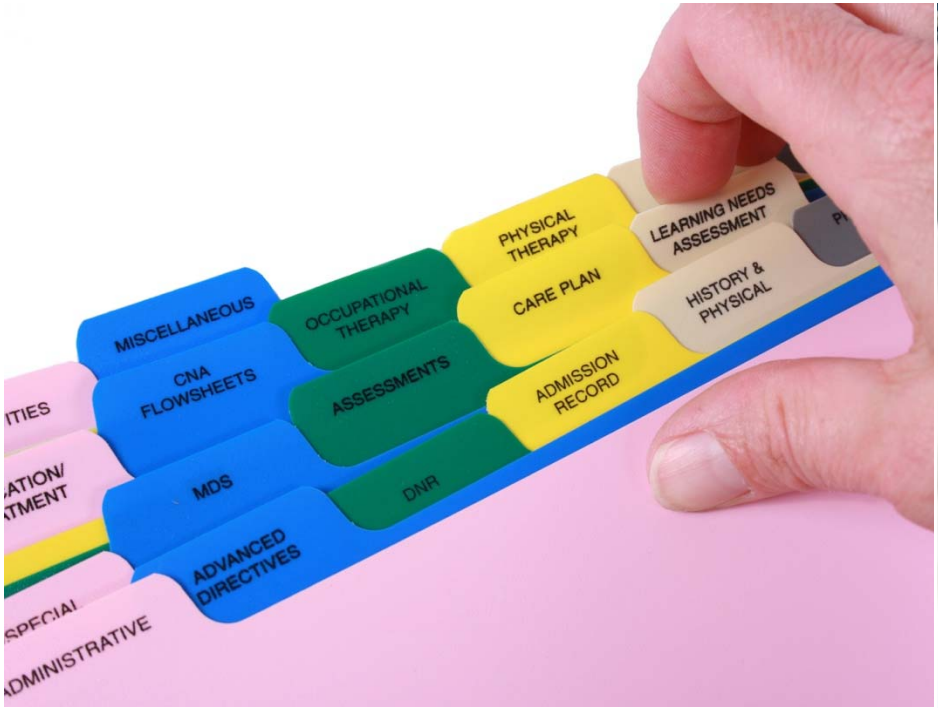
KCE REPORT 203S2

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

A NATIONAL GUIDELINE FOR THE TREATMENT OF PRESSURE ULCERS

APPENDIX VOLUME II



KCE REPORT 203S2
GOOD CLINICAL PRACTICE

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

A NATIONAL GUIDELINE FOR THE TREATMENT OF PRESSURE ULCERS

APPENDIX VOLUME II (APPENDICES 3-4)

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2012 www.kce.fgov.be

COLOPHON

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Acknowledgements:	We thank Liz Avital (NCGC, UK), Katie Jones (NCGC, UK) and Julie Neilson (NCGC, UK) for the collaboration in the preparation of the evidence reports.
External validators:	Nicky Cullum (University of Manchester, United Kingdom); Bart Geurden (CEBAM); Sylvie Meaume (Hôpital Rothschild, France)
Other reported interests:	Dominique Putzeys and Dimitri Beeckman declared to have received funding for research related to the prevention and/or treatment of pressure ulcers. Diégo Backaert, Hilde Beele, Anne Hermand, Adinda Toppets, Geert Vanwalleghem, Dimitri Beeckman declared to have received a fee to lecture or reimbursement for training, travelling or participation to conferences related to the prevention and/or treatment of pressure ulcers

Publication date:	04 July 2013
Domain:	Good Clinical Practice (GCP)

MeSH: Pressure ulcer ; Practice Guidelines

NLM Classification: WR 598

Language: English

Format: Adobe® PDF™ (A4)

Legal depot: D/2013/10.273/32

How to refer to this document? Beeckman D, Matheï C, Van Lancker A, Vanwalleghem G, Van Houdt S, Gryson L, Heyman H, Thyse C, Toppets A, Stordeur S, Van Den Heede K. A national guideline for the treatment of pressure ulcers – Appendix volume II. Good Clinical Practice (GCP) Brussels: Belgian Health Care Knowledge Centre (KCE). 2013. KCE Reports 203S1. D/2013/10.273/32.

This document is available on the website of the Belgian Health Care Knowledge Centre.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ACA	Available case analysis
ADL	Activity of daily living
AE	Adverse events
BMI	Body mass index
BUN	Blood urea nitrogen
CBC	Complete blood count
IHD	Ischemic heart disease
IQR	Interquartile range
ITT	Intention-to-treat analysis
LTC	Long-term care
MID	Minimal important difference
MMSE	Mini-mental state examination
NDT	Neurodevelopmental treatment
NR	Not reported
OR	Odds ratio
PSST	Pressure sore status tool
PU	Pressure ulcer
PUSH	Pressure ulcer scaling for healing
RD	Risk difference
RN	Registred nurse
RR	Relative risk
SCI	Spinal cord injury
SD	Standard deviation
SEM	Standard error of the mean

TAO	Topical antibiotic ointment
TIBC	Total iron binding capacity
USD	US Dollar

3. DEBRIDEMENT

3.1. Review protocol

3.1.1.1. General

Table 1 – Protocol review question

Protocol	Debridement
Population	Individuals of all ages, with at least one pressure ulcer with non-viable tissue.
Intervention	Debridement (sharp debridement, dressings which promote autolysis e.g. hydrogels and hydrocolloids enzymatic, mechanical, maggot)
Comparison	• No debridement • Comparison between debridement methods • Other type of therapy for pressure ulcer treatment
Outcomes	**Critical outcomes for decision-making** • Time to complete healing (time to event data) • Rate of healing • Rate of reduction in size and volume of pressure ulcer • Proportion of patients completely healed within trial period **Important outcomes** • Wound related pain • Health-related quality of life • Acceptability of treatment (e.g. compliance, tolerance) • Time in hospital • Side effects (skin irritation, treatment related pain, bleeding, healthy tissue damage, health skin damage, rash, toxicity) • Mortality
Study design	• High quality systematic reviews of RCTs and/or RCTs only.

	• Cochrane reviews will be included if they match our inclusion criteria and have appropriate assumptions for missing data such as available case analysis or ITT (with the appropriate assumptions) • Cohort studies will be considered if no RCTs are available. •
Exclusion	• Studies with another population, intervention, comparison or outcome. • Non-English, non-French, non-Dutch language papers
Search strategy	**The electronic databases to be searched are**: • Medline (OVID interface), Cinahl (EBSCO-interface), Embase, Library of the Cochrane Collaboration • All years
Review strategy	**How will individual PICO characteristics be combined across studies in a meta-analysis (for intervention reviews)** • Population – any population will be combined for meta-analysis except combination of children and adults. Must have active pressure ulcers at time of enrolment. • Intervention – any type of debridement will be combined for meta-analysis. • Comparison – any comparison which fits the inclusion criteria will be meta-analysed • Outcomes – same outcomes will be combined for meta-analysis. • Blinding – Blinded and unblinded studies will be meta-analysed together. • Unit of analysis – patients, individual pressure ulcers • Minimum duration of treatment = no minimum. • Minimum follow up = no minimum. • Minimum total sample size = no minimum.Use available case analysis for dealing with missing data if there is a 10% differential or higher between the groups or if the missing data is higher than the event rate, if cannot work out the available case analysis will take the author's data.
Analysis	**The following groups will be considered separately if data are present:** • Children and adults (neonates, infants, children); **Subgroups:** The following groups will be considered separately as subgroups if data are present: • Different categories of pressure ulcers (from category 2 upwards where outcomes are reported separately) • Different locations of pressure ulcers: sacral, heel and others • Infection

3.1.1.2. Maggots

Protocol	Maggot debridement
Review question	What are the most clinically effective methods of maggot debridement of non-viable tissue for treatment of pressure ulcers?
Population	Individuals of all ages, with at least one pressure ulcer with non-viable tissue.
Intervention	Maggot debridement
Comparison	• No debridement • Comparison between maggot debridement methods • Other type of therapy for pressure ulcer treatment
Outcomes	**Critical outcomes for decision-making** • Time to complete healing (time to event data) • Rate of healing • Rate of reduction in size and volume of pressure ulcer • Proportion of patients completely healed within trial period **Important outcomes** • Wound related pain • Health-related quality of life • Acceptability of treatment (e.g. compliance, tolerance) • Time in hospital • Side effects (skin irritation skin, treatment related pain, bleeding, healthy tissue damage, health skin damage, rash, toxicity) • Mortality
Study design	• High quality systematic reviews of RCTs and/or RCTs only. • Cochrane reviews will be included if they match our inclusion criteria and have appropriate assumptions for missing data such as available case analysis or ITT (with the appropriate assumptions) • Cohort studies will be considered if no RCTs are available
Exclusion	• Studies with another population, intervention, comparison or outcome.

	• Non-English, non-French, non-Dutch language papers
Search strategy	**The electronic databases to be searched are**: • Medline (OVID interface), Cinahl (EBSCO-interface), Embase, Library of the Cochrane Collaboration • All years
Review strategy	**How will individual PICO characteristics be combined across studies in a meta-analysis (for intervention reviews)** • Population – any population will be combined for meta-analysis except combination of children and adults. Must have active pressure ulcers at time of enrolment. • Intervention – any type of maggot debridement will be combined for meta-analysis. • Comparison – any comparison which fits the inclusion criteria will be meta-analysed • Outcomes – same outcomes will be combined for meta-analysis. • Blinding – Blinded and unblinded studies will be meta-analysed together. • Unit of analysis – patients, individual pressure ulcers • Minimum duration of treatment = no minimum. • Minimum follow up = no minimum. • Minimum total sample size = no minimum.Use available case analysis for dealing with missing data if there is a 10% differential or higher between the groups or if the missing data is higher than the event rate, if cannot work out the available case analysis will take the author's data.
Analysis	**The following groups will be considered separately if data are present:** • Children and adults (neonates, infants, children); **Subgroups:** The following groups will be considered separately as subgroups if data are present: • Different categories of pressure ulcers (from category 2 upwards where outcomes are reported separately) • Different locations of pressure ulcers: sacral, heel and others • Infection

3.2. Search strategy

3.2.1. Search filters

Table 2 – Search filters in OVID Medline

Search strategy	Debridement	Results
Date	25/09/2012	
Database	Medline-Ovid	
Search strategy	1. Pressure ulcer.sh	9 146
	2. decubit*.ti,ab.	3 961
	3. (pressureadj (sore* or ulcer* or damage)).ti,ab.	6 303
	4. (bedsore* or bed-sore*).ti,ab.	506
	5. ((moist* or friction or shear) adj2 (sore* or ulcer* or damage or wound* or injur* or lesion*)).ti,ab.	656
	6. OR/1 – 5	13 891
	7. Debridement.sh	11 012
	8. (Debridement* and (surg* or autolytic* or enzymatic* or mechanic* or maggot* or wound or ulcer)).tw	10 870
	9. Excis*.tw	119 195
	10. Collagenases.sh	5 791
	11. Collagenase.ti,ab	17 068
	12. Papain.sh	5 619
	13. Papain.ti,ab	6 734
	14. Urea.sh	36497
	15. Urea.ti,ab	65 927
	16. Papain-urea.ti,ab	16
	17. OR/7 - 16	246 243
	18. randomized controlled trial.pt.	337 273
	19. controlled clinical trial.pt.	85 205
	20. randomi#ed.ab.	302 707
	21. placebo.ab.	139 666
	22. randomly.ab.	184 937
	23. Clinical Trials as topic.sh	162 510
	24. trial.ti	108 714
	25. OR/18 – 24	826 371
	26. AND/6, 17, 25	52
	27. Limit language: ‘English, Dutch, Flemish, French’	47

Table 3 – Search filters in Embase

Search strategy	Debridement	Results
Date	25/09/2012	
Database	Embase-OVID	
Search strategy	1. 'decubitus'/exp	13 401
	2. decubit*:ti,ab	5 477
	3. (pressure NEAR/1 (sore* OR ulcer* OR damage)):ab,ti	7 496
	4. (bed NEAR/2 sore*):ab,ti OR bedsore*:ti,ab	742
	5. ((moist* or friction or shear) near/2 (sore* or ulcer* or damage or wound* or injur* or lesion*)):ti,ab	819
	6. OR/1 – 5	18 325
	7. 'debridement'/exp	21 343
	8. debridement*:ti,ab	17 129
	9. (debridement* and (surg* or autolytic* or enzymatic* or mechanic* or maggot* or wound or ulcer)): ti,ab	13 017
	10. Excis*:ti,ab	143 608
	11. 'Collagenase'/exp	11 386
	12. Collagenase:ti,ab	18 983
	13. 'Papain'/exp	6 718
	14. Papain:ti,ab	7 297
	15. 'Urea'/exp	48 979
	16. Urea:ti,ab	67 879
	17. 'Papain plus urea'/exp	24
	18. Papain-urea:ti,ab	14
	19. OR/7 – 18	290 090
	20. 'clinical trial'/exp	922 311
	21. 'clinical trial (topic)'/exp	45 223
	22. random*:ti,ab	756 348
	23. factorial*:ti,ab	19 922
	24. crossover*:ti,ab OR(cross NEXT/1 over*):ti,ab	64 303
	25. ((doubl* or singl*) NEAR/2 blind*):ti,ab	146 904
	26. (assign* or allocat* or volunteer* or placebo*):ti,ab	585 391
	27. 'crossover procedure'/exp	34 075
	28. 'single blind procedure'/exp	15 777
	29. 'double blind procedure'/exp	109 929
	30. OR/20 - 29	1 772
	31. AND/6, 19, 30	671

Search strategy	Debridement	Results
	32. Limit language: 'English, Dutch, French' exclude medline	123 84
Notes		

Table 4 – Search filters in CINAHL

Search strategy	Debridement	Results
Date	25/09/2012	
Database	CINAHL	
Search strategy	1. MH "Pressure Ulcer"	7 783
	2. Decubit*	488
	3. Pressure n1 sore* OR pressure n1 ulcer* OR pressure n1 damage*	8 568
	4. Bedsore* OR bed-sore*	157
	5. ((moist* or friction or shear) and (sore* or ulcer* or damage or wound* or injur* or lesion*))	1 430
	6. OR/1 – 5	9 910
	7. MH "debridement"	2 740
	8. Debridement* n1 (surg* or autolytic*or enzymatic* or mechanic* or maggot* or wound or ulcer*)	736
	9. Excis*	5 098
	10. Collagenase	207
	11. Papain	61
	12. Urea	1 942
	13. MH "Urea"	21
	14. Papain-urea	654
	15. OR/7 – 14	10 251
	16. MH "Clinical Trials+"	108 159
	17. "trial*"	138 823
	18. "randomi#ed"	67 091
	19. "randomly"	25 466
	20. "randomized controlled trial"	13 120
	21. PT "randomized controlled trial"	11 314
	22. PT "clinical trial"	51 517
	23. OR/16 - 22	170 094
	24. AND/6, 15, 23	44
	25. Limit language='English, Dutch, French' AND exclude medline records	12

Search strategy	Debridement	Results
Notes		

Table 5 – Search filters in Cochrane

Search strategy	Debridement	Results
Date	25/09/2012	
Database	Cochrane (- CDSR [3/2012]; DARE; Central [3/2012]; NHS EED; HTA)	
Search strategy	1. MeSH descriptor “Pressure ulcer” explode all trees	459
	2. Decubit*:ti,ab,kw	353
	3. (pressure near/2 (sore* or ulcer* or damage*)):ti,ab,kw	867
	4. (bedsore* or bed-sore*):ti,ab,kw	34
	5. ((moist* or friction or shear) near/2 (sore* or ulcer* or damage or wound* or injur*or lesion*)):ti,ab,kw	64
	6. OR/1 – 5	1 204
	7. MeSH descriptor “Debridement” explode all trees	409
	8. (debridement* and (surg* or autolytic* or enzymatic* or mechanic* or maggot* or wound or ulcer)):ti,ab,kw	782
	9. Excis*:ti,ab,kw	2 675
	10. MeSH descriptor “Collagenases” explode all trees	3 438
	11. Collagenase:ti,ab,kw	289
	12. MeSH descriptor “Papain” explode all trees	169
	13. Papain:ti,ab,kw	34
	14. MeSH descriptor “Urea” explode all trees	57
	15. Urea:ti,ab,kw	3 411
	16. Papain-urea:ti,ab,kw	3 472
	17. OR/7 – 16	5
	18. “Clinical Trial”:pt	9 725
	19. “Randomized Controlled Trial”:pt	294 598
	20. MeSH descriptor “clinical trials as topic” explode all trees	313 814
	21. (trial*):ti,ab,kw	51 551
	22. (randomized or randomised):ti,ab,kw	249 179
	23. (randomly):ti,ab,kw	265 750
	24. (group*):ti,ab,kw	86 115
	25. OR/18– 24	274 663
	26. AND/6, 17, 25	534 765
		47

Search strategy	Debridement	Results
Notes		

Table 6 – Search filters in OVID Medline

Search strategy	Debridement	Results
Date	22/11/2012	
Database	Medline-Ovid	
Search strategy	1. Pressure ulcer.sh	9 281
	2. decubit*.ti,ab.	4 055
	3. (pressureadj (sore* or ulcer* or damage)).ti,ab.	6 416
	4. (bedsore* or bed-sore*).ti,ab.	522
	5. ((moist* or friction or shear) adj2 (sore* or ulcer* or damage or wound* or injur* or lesion*)).ti,ab.	678
	6. OR/1 – 5	14 148
	7. (maggot* or larv* or larval) and (debridement or debriding).ti,ab	175
	8. AND/6, 7	12
	9. Limit language: 'English, Dutch, Flemish, French'	10

Table 7 – Search filters in Embase

Search strategy	Debridement	Results
Date	22/11/2012	
Database	Embase-OVID	
Search strategy	1. 'decubitus'/exp	13 596
	2. decubit*:ti,ab	5 542
	3. (pressure NEAR/1 (sore* OR ulcer* OR damage)):ab,ti	7 618
	4. (bed NEAR/2 sore*):ab,ti OR bedsore*:ti,ab	745
	5. ((moist* or friction or shear) near/2 (sore* or ulcer* or damage or wound* or injur* or lesion*)):ti,ab	829
	6. OR/1 – 5	18 576
	7. (maggot* or larv* or larval) and (debridement or debriding):ti,ab	244
	8. AND/6, 7	30
	9. Limit language: 'English, Dutch, French' exclude medline	20
Notes		

Table 8 – Search filters in CINAHL

Search strategy	Debridement	Results
Date	22/11/2012	
Database	CINAHL	
Search strategy	1. MH "Pressure Ulcer"	7 906
	2. Decubit*	493
	3. Pressure n1 sore* OR pressure n1 ulcer* OR pressure n1 damage*	8 690
	4. Bedsore* OR bed-sore*	160
	5. ((moist* or friction or shear) and (sore* or ulcer* or damage or wound* or injur* or lesion*))	1448
	6. OR/1 – 5	10 051
	7. (maggot* or larv* or larval) and (debridement or debriding)	201
	8. AND/6, 7	20
	9. Limit language='English, Dutch, French' AND exclude medline records	6
Notes		

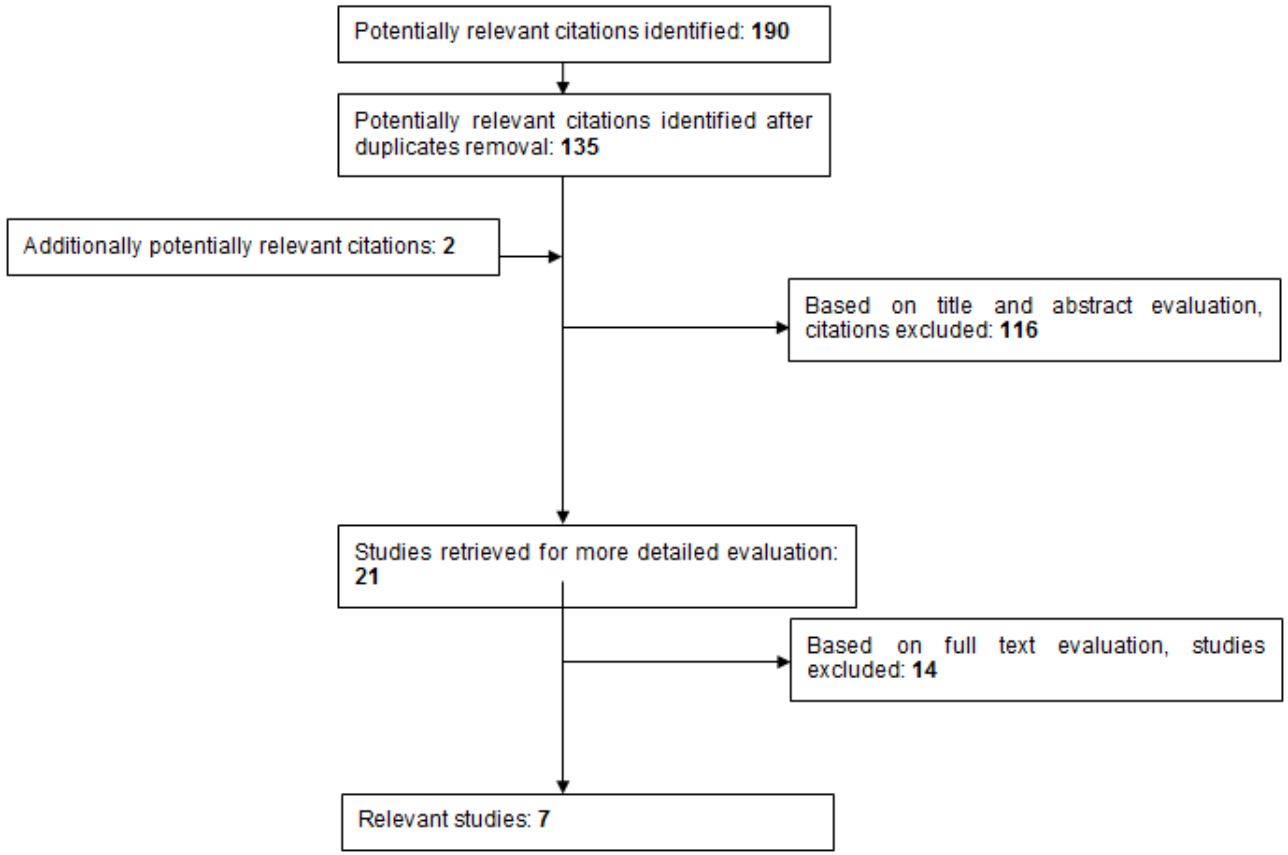
Table 9 – Search filters in Cochrane

Search strategy	Debridement	Results
Date	22/11/2012	
Database	Cochrane (- CDSR [3/2012]; DARE; Central [3/2012]; NHS EED; HTA)	
Search strategy	1. MeSH descriptor "Pressure ulcer" explode all trees	490
	2. Decubit*:ti,ab,kw	353
	3. (pressure near/2 (sore* or ulcer* or damage*)):ti,ab,kw	872
	4. (bedsore* or bed-sore*):ti,ab,kw	34
	5. ((moist* or friction or shear) near/2 (sore* or ulcer* or damage or wound* or injur*or lesion*)):ti,ab,kw	64
	6. OR/1 – 5	1 209
	7. (maggot* or larv* or larval) and (debridement or debriding):ti,ab,kw	25
	8. AND/6, 7	2
Notes		

3.2.2. Selection of articles

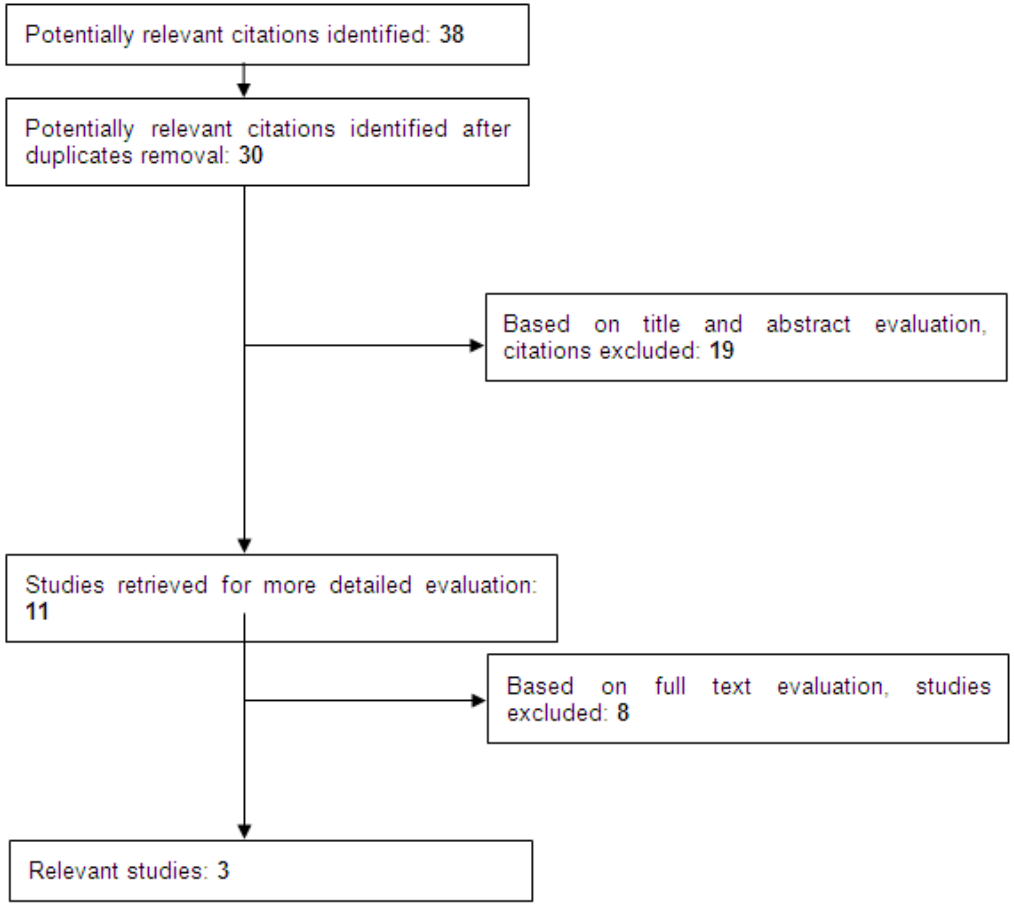
3.2.2.1. General

Figure 1 – Flow chart debridement review - general



3.2.2.2. Maggots

Figure 2 – Flow chart debridement review – maggots



3.2.3. Excluded clinical studies

3.2.3.1. General

Table 10 – Excluded studies – General

Reference	Reason of exclusion
Agren 1985	Intervention: no debridement, but autolytic debridement enhancement
Alvarez 2002	Same study as in Alvarez 2000 but less complete outcome reporting (no critical outcome)
Alvarez 2003	Design (erratum)
Bale 1998	Intervention: no debridement, but autolytic debridement enhancement
Bass 2007	Design
Bello 2000	Design
Colin 1996	Intervention: no debridement, but autolytic debridement enhancement
Cullen 2009	Design
Martin 1996	Intervention: no debridement, but autolytic debridement enhancement
Milne 2010	No critical or important outcomes
Milne 2011	Other (only abstract, no full text)
Settel 1969	Essential information to assess quality is missing (no information about control and experimental group, no information about placebo, no information about protocol); author developed the experimental product; language is very coloured.
Van Leen 1994	Design
Varma 1973	Outcome

3.2.3.2. Maggots

Table 11 – Excluded studies - Maggots

Reference	Reason of exclusion
Bolton 2006	Design
Fiorini 2012	Design
Gilead 2012	Design
Greene 2008	Design
Lee 2011	Design
Lee 2011a	Design
Mumcuoglu 1999	Design
Tanyuksel 2009	Design

3.3. Clinical evidence

Ten records, seven randomised controlled trials[34-39] and three observational studies[40-42], were included in this review. One observational study was not taken into account due to limited information available to assess the clinical effectiveness.

3.3.1. Summary of included studies

3.3.1.1. General

Table 12 Summary of included studies – general

Study	Intervention/comparator	Population	Outcome	Length of study
Alvarez, 2000[34]	Collagenase ointment (Santyl) versus papain/urea ointment (Accuzyme)	Patients with pressure ulcers requiring debridement, who were stable or improving after a two-week screening period	Percent reduction of ulcer size from baseline Side effects	2 weeks screening and 4 weeks period of the study
Burgos, 2000 (a)[36]	Collagenase Ointment (Iruxol) versus hydrocolloid dressing (Varihesive)	Patients >= 55 years presenting with stage III pressure ulcers (skin	Proportion of patients with reduction in pressure ulcer area after 12 weeks	12 weeks of treatment or until healing of the pressure ulcer, whichever occurred

		disruption, tissue damage and exudate and subcutaneous tissue involvement)	of treatment Proportion of patients with complete healing of pressure ulcer after 12 weeks of treatment Mean reduction in ulcer area after 12 weeks of treatment (cm^2) Decrease in pain intensity Patients with adverse reactions	first.
Burgos, 2000 (b)[35]	Collagenase ointment application every 24 hours versus collagenase ointment application every 48 hours	Hospitalized or institutionalized patients aged 55 years or older presenting with stage III pressure ulcer for less than 1 year.	Proportion of pressure ulcers that showed complete healing after 8 weeks (intention-to-treat) Relative risk of non-healing among group 2 (collagenase ointment every 48 hours)as compared with group 1 (collagenase ointment every 24 hours)after 8 weeks (intention-to-treat) when granulation tissue covered 11 to 30% of the ulcer surface. Mean reduction of PU area (cm^2) during 8 weeks (per-protocol) Decrease in pain intensity after 8 weeks(intention-to-treat)	Treatment during maximum 8 weeks or until complete healing of the PU whatever occurred first

				Decrease in pain intensity after 8 weeks(per-protocol) Proportion with adverse reactions after 8 weeks	
Lee, 1975[37]	Collagenase (Santyl) versus preparation of inactivated collagenase		11 patients with chronic diseases in poor physical condition. Four had neoplastic disease; 4 atherosclerotic heart diseases or cerebrovascular accident or both; 2 had Parkinson's disease and 1 had a femorla neck fracture.	Proportion of PU that reduced in volumeassessed with the aid of a volume mold Proportion of PU that increased in volume assessed with the aid of a volume mold Proportion of PU with odor at the end of treatment Side effects	4 weeks of treatment and follow-up unless complications developed or patient died
Müller 2001[43]	Hydrocolloid dressing (Duoderm) versus collagenase (Novuxol)		Female inpatients with a grade IV heel PU	Proportion of patients completely healed Time to healing	Maximum 16 weeks
Parish, 1979[38]	Dextranomer powder (Debrisan) versus collagenase (Santyl) versus sugar and egg white		Patients with pressure ulcers in a long-term care institution for the chronically ill and physically disabled.	Proportion of PU improved for patients treated with dextranomer versus patients treated with collagenase (%) Proportion of PU improved for patients treated with collagenase versus patients treated with sugar and egg white Proportion of patients with	The initial study was to have lasted four weeks, but many subjects were treated and observed for up to four months or longer.

				ulcer closure for patients treated with dextranomer versus patients treated with collagenase	
				Proportion of patients with ulcers closure for patients treated with collagenase versus patients treated with sugar and egg white	
				Proportion of PU closed for patients treated with dextranomer versus patients treated with collagenase	
				Proportion of PU closed for patients treated with collagenase versus patients treated with sugar and egg white	
				Proportion of patients improved treated with dextranomer versus patients treated with collagenase	
				Proportion of PU closed treated with dextranomer versus collagenase after 1 week	
				Proportion of PU closed treated with dextranomer versus collagenase after	

			1 month Proportion of PU closed treated with dextranomer versus collagenase after 2 months Proportion of PU closed treated with dextranomer versus collagenase after more than 2 months	
			Proportion of patients improved treated with collagenase versus patients treated with sugar and egg white	
			Proportion of PU closed treated with collagenase versus sugar and egg white after 1 week	
			Proportion of PU closed treated with collagenase versus sugar and egg white after 1 month	
			Proportion of PU closed treated with collagenase versus sugar and egg white after 2 months	
			Proportion of PU closed treated with collagenase versus sugar and egg	

			white after more than 2 months Side effects	
Püllen, 2002[39]	Twice-daily treatment with collagenase (1.2 U/g) (Novuxal) versus Twice-daily treatment fibrinolysin/DNAse (1 U Loomis and 666 Christensen/g) (Fibrolan)	Patients with pressure ulcers, Seiler stage 2,3 or 4, in the pelvic region with fibrinous and/or necrotic slough from 17 hospitals	Proportion of persons reporting adverse events Proportion of serious adverse events reported	4 weeks of treatment or until complete wound debridement whichever occurred first.

3.3.1.2. Maggots

Table 13 – Summary of included studies - Maggots

Study	Intervention/comparator	Population	Outcome	Length of study
Sherman, 1995[41]	Maggot therapy administered by disinfected fly larvae of the species Phaeniciasericata versus conventional treatment.	Patients with pressure ulcers stage III and IV for at least one month	average change in surface area per week	Patients were followed up for three-four weeks prior to maggot therapy
Sherman, 2002[40]	Maggot therapy administered by applying disinfectedfly larvae (Phaeniciasericata) to the wound at a density offive to eight per cm2 versus conventional treatment prescribed by their primary care provider or the hospital's wound care team.	Patients with pressure ulcers	Change in surface area during treatment (cm²) Change in surface area per week Percentage of wounds which decreased in surface area within 4 weeks Healing rate at 4 weeks Healing rate at 8 weeks Percentage of wounds that completely healed Average time until wounds completely healed (weeks) Proportion of wounds decreased during	Wounds were first followed for 2 to 8 weeks (average 4.8 weeks) while still receiving conventional therapy. Then the wounds were treated for 2 weeks or more (average 5.2 weeks) with maggot therapy.

			treatment	
Wang, 2010[42]	Maggot therapy administered by applying disinfected larvae of Luciliasericata to the wound at a density of five to ten per cm² versus a dressing applied daily with normal saline only and if necessary surgical debridement.	Patients with pressure ulcers after *spinal cord injury treated in the hospital.*	Time to wound healing (days)	All patients were followed up for 2 to 6 months (mean 3.5 months).

3.3.2. Clinical evidence GRADE-tables

3.3.2.1. General

Table 14 – clinical GRADE evidence profile: Collagenase versus preparation of inactivated collagenase for treatment of Pressure ulcers

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Collagenase	Preparation of inactivated collagenase	Relative (95% CI)	Absolute		
Proportion of pressure ulcers that decreased in volume – patients with chronic diseases- stage not reported- claasification system not reported- follow-up 4 weeks												
1(Lee 1975)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	Very serious[3]	none	8/17 (47.1%)	0/11 (0%)	OR 20.58 (1.05 to 404.67)	470 more per 1000 (from 210 more to 730 more)	⊕OOO VERY LOW	CRITICAL
								0%		470 more per 1000 (from 210 more to 730 more)		
Proportion of PU that increased in size– patients with chronic diseases- stage not reported- claasification system not reported- follow-up 4 weeks												
1(Lee 1975)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	Serious[2]	none	4/17 (23.5%)	6/11 (54.5%)	RR 0.43 (0.16 to 1.19)	311 fewer per 1000 (from 458 fewer to 104 more)	⊕OOO VERY LOW	CRITICAL
								54.6%		311 fewer per 1000 (from 459 fewer to 104 more)		
Proportion of PU with odor at the end of treatment– patients with chronic diseases- stage not reported- claasification system not reported- follow-up 4 weeks												
1(Lee	randomised	very	no serious	no serious	very	none	7/17	5/11	RR 0.91 (0.38	41 fewer per 1000	⊕OOO	IMPORTANT

1975)	trials	serious[1]	inconsistency	indirectness	serious[3]		(41.2%)	(45.5%)	to 2.14)	(from 282 fewer to 518 more)	VERY LOW	
								45.5%		41 fewer per 1000 (from 282 fewer to 519 more)		
Number of side effects observed– patients with chronic diseases- stage not reported- classification system not reported- follow-up 4 weeks												
1(Lee 1975)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/17 (5.9%)	0/11 (0%)	OR 2 (0.09 to 45.12)	60 more per 1000 (from 11 more to 23 more)	⊕OOO VERY LOW	IMPORTANT
								0%		60 more per 1000 (from 11 more to 23 more)		

[1] *unclear randomization process, unclear allocation concealment, blinding unclear*
[2] *small sample size, confidence interval crossed 1 MID points*
[3] *small sample size, confidence interval crossed 2 MID points*

Table 15 – Clinical GRADE evidence profile: Collagenase versus Dextranomer for treatment of pressure ulcers

Quality assessment						No of patients			Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Collagenase**	**Dextranomer**	**Relative (95% CI)**	**Absolute**		
Proportion of pressure ulcers that improved –chronically ill and disabled patients- stage not reported – classification system not reported												
1(Parish 1979)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	Serious[2]	none	5/11 (45.5%)	12/14 (85.7%)	RR 0.53 (0.27 to 1.05)	403 fewer per 1000 (from 626 fewer to 43 more)	⊕OOO VERY LOW	CRITICAL
								85.7%		403 fewer per 1000 (from 626 fewer to 43 more)		
Proportion of pressure ulcers that closed–chronically ill and disabled patients- stage not reported – classification system not reported												
1(Parish 1979)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/11 (9.1%)	6/14 (42.9%)	RR 0.21 (0.03 to 1.51)	339 fewer per 1000 (from 416 fewer to 219 more)	⊕OOO VERY LOW	CRITICAL
								42.9%		339 fewer per 1000 (from 416 fewer to 219 more)		
Proportion of patients with pressure ulcers closure–chronically ill and disabled patients- stage not reported – classification system not reported												
1(Parish	randomised	very	no serious	no serious	very	none	1/5	4/7	RR 0.35 (0.05	371 fewer per 1000 (from	⊕OOO	CRITICAL

1979)	trials	serious[1]	inconsistency	indirectness	serious[3]		(20%)	(57.1%)	to 2.26)	543 fewer to 720 more)	VERY LOW	
								57.1%		371 fewer per 1000 (from 542 fewer to 719 more)		
Proportion of patients that improved–chronically ill and disabled patients- stage not reported – classification system not reported												
1(Parish 1979)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	Serious[2]	none	2/5 (40%)	7/7 (100%)	RR 0.44 (0.17 to 1.16)	560 fewer per 1000 (from 830 fewer to 160 more)	⊕OOO VERY LOW	CRITICAL
								100%		560 fewer per 1000 (from 830 fewer to 160 more)		

[1] *randomisation and concealment method not reported, blinding failed*
[2] *small sample size, confidence interval crossed1MID point*
[3] *small sample size, confidence interval crossed 2 MID points*

Table 16 – clinical GRADE evidence profile: Collagenase versus sugar and egg white for treatment of pressure ulcers

Quality assessment						No of patients			Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Collagenase**	**Sugar and egg white**	**Relative (95% CI)**	**Absolute**		
Proportion of pressure ulcers that improved – chronically ill and disabled patients- no stage reported- no classification system reported												
1(Parish 1979)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/11 (45.5%)	0/9 (0%)	OR 9.17 (0.57 to 146.4)	45 more per 1000 (from 17 more to 77 more)	⊕OOO VERY LOW	CRITICAL
								0%		45 more per 1000 (from 17 more to 77 more)		
Proportion of pressure ulcers that closed– chronically ill and disabled patients- no stage reported- no classification system reported												
1(Parish 1979)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/11 (9.1%)	0/9 (0%)	OR 2.5 (0.11 to 54.87)	9 more per 1000 (from 14 more to 32 more)	⊕OOO VERY LOW	CRITICAL
								0%		-9 more per 1000 (from 14 more to 32 more)		
Proportion of patients with pressure ulcer closure– chronically ill and disabled patients- no stage reported- no classification system reported												
1(Parish 1979)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/5 (20%)	0/5 (0%)	OR 3 (0.15 to 59.89)	90 more per 1000 (from 21 more to 61 more)	⊕OOO VERY LOW	CRITICAL
								0%		90 more per 1000 (from 21 more to 61 more)		

Proportion of patients that improved– chronically ill and disabled patients- no stage reported- no classification system reported												
1(Parish 1979)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/5 (40%)	0/5 (0%)	OR 5 (0.3 to 83.69)	40 more per 1000 (from 5 more to 85 more)	⊕OOO VERY LOW	CRITICAL
								0%		40 more per 1000 (from 5 more to 85 more)		

[1] *randomization and concealment method not reported, blinding failed*
[2] *small sample size, confidence interval crossed 2 MID points*
[3] *small sample size, no events*

Table 17 – clinical GRADE evidence profile: Collagenase versus papain/urea for treatment of pressure ulcers

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Collagenase**	**papain/urea**	**Relative (95% CI)**	**Absolute**		
Percentage reduction in pressure ulcer size after 4 weeks – patients with pressure ulcers- stage II-IV- classification system not reported												
1(Alvarez, 2000)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	33.9 (n=10)	55.4 (n=11)	-	MD 21.5 lower (47.09 lower to 4.09 higher)	⊕OOO VERY LOW	CRITICAL
Number of side effects observed (follow-up 4 weeks)												
1(Alvarez, 2000)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/10 (10%)	0/11 (0%)	OR 3.27 (0.15 to 72.23)	10 more per 1000- (from 13 more to 33 more)-----	⊕OOO VERY LOW	IMPORTANT
								0%		10 more per 1000- (from 13 more to 33 more)------		

[1] *concealment method and blinding not reported*
[2] *small sample, MD is greater or smaller than SD of outcome in control group*
[3] *small sample size, small event rate, confidence interval crossed 2 MID points*

Table 18 – clinical GRADE evidence profile: Collagenase versus fibrinolysis/DNAse for treatment of pressure ulcers

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Collagenase	fibrinolysis/DNAse	Relative (95% CI)	Absolute		
Proportion of persons reporting adverse events -elderly patients with pressure ulcer in pelvic region- stages II-IV- Seiler classification												
1 (Püllen, 2002)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	45/66 (68.2%)	34/69 (49.3%)	RR 1.38 (1.03 to 1.85)	187 more per 1000 (from 15 more to 419 more)	⊕OOO VERY LOW	IMPORTANT
								49.3%		187 more per 1000 (from 15 more to 419 more)		
Proportion of serious adverse events -elderly patients with pressure ulcer in pelvic region- stages II-IV- Seiler classification												
1(Püllen, 2002)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	54/118 (45.8%)	24/103 (23.3%)	RR 1.96 (1.31 to 2.93)	224 more per 1000 (from 72 more to 450 more)	⊕⊕OO LOW	IMPORTANT
								23.3%		224 more per 1000 (from 72 more to 450 more)		

[1] *unclear sequence generation, unclear allocation concealment, relatively high drop out rate*
[2] *confidence interval crossed 1 MID point*

Table 19 – clinical GRADE evidence profile: Collagenase versus hydrocolloid dressing for treatment of pressure ulcers

Quality assessment						No of patients			Effect		Quality Importance	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Collagenase	Hydrocolloid dressing	Relative (95% CI)	Absolute		
Proportion of patients with reduction in pressure ulcer area – patients with pressure ulcer stage II- classification system not reported												
1(Burgos 2000a)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	15/18 (83.3%)	14/19 (73.7%)	RR 1.13 (0.81 to 1.59)	96 more per 1000 (from 140 fewer to 435 more)	⊕OOO VERY LOW	CRITICAL
								73.7%		96 more per 1000 (from 140 fewer to 435 more)		
Proportion of patients with complete healing of PU– patients with pressure ulcer stage II and IV- classification system not reported												
2(Burgos 2000a, Muller 2001)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	14/30 (46.7%)	10/30 (33.3%)	RR 1.33 (0.8 to 2.23)	110 more per 1000 (from 67 fewer to 410 more)	⊕OOO VERY LOW	CRITICAL
								39.7%		131 more per 1000 (from 79 fewer to 488 more)		
Mean reduction in PU area after 12 weeks of treatment – patients with pressure ulcer stage II- classification system not reported												
1(Burgos 2000a)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	Very serious[2]	none	9.1 (n=18)	6.2 (n=19)	-	MD 2.9 higher (4.44 lower to 10.24 higher)	⊕OOO VERY LOW	CRITICAL
Proportion of patients reporting adverse events— patients with pressure ulcer stage II- classification system not reported												
1(Burgos 2000a)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	Very serious[2]	none	1/18 (5.6%)	2/19 (10.5%)	RR 0.53 (0.05 to 5.33)	49 fewer per 1000 (from 100 fewer to 456 more)	⊕OOO VERY LOW	IMPORTANT
								10.5%		49 fewer per 1000 (from 100 fewer to 455 more)		
Mean time to healing (weeks) of pressure ulcer- female hospitalized patients- grade IV heel ulcers-classification system not reported												
1 (Muller 2001)	randomised trials	very serious	no serious inconsistency	no serious indirectness	Serious[3]	none	12 (n=12)	11 (n=11)	-	MD 4 lower (5.11 to 2.89 lower)	⊕OOO VERY LOW	CRITICAL

[1] *unclear allocation concealment, not all assessors were blinded, relatively high drop out, no baseline differences reported*
[2] *small sample size, confidence interval crossed1MID point*
[3] *small sample size, confidence interval contains 2MID points*
[4] *small sample, MD is greater or smaller than SD of outcome in control group*

Table 20 – clinical GRADE evidence profile: Collagenase ointment application every 24 hours versus every 48 hours for treatment of pressure ulcers

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Collagenase ointment application every 24 hours	Collagenase ointment application every 48 hours	Relative (95% CI)	Absolute		
Proportion of pressure ulcers that showed complete healing after 8 weeks –hospitalized patients-stage III- NPUAP classification												
1 (Burgos 2000b)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12/43 (27.9%)	9/43 (20.9%)	RR 1.33 (0.63 to 2.83)	69 more per 1000 (from 77 fewer to 383 more)	⊕OOO VERY LOW	CRITICAL
								20.9%		69 more per 1000 (from 77 fewer to 382 more)		
Proportion of patients reporting adverse events (rash, necrosis in ulcer bed, ulcer worsening, infection) –hospitalized patients-stage III- NPUAP classification												
1 (Burgos 2000b)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/46 (6.5%)	3/46 (6.5%)	RR 1 (0.21 to 4.7)	0 fewer per 1000 (from 52 fewer to 241 more)	⊕OOO VERY LOW	CRITICAL
								6.5%		0 fewer per 1000 (from 51 fewer to 240 more)		

[1] *unclear allocation concealment, not all assessors were blinded, relatively high drop out, no baseline differences reported*
[2] *small sample size, confidence interval crossed 2 MID points*

3.3.2.2. Maggots

Table 21 – clinical GRADE evidence profile: Maggot therapy versus conservative treatment for treatment of pressure ulcers

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Maggot therapy	Conservative treatment	Relative (95% CI)	Absolute		
Change in surface area during treatment (cm²) in patients with pressure ulcers III-IV (classification system not reported - follow-up mean 5.2 weeks)												
1 (Sherman 2002)	cohort trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-7.3 (n=43)	6.3 (n=49)	-	MD 13.6 lower (15.01 to 12.19 lower)	⊕OOO VERY LOW	CRITICAL
Change in surface area per week in patients with pressure ulcers III-IV (classification system not reported - follow-up mean 5.2 weeks												
1 (Sherman 2002)	cohort trial	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	-1.5 (n=43)	1.4 (n= 49)	-	MD 2.9 lower (3.25 to 2.55 lower)	⊕OOO VERY LOW	CRITICAL
Proportion wounds decreased in surface area within 4 weeks in patients with pressure ulcers III-IV (classification system not reported - follow-up mean 5.2 weeks												
1 (Sherman 2002)	cohort trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	34/43 (79.1%)	22/49 (44.9%)	RR 1.76 (1.25 to 2.49)	341 more per 1000 (from 112 more to 669 more)	⊕OOO VERY LOW	CRITICAL
								44.9%		341 more per 1000 (from 112 more to 669 more)		
Healing rate at 8 weeks in patients with pressure ulcers III-IV (classification system not reported - follow-up mean 5.2 weeks												
1 (Sherman 2002)	cohort trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0.096 (n=43)	0.027 (n=49)	-	MD 0.12 higher (0.11 to 0.14 higher)	⊕OOO VERY LOW	CRITICAL

Proportion of wounds that completely healed in patients with pressure ulcers III-IV (classification system not reported - follow-up mean 5.2 weeks												
1 (Sherman 2002)	cohort trial	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	17/43 (39.5%)	10/49 (20.4%)	RR 1.94 (1 to 3.77)	192 more per 1000 (from 0 more to 565 more)	⊕OOO VERY LOW	CRITICAL
								20.4%		192 more per 1000 (from 0 more to 565 more)		
Time to wound healing (days) Sherman 2002: in patients with pressure ulcers III-IV (classification system not reported - follow-up mean 5.2 weeks; Wang 2010: spinal cord injured patients with pressure ulcers –follow-up mean 3.5 months												
2 (Sherman 2002, Wang 2010))	cohort trial	very serious[1]	no serious inconsistency	Serious[4]	Serious[3]	none	71.7 (n=53)	85.1 N=57	-	MD 11.27 lower (19.97 to 2.57 lower)	⊕OOO VERY LOW	CRITICAL

[1] High risk of selection bias (method of allocation was potentially related to confounding factors, no attempts to balance comparison groups and comparison groups were not comparable at baseline), high risk of performance bias (participants and administrators of care were not kept blind to treatment allocation), high risk of detection bias (investigators were not kept blind for exposure to intervention and other confounding/prognostic factors)

[2] confidence interval crossed2MID points(0.5 x standard deviation for continuous outcomes and 0.75 to 1.25 for dichotomous outcomes)

[3] confidence interval crossed1MID point(0.5 x standard deviation for continuous outcomes and 0.75 to 1.25 for dichotomous outcomes)

[4] heterogeneity shows a low p-value

3.3.3. Forrest Plots

3.3.3.1. General

Figure 3 – Collagenase versus preparation of inactivated collagenase - proportion of PU that decreased in size.

	Collagenase		Inactivated collagenase			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Lee 1975	8	17	0	11	100.0%	11.33 [0.72, 178.54]	
Total (95% CI)		**17**		**11**	**100.0%**	**11.33 [0.72, 178.54]**	
Total events	8		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.73 (P = 0.08)							

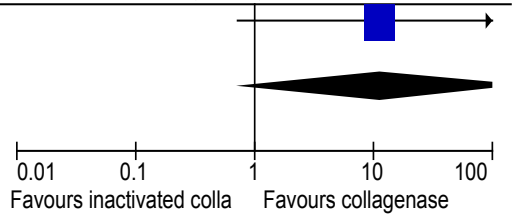


Figure 4 – Forest plot of Collagenase versus preparation of inactivated collagenase - proportion of PU that increased in size.

	Collagenase		Inactivated collagenase			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Lee 1975	4	17	6	11	100.0%	0.43 [0.16, 1.19]	
Total (95% CI)		**17**		**11**	**100.0%**	**0.43 [0.16, 1.19]**	
Total events	4		6				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.63 (P = 0.10)							

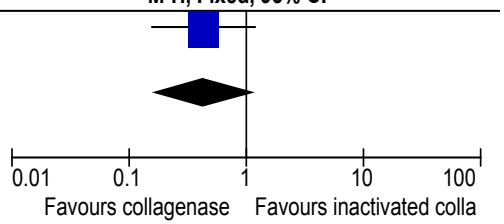


Figure 5 – forest plot of Collagenase versus preparation of inactivated collagenase - proportion of PU with odor at the end of treatment.

	Collagenase		Inactivated collagenase			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Lee 1975	7	17	5	11	100.0%	0.91 [0.38, 2.14]
Total (95% CI)		**17**		**11**	**100.0%**	**0.91 [0.38, 2.14]**
Total events	7		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.22 (P = 0.82)

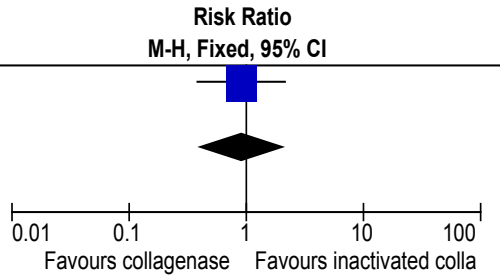


Figure 6 – forest plot of Collagenase versus preparation of inactivated collagenase - number of side effects observed

	Collagenase		Inactivated collagenase			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Lee 1975	1	17	0	11	100.0%	2.00 [0.09, 45.12]
Total (95% CI)		**17**		**11**	**100.0%**	**2.00 [0.09, 45.12]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.44 (P = 0.66)

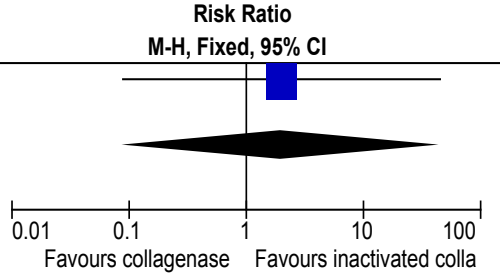


Figure 7 – forest plot of Collagenase versus Dextranomer - proportion of PU that improved.

Study or Subgroup	Collagenase Events	Collagenase Total	Inactivated collagenase Events	Inactivated collagenase Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Lee 1975	1	17	0	11	100.0%	2.09 [0.08, 56.01]
Total (95% CI)		**17**		**11**	**100.0%**	**2.09 [0.08, 56.01]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.44 (P = 0.66)

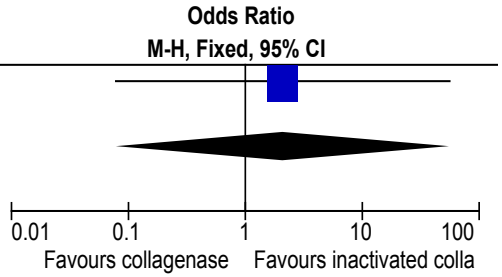


Figure 8 – forest plot of Collagenase versus Dextranomer - proportion of PU that closed.

Study or Subgroup	Collagenase Events	Collagenase Total	Dextranomer Events	Dextranomer Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Parish 1979	1	11	6	14	100.0%	0.21 [0.03, 1.51]
Total (95% CI)		**11**		**14**	**100.0%**	**0.21 [0.03, 1.51]**
Total events	1		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.55 (P = 0.12)

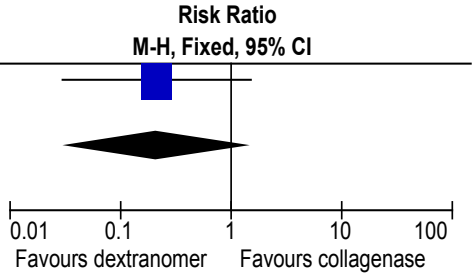


Figure 9 – forest plot of Collagenase versus Dextranomer, outcome: 2.3 Proportion of patients with PU closure

Study or Subgroup	Collagenase Events	Collagenase Total	Dextranomer Events	Dextranomer Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Parish 1979	1	5	4	7	100.0%	0.35 [0.05, 2.26]
Total (95% CI)		**5**		**7**	**100.0%**	**0.35 [0.05, 2.26]**
Total events	1		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.10 (P = 0.27)

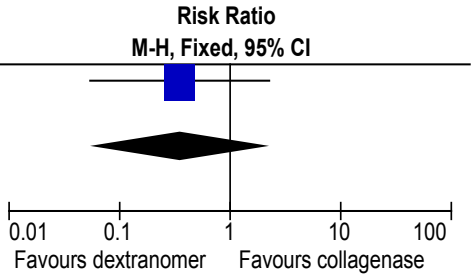


Figure 10 – forest plot of Collagenase versus Dextranomer - proportion of patients that improved.

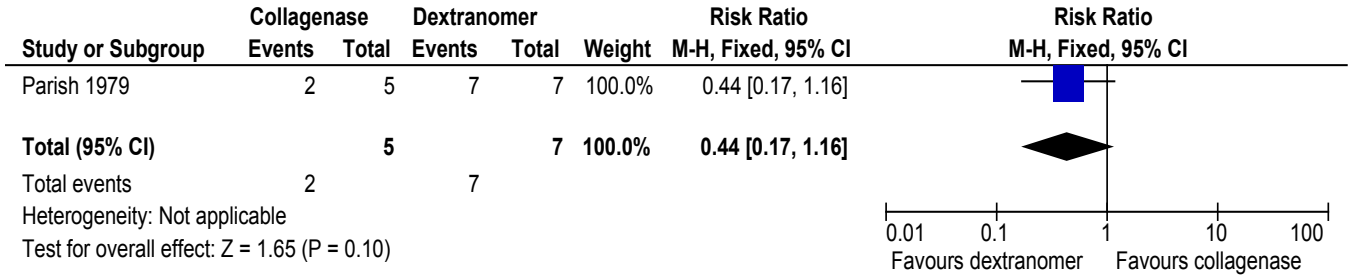


Figure 11 – forest plot of Collagenase versus sugar and egg white - proportion of PU that improved.

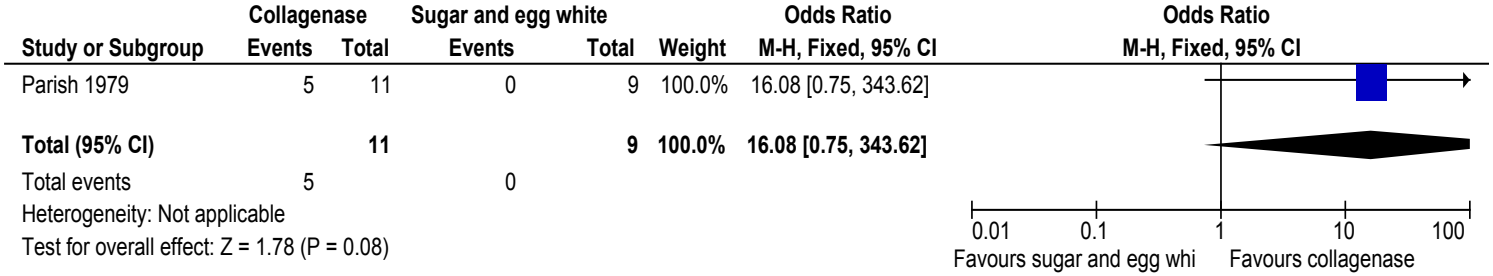


Figure 12 – forest plot of Collagenase versus sugar and egg white - proportion of PU that closed.

	Collagenase		Sugar and egg white			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Parish 1979	1	11	0	9	100.0%	2.71 [0.10, 74.98]
Total (95% CI)		**11**		**9**	**100.0%**	**2.71 [0.10, 74.98]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.56)						

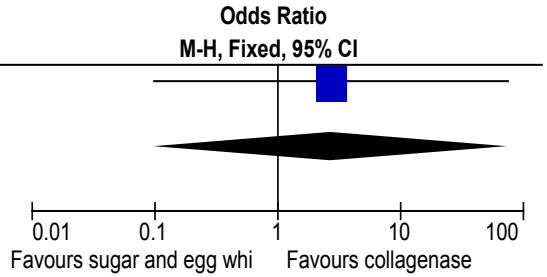


Figure 13 – forest plot of Collagenase versus sugar and egg white - proportion of patients with PU closure

	Collagenase		Sugar and egg white			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Parish 1979	1	5	0	5	100.0%	3.67 [0.12, 113.73]
Total (95% CI)		**5**		**5**	**100.0%**	**3.67 [0.12, 113.73]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.74 (P = 0.46)						

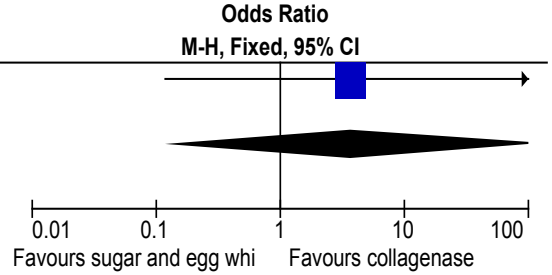


Figure 14 – forest plot of Collagenase versus sugar and egg white - proportion of patients that improved.

Study or Subgroup	Collagenase Events	Collagenase Total	Sugar and egg white Events	Sugar and egg white Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Parish 1979	2	5	0	5	100.0%	7.86 [0.28, 217.11]
Total (95% CI)		**5**		**5**	**100.0%**	**7.86 [0.28, 217.11]**
Total events	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.22 (P = 0.22)

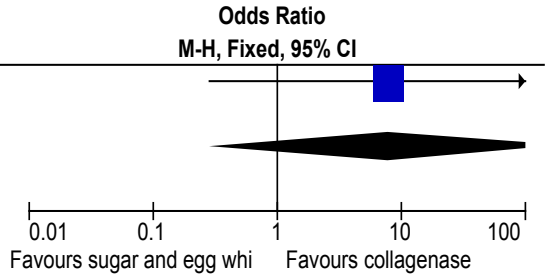


Figure 15 – forest plot of Collagenase versus papain/urea, outcome - percentage reduction in PU size after 4 weeks.

Study or Subgroup	Collagenase Mean	Collagenase SD	Collagenase Total	Papain/urea Mean	Papain/urea SD	Papain/urea Total	Weight	Mean Difference IV, Fixed, 95% CI
Alvarez 2000	33.9	26.17	10	55.4	33.5	11	100.0%	-21.50 [-47.09, 4.09]
Total (95% CI)			**10**			**11**	**100.0%**	**-21.50 [-47.09, 4.09]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.65 (P = 0.10)

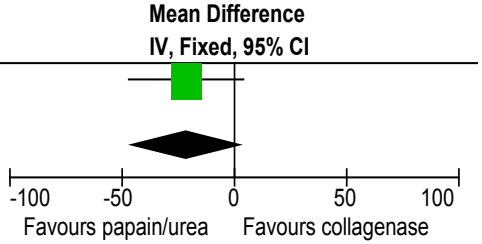


Figure 16 – forest plot of Collagenase versus papain/urea, outcome - number of side effects observed.

Study or Subgroup	Collagenase Events	Collagenase Total	Papain/urea Events	Papain/urea Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Alvarez 2000	1	10	0	11	100.0%	3.63 [0.13, 99.85]
Total (95% CI)		**10**		**11**	**100.0%**	**3.63 [0.13, 99.85]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.76 (P = 0.45)

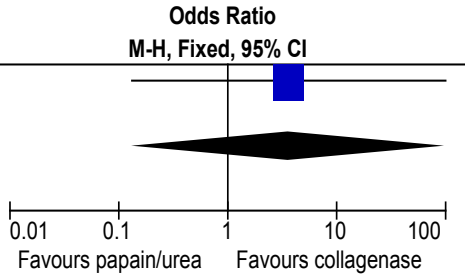


Figure 17 – forest plot of Collagenase versus fibrinolysis/DNAse - proportion of persons reporting adverse events.

	Collagenase		Fibrinolysis/DNAse			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Püllen 2002	45	66	34	69	100.0%	1.38 [1.03, 1.85]
Total (95% CI)		**66**		**69**	**100.0%**	**1.38 [1.03, 1.85]**
Total events	45		34			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.19 (P = 0.03)

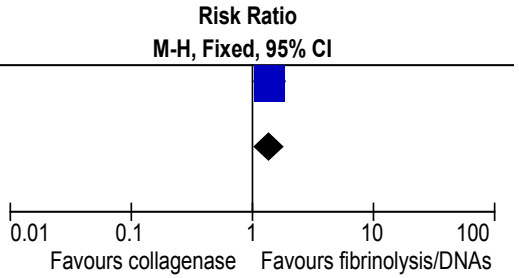


Figure 18 – forest plot of Collagenase versus fibrinolysis/DNAse - proportion of serious adverse events.

	Collagenase		Fibrinolysis/DNAse			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Püllen 2002	45	66	34	69	100.0%	1.38 [1.03, 1.85]
Total (95% CI)		**66**		**69**	**100.0%**	**1.38 [1.03, 1.85]**
Total events	45		34			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.19 (P = 0.03)

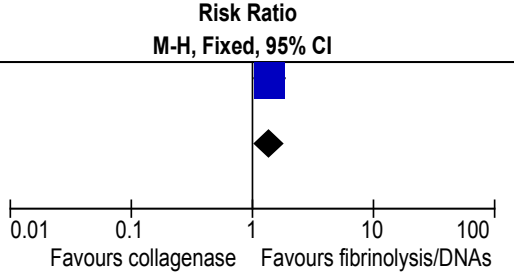


Figure 19 – forest plot of Collagenase versus hydrocolloid dressing - proportion of patients with reduction in PU area after 12 weeks of treatment.

	Collagenase		Hydrocolloid dressing			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Burgos 2000 (a)	15	18	14	19	100.0%	1.13 [0.81, 1.59]
Total (95% CI)		**18**		**19**	**100.0%**	**1.13 [0.81, 1.59]**
Total events	15		14			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)

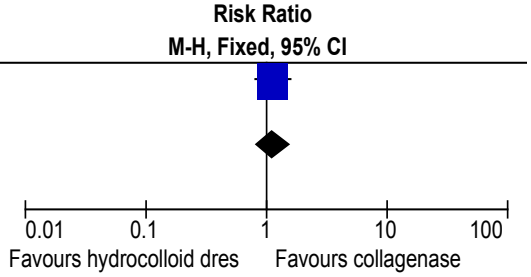


Figure 20 – forest plot of Collagenase versus hydrocolloid dressing - proportion of patients with complete healing of PU.

	Collagenase		Hydrocolloid dressing			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Burgos 2000 (a)	3	18	3	19	28.6%	1.06 [0.24, 4.57]
Muller 2001	11	12	7	11	71.4%	1.44 [0.89, 2.32]
Total (95% CI)		**30**		**30**	**100.0%**	**1.33 [0.80, 2.23]**
Total events	14		10			

Heterogeneity: Chi² = 0.20, df = 1 (P = 0.65); I² = 0%

Test for overall effect: Z = 1.09 (P = 0.28)

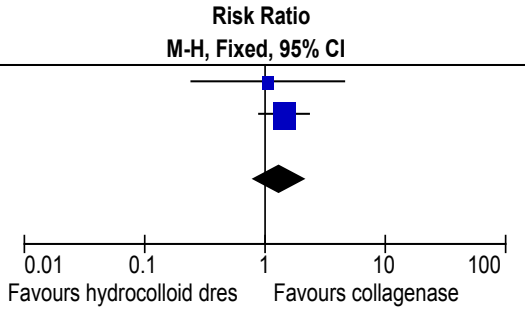


Figure 21 – forest plot of Collagenase versus hydrocolloid dressing - mean reduction in PU area after 12 weeks of treatment

	Collagenase			Hydrocolloid dressing				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Burgos 2000 (a)	9.1	12.7	18	6.2	9.8	19	100.0%	2.90 [-4.44, 10.24]
Total (95% CI)			**18**			**19**	**100.0%**	**2.90 [-4.44, 10.24]**

Heterogeneity: Not applicable

Test for overall effect: Z = 0.77 (P = 0.44)

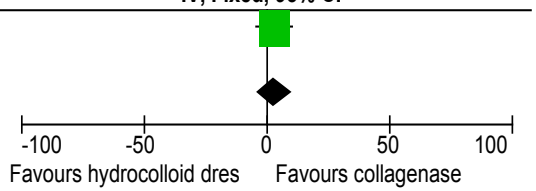


Figure 22 – forest plot of Collagenase versus hydrocolloid dressing - proportion of patients reporting adverse events.

Study or Subgroup	Collagenase Events	Collagenase Total	Hydrocolloid dressing Events	Hydrocolloid dressing Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Burgos 2000 (a)	1	18	2	19	100.0%	0.53 [0.05, 5.33]
Total (95% CI)		**18**		**19**	**100.0%**	**0.53 [0.05, 5.33]**
Total events	1		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)

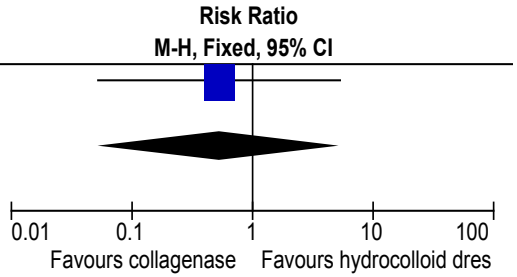


Figure 23 – forest plot of Collagenase versus hydrocolloid dressing - mean time to healing

Study or Subgroup	Collagenase Mean	Collagenase SD	Collagenase Total	Hydrocolloid dressing Mean	Hydrocolloid dressing SD	Hydrocolloid dressing Total	Weight	Mean Difference IV, Fixed, 95% CI
Muller 2001	10	1.5	12	14	1.2	11	100.0%	-4.00 [-5.11, -2.89]
Total (95% CI)			**12**			**11**	**100.0%**	**-4.00 [-5.11, -2.89]**

Heterogeneity: Not applicable
Test for overall effect: Z = 7.09 (P < 0.00001)

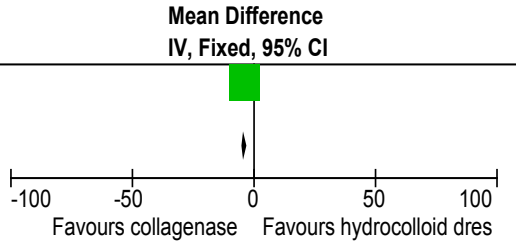


Figure 24 – forest plot of Collagenase ointment application every 24 hours versus every 48 hours - proportion of PU that showed complete healing after 8 weeks.

	Collagenase every 24 h		Collagenase every 48 h			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Burgos 2000 (b)	12	43	9	43	100.0%	1.33 [0.63, 2.83]
Total (95% CI)		**43**		**43**	**100.0%**	**1.33 [0.63, 2.83]**
Total events	12		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.75 (P = 0.45)						

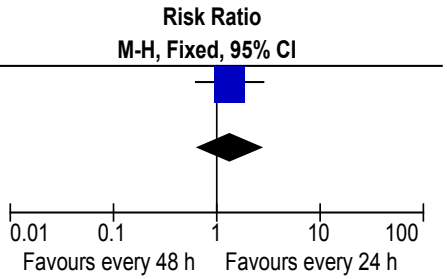
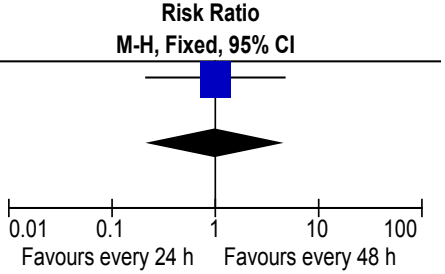


Figure 25 – forest plot of Collagenase ointment application every 24 hours versus every 48 hours – proportion of patients reporting adverse events.

	Collagenase every 24 h		Collagenase every 48 h			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Burgos 2000 (b)	3	46	3	46	100.0%	1.00 [0.21, 4.70]
Total (95% CI)		**46**		**46**	**100.0%**	**1.00 [0.21, 4.70]**
Total events	3		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						



3.3.3.2. Maggots

Figure 26 – Forest plot of maggot therapy versus conservative treatment - change in surface area during treatment (cm²).

Study or Subgroup	Maggot therapy Mean	SD	Total	Conservative Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Sherman 2002	-7.3	3.1	43	6.3	3.8	49	100.0%	-13.60 [-15.01, -12.19]
Total (95% CI)			**43**			**49**	**100.0%**	**-13.60 [-15.01, -12.19]**

Heterogeneity: Not applicable
Test for overall effect: Z = 18.89 (P < 0.00001)

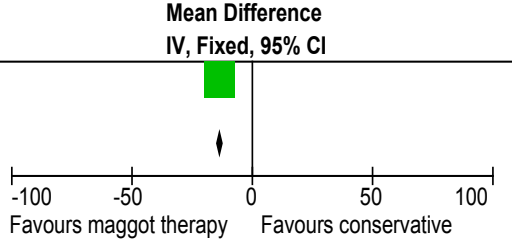


Figure 27 – Forest plot of maggot therapy versus conservative treatment, outcome - change in surface area per week.

Study or Subgroup	Maggot therapy Mean	SD	Total	Conservative Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Sherman 2002	-1.5	0.8	43	1.4	0.9	49	100.0%	-2.90 [-3.25, -2.55]
Total (95% CI)			**43**			**49**	**100.0%**	**-2.90 [-3.25, -2.55]**

Heterogeneity: Not applicable
Test for overall effect: Z = 16.36 (P < 0.00001)

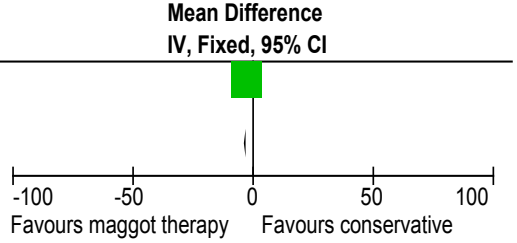


Figure 28 – forest plot of maggot therapy versus conservative treatment, outcome - proportion wounds decreased in surface area within 4 weeks.

Study or Subgroup	Maggot therapy Events	Total	Conservative Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sherman 2002	34	43	22	49	100.0%	1.76 [1.25, 2.49]
Total (95% CI)		**43**		**49**	**100.0%**	**1.76 [1.25, 2.49]**
Total events	34		22			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.20 (P = 0.001)

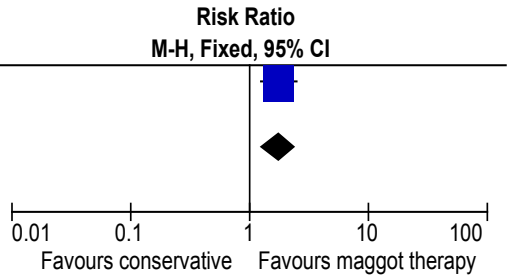


Figure 29 – forest plot of maggot therapy versus conservative treatment, outcome - proportion of wounds decreased during treatment.

Study or Subgroup	Maggot therapy Events	Total	Conservative Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sherman 2002	36	43	18	49	100.0%	2.28 [1.54, 3.37]
Total (95% CI)		**43**		**49**	**100.0%**	**2.28 [1.54, 3.37]**
Total events	36		18			

Heterogeneity: Not applicable
Test for overall effect: Z = 4.14 (P < 0.0001)

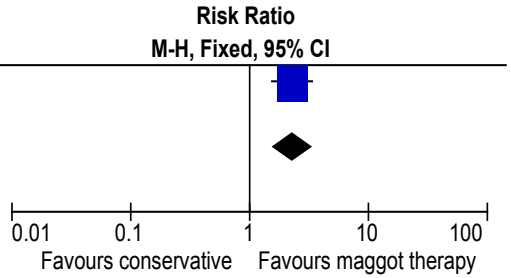


Figure 30 – forest plot of maggot therapy versus conservative treatment - healing rate at 8 weeks.

Study or Subgroup	Maggot therapy Mean	SD	Total	Conservative Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Sherman 2002	0.096	0.039	43	-0.027	0.047	49	100.0%	0.12 [0.11, 0.14]
Total (95% CI)			**43**			**49**	**100.0%**	**0.12 [0.11, 0.14]**

Heterogeneity: Not applicable
Test for overall effect: Z = 13.71 (P < 0.00001)

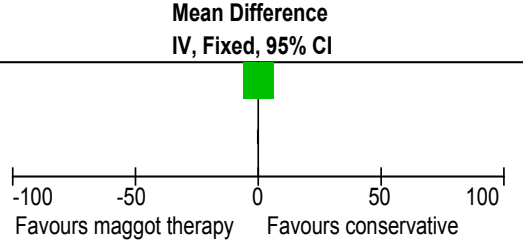


Figure 31 – forest plot of maggot therapy versus conservative treatment - proportion of wounds that completely healed.

Study or Subgroup	Maggot therapy Events	Total	Conservative Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sherman 2002	17	43	10	49	100.0%	1.94 [1.00, 3.77]
Total (95% CI)		**43**		**49**	**100.0%**	**1.94 [1.00, 3.77]**
Total events	17		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.95 (P = 0.05)

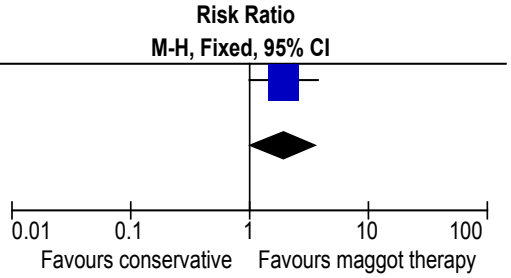
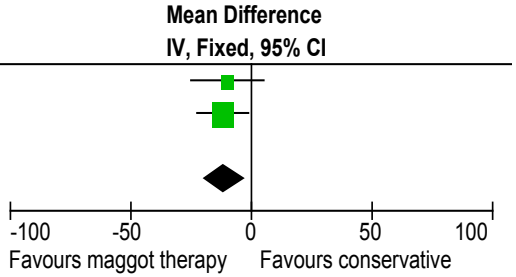


Figure 32 – forest plot of maggot therapy versus conservative treatment, outcome - time to wound healing (days)

Study or Subgroup	Maggot therapy Mean	SD	Total	Conservative Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Sherman 2002	84	35	43	94	39	49	33.1%	-10.00 [-25.12, 5.12]
Wang 2010	18.7	10.4	10	30.6	12.2	8	66.9%	-11.90 [-22.53, -1.27]
Total (95% CI)			**53**			**57**	**100.0%**	**-11.27 [-19.97, -2.57]**

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%

Test for overall effect: Z = 2.54 (P = 0.01)



3.3.4. Evidence tables

3.3.4.1. General

Table 22 – Burgos 2000 - a

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: Burgos, 2000 (a) **Title:** Cost, Efficacy, Efficiency and Tolerability of Collagenase Ointment versus Hydrocolloid Occlusive Dressing in the Treatment of Pressure Ulcers **Journal:** Clin Drug Invest, 2000; 19 (5): 357-365 **Study type:** Muliticentrerandomizednon-blinded parallel group study **Sequence generation:** Computer generated randomization list into blocks of 4 patients **Allocation concealment:** no details **Blinding:** Total surface area of the ulcers was calculated using	**Patient group:** Patients ≥ 55 years presenting with stage III pressure ulcers (skin disruption, tissue damage and exudate, and subcutaneous tissue involvement) **All patients** **Randomised N:** 37 **Completed N:** 23 **Drop-outs:** 14 Reasons in group 1: ➢ Unrelated death (N=3) ➢ Discharge from hospital (N=3) ➢ Transfer to other centre (N=3) Reasons in group 2: ➢ Unrelated death (N=1) ➢ Deterioration of general condition (N=1)	**Group 1:** Collagenase ointment (Iruxol® Mono, Laboratorios Knoll, SA) applied once daily in a 1 to 2 mm thick layer to the ulcer bed **Group 2:** Application of a hydrocolloid dressing (Varihesive®, Convatec, SA) that was changed every 3 days. If hydrocolloid dressings showed leakage due to excessive exudate, dressings were changed more frequently. Varihesive® paste was applied to deep ulcers or ulcers with a large amount of exudate according to the investigator's judgment.	**Outcome 1:** Proportion of PU with reduction in pressure ulcer area after 12 weeks of treatment **Outcome 2:** Proportion of PU with complete healing of pressure ulcer after 12 weeks of treatment **Outcome 3:** Mean reduction in ulcer area after 12 weeks of treatment (cm^2)	**Outcome 1:** **Group 1:** 15/18 (83.3%) **Group 2:** 14/19 (73.7%) **Relative risk:** 1.13 **95% CI:**0.81-1.59 **P value:**0.754 **Outcome 2:** **Group 1:** 3/18 (16.6%) **Group 2:** 3/19 (15.8%) **Relative risk:** 1.06 **95% CI:**0.24-4.57 **P value:**0.451 **Outcome 3:** **Group 1:** 9.1 ± 12.7 **Group 2:** 6.2 ± 9.8 **Relative risk:**	**Funding:** this study was supported by Labotorios Knoll, SA, Madrid **Limitations:** Underpowered Unclear allocation concealment Not all outcome assessors were blinded Relatively high drop-out No baseline differences reported. **Additional outcomes:** No significant differences were observed in cost and efficiency between collagenase ointment and hydrocolloid dressing in the treatment of

planimetryby an observer blind to therapeutic assignment **Addressing incomplete outcome data:** For those patients who did not complete the study, final ulcer area was that recorded at the last measurement, for those who presented complete healing, the final ulcer area was zero. To ascertain the potential effect of study discontinuation, mean ulcer area and mean reduction of ulcer area in patients who discontinued the study and those who completed the study were compared. Intra- and intergroup comparisons were performed. Normal distribution of data was assessed with the Kolmogorov-Smirnov test, and Student's t –test or the Mann-Whitney U test were used for intergroup comparisons **Statistical analysis:** Efficacy analysis by intention-to –treat was carried out using Student's t-test and the Mann-	➢ Discharge from hospital (N=1) ➢ Protocol violation (N=2) ➢ Lack of efficacy (N=1) **Group 1** **Randomised N:** 18 **Completed N:** 9 **Dropouts:**9 **Age:** 81.9 ± 12.7 **Gender (m/f):** 8/10 **Other relevant patient characteristics:** Amell scale score (range): 17.7 ± 3.4 Ulcer age : 3.2 ± 2.0 months Previously treated ulcers (No. (%)): 15 (83.33) Localisation (no. (%)): Sacrum: 8 (44.44) Trochanter: 4 (22.22) Heel: 3 (16.66) Other: 3 (16.66) **Group 2** **Randomised N:** 19 **Completed N:** 13 **Dropouts:** 6 **Age:** 78.6 ± 10.4	Both groups: /	**Outcome 4:** Pain intensity decrease **Outcome 5:** Patients with adverse reactions	**95% CI:** **P value:**0.369 **Outcome 4:** **Group 1:** **Group 2:** **Relative risk:** **95% CI:** **P value:** 0.001 **Outcome 5:** **Group 1:** 1/18 **Group 2:** 2/19 **Relative risk:** 0.53 **95% CI:** 0.05-5.33 **P value:**	pressure ulcers. Granulation tissue formulation increased (p>0.0005) and exudate production decreased (p>0.0005) in both treatment groups. Odour was not modified throughout the study period.* *no concrete data provided **Notes:** any notes the reviewer thinks may be important

Whitney U test. Efficacy analysis per protocol was carried out using factorial analysis of variance 2X9 with repeated measurements of the last factor. Primary outcome measure, ulcer area decrease in absolute terms expressed in cm^2, was obtained by subtracting ulcer area at the end of the study treatment from baseline ulcer area. Cost analyses by intention-to – treat and per protocol were carried out using Student's t-test. The mean cost per patient and 95% confidence intervals were calculated. Overall cost efficacy and subanalysis of the study products costs on outcome was analyzed. To assess reliability of ulcer measurements absolute differences in mean ulcer area between transparent acetate film and slide measurements at baseline and at the end of the study were calculated. Similarly, differences in percentages of mean ulcer areas in both treatment groups were calculated according to the formula $(\sigma_t-\sigma_s/\sigma_t)$ x 100,	**Gender (m/f):** 9/10 Amell scale score (range): 20.2 ±5.9 Ulcer age (range): 2.6 ± 1.9 months Previously treated ulcers (No. (%)): 17 (89.47) Localisation (no. (%)): Sacrum: 7 (36.84) Trochanter: 4 (21.05) Heel: 6 (31.57) Other: 2 (10.53) **Inclusion criteria:** ➢ 55 y ➢ Stage III ulcer for < 1 year **Exclusion criteria:** ➢ End-stage organ disease ➢ Localized or systemic signs or symptoms of infection ➢ Hypersensitivity to collagenase	

where σ_t is the mean value obtained from transparent acetate films and σ_s is the mean value obtained from the slides. The statistics used were the t-test for mean equality. Analysis of ulcer characteristics was carried out using the Friedman test for longitudinal analysis and the Mann-Whitney U test for cross-sectional analysis. The number and percentage of patients presenting ulcer bacterial colonization and the location of colonized ulcers were analyzed by chi-square test and Fisher's exact test. Analysis of tolerability was carried out by calculating the relative risk of adverse reaction occurrence. Statistical significance was set at $p \leq 0.05$.

Baseline differences: Not reported

Study power/sample size:

No a priori sample size calculation

Setting:

7 hospitals in Spain

Length of study:

12 weeks of treatment or

until healing of the ulcer, whichever occurred first

Assessment of PUs:

Indirect procedure:

After placing an adhesive identification label at one of its margins, the ulcers were photographed according to a standardized method at 50 cm from the focus. The slide of each ulcer was projected and focused in such a way that the size of the attached label matched the actual label size (2.5 cmx 5 cm), and then the contour of each ulcer was transferred to a transparent acetate film.

Direct procedure:

Were performed by tracing the outline of each ulcer perimeter onto on adequately labeled transparent acetate film.

Total surface area of the ulcers was calculated usingplanimetry (HAFF-Planimeter no. 315, GebrüderHaff, Germany, calibrated for measurements in cm^2).

Examinations were made at 1-week intervals.

Ulcer characteristics were

measured on a 5-point scale and included: Pain (no pain, minimal, bearable, intense, unbearable) % granulation tissue (≤ 10%, 11 to 30%, 31 to 60%, 61 to 90%, ≥ 90%) Exudate (none, minimal, moderate, intense, excessive) Odour (none, minimal, tolerable, intense, repulsive) **Multiple ulcers:** No details Unit of analysis = patient. However no patient had more than 1 PU.					

Table 23 – Burgos 2000 -b

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: Burgos 2000 (b) **Title:** Collagenase Ointment Application at 24- versus 48-hour Intervals in the Treatment of Pressure Ulcers. A RandomisedMulticentre	**Patient group:** Hospitalised or institutionalised patients aged 55 years or older presenting with stage 3 PU for < 1 year. **All patients**	**Group 1:** collagenase ointment application every 24 hours **Group 2:** collagenase ointment application every 48 hours **Both groups:**	**Outcome 1:** Proportion of PU that showed complete healing after 8 weeks (intention-to-treat)	**Outcome 1:** **Group 1:** 12/43 **Group 2:** 9/43 **Relative risk:** 1.33 **95% CI:**0.63-2.83 **P value:**0.451	**Funding:** Study was supported by Knoll, SA, Madrid, Spain **Limitations:** Unclear randomization process Unclear allocation

Study. **Journal:** Clin Drug Invest, 2000; 19 (6): 399-407 **Study type:** Multicentre, randomised,nonblind, open, parallel-group study **Sequence generation:** No details **Allocation concealment:** No details **Blinding:** An observer blind to therapeutic assignment performed all measurements **Addressing incomplete outcome data:** No details **Statistical analysis:** Comparability at baseline between treatment groups was evaluated by the Student's t-test and by the chi-square test. Efficacy analysis by intention-to-treat and per-protocol was carried out using repeated	**Randomised N:** 92 **Completed N:** 63 **Drop-outs:** 29 **Group 1** **Randomised N:** 46 **Completed N:** 34 **Dropouts:** 12 Death due to unrelated cause: 4 Hospital discharge for deterioration in patient's general condition:3 Protocol violation: 3 Failure to have granulation tissue in 10% of PU area:0 Adverse event: 1 Voluntary withdrawal:1 **Age:** 80.1±9.7 (56-92) **Gender (m/f):** 16/30 **Other relevant patient characteristics:** Mean (+SD) PU age (months)(range): 3.3±2.3(1-11) No of previously treated PU (%): 43 (93.5) Localisation (no patients) (%) Sarum: 18 (39.1) Tochanter: 7 (15.2) Heel: 12 (26.1)	All patients were entered in an active run-in period with collagenase ointment (Iruxol® Mono, Laboratoires Knoll, SA, Madrid, Sapin) in order to develop 10 tot 30% granulation tissue. This run-in period lasted from 1 to 5 weeks depending on ulcer progression. Patients developing 10 to 30% granulation tissue qualified for randomisation	**Outcome 2:** Relative risk of non-healing among group 2 as compared with group 1 after 8 weeks (intention-to-treat) when granulation tissue covered 11 to 30% of the ulcer surface. **Outcome 3:** Mean reduction of PU area (cm^2) during 8 weeks (per-protocol) **Outcome 4:** Decrease in pain intensity after 8 weeks (intention-to-treat) **Outcome 5:** Decrease in pain	**Outcome 2:** **Group 1:** **Group 2:** **Relative risk:** 1.097 **95% CI:** 0.86-1.39 **P value:** **Outcome 3:** **Group 1:** **Group 2:** **Relative risk:** **95% CI:** **P value:** 0.59 **Outcome 4:** **Group 1:** **Group 2:** **Relative risk:** **95% CI:** **P value:** 0.004 (favourable in 24-hour group) **Outcome 5:** **Group 1:**	concealment Not all outcome assessors were blinded **Additional outcomes:** No significant differences between groups in terms of exudate, odor and granulation tissue were observed after 8 weeks. **Notes:** any notes the reviewer thinks may be important

analysis of variance, including factors for regimen, time (week) and interaction. When appropriate, degree of freedom was adjusted using the Greenhouse-Geisser method. To analyze the frequency of completely healed PU in each group chi-square and Fisher's exact tests were used. Equivalence analysis was carried out per-protocol. The equivalence margins (the largest difference that can be accepted as not clinically relevant) specified in advance were ±20% of the PU surface. Additionally, 90% confidence intervals were calculated, so that if the confidence interval was inside the limits of the equivalence margins, the 2 regimens could be considered equivalent. PU characteristics were analyzed with the Wilcoxon's test and the Mann-Whitney U test. Tolerability analysis	Other: 9 (19.5) **Group 2** **Randomised N:** 46 **Completed N:** 29 **Dropouts:** 17 Death due to unrelated cause: 7 Hospital discharge for deterioration in patient's general condition:6 Protocol violation: 2 Failure to have granulation tissue in 10% of PU area:0 Adverse event: 2 Voluntary withdrawal:0 **Age:** 79.0±11.7 (55-106) **Gender (m/f):** 14/32 **Other relevant patient characteristics:** Mean (+SD) PU age (months)(range): 18.5±6.0 (4-29) No of previously treated PU (%): 43 (93.5) Localisation (no patients) (%) Sarum: 21 (45.7) Tochanter: 10 (21.7) Heel: 7 (15.2) Other: 8 (17.4)		intensity after 8 weeks (per-protocol) **Outcome 6:** Proportion with adverse reactions after 8 weeks	**Group 2:** **Relative risk:** **95% CI:** **P value:** NS **Outcome 6:** **Group 1:** 3/46 **Group 2:** 3/46 **Relative risk:** 1 **95% CI:** 0.21-4.7 **P value:** NS

was carried out calculating the relative risk of adverse reaction occurrence. Statistical significance was set at $p \leq 0.05$. **Baseline differences:** None **Study power/sample size:** No a priori sample size calculation. **Setting:** 8 hospitals in Spain **Length of study:** Treatment during maximum 8 weeks or until complete healing of the PU whatever occurred first **Assessment of PUs:** Ulcers were staged according to the American Pressure Ulcer Advisory Panel. PU area measurements were performed by tracing the outline of each PU perimeter onto a transparent acetate film appropriately labeled. Total surface area of the ulcer was calculated using planimetry (HAFF-	**Inclusion criteria:** ➢ 55 years or older ➢ institutionalised or hospitalised ➢ stage 3 PU for < 1 year **Exclusion criteria:** ➢ End-stage disease ➢ Localized or systemic signs and/or symptoms of infection ➢ Hypersensitivity to collagenase	

Planimeter No 315, GebrüderHaff, Germany). The planimeter was calibrated for measurements in cm^2. After placing an identification adhesive label at one of its margins, all PU were photographed according to a standardized method at 50 cm from the focus. Ulcers were then cleaned with saline, collagenase ointment was applied and PU were covered with paraffin gauze and a conventional dressing. Study assessments were made at 1-week intervals and consisted of a photograph of the PU, measurement of the PU area, assessment on a 5-point scale of 4 PU characteristics (pain, % granulation tissue, exudate and odor) and assessment of any adverse reaction to study treatment. **Multiple ulcers:**					

No details Patients were unit of analysis					

Table 24 – Lee 1975

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: Lee, 1975 **Title:** Collagenase therapy for decubitus ulcers. **Journal:** Geriatrics, 1975; 30 (5): 91-8 **Study type:** Double-blinded randomized clinical trial **Sequence generation:** no details **Allocation concealment:** No details **Blinding:** No details **Addressing incomplete outcome data:** No details **Statistical analysis:**	**Patient group:** 11 patients with chronic diseases in poor physical condition. Four had neoplastic disease; 4 atherosclerotic heart diseases or cerebrovascular accident or both; 2 had Parkinson's disease and 1 had a femoral neck fracture. **All patients** **Randomised N:** 11 patients with a total of 28 advanced PU **Completed N:** 28 PU in 11 patients **Drop-outs:** 0 **Age:** 67. 6 (47-90) **Gender (m/f):** 3/8 **Other relevant patient characteristics:** /	**Group 1:** Collagenase (Santyl) was given as 250 units per gram of white petrolatum. **Group 2:** The placebo was a heat- inactivated preparation of the ointment used in the experimental group. **Both groups:** The ointment was applied once daily to each ulcer except when the ulcer required more frequent cleaning because of occasional contamination from incontinence of urine or faeces, or both. In the latter instance, the ointment was applied twice daily. Before the ointment was applied, the area was washed with liberal	**Outcome 1:** Proportion of PU that reduced in volume of PU assessed with the aid of a volume mold **Outcome 2:** Proportion of PU that increased in volume of PU assessed with the aid of a volume mold **Outcome 3:** Proportion of PU with odor at the end of treatment	**Outcome1:** **Group 1:** 8/17 **Group 2:** 0/11 **Relative risk:** 11.33 **95% CI:**0.72-178.54 **P value:** **Outcome 2:** **Group 1:** 4/17 **Group 2:** 6/11 **Relative risk:** 0.43 **95% CI:**0.16-1.19 **P value:** **Outcome3:** **Group 1:** 7/17 **Group 2:** 5/11 **Relative risk:** 0.91 **95% CI:**0.38-2.14 **P value:**	**Funding:** none mentioned **Limitations:** Underpowered Unclear randomization process Unclear allocation concealment Not clear whether outcome assessors were blinded **Additional outcomes:** A corollary immune diffusion study was carried out in 10 patients who had been treated with collagenase. After 6 to 30 days of treatment, no circulating collagenase or anticollagenase precipitin-type antibodies could be demontsrated by the

Only descriptive statistics **Baseline differences:** No details **Study power/sample size:** No apriori sample size calculation **Setting:** US, no further details **Length of study:** 4 weeks of treatment and follow-up unless complications developed or patient died **Assessment of PUs:** Two diameters of the PU were measured and a color photograph of the lesion was made. A volume mold was made with Jeltrate®. Five scoopfuls of Jeltrate were mixed with 7 oz of water and vigorously stirred to eliminate air bubbles. The mixture was then poured into the PU with the aid of a spatula, was allowed to set for 3 minutes and then was removed. The volume of the mold was	**Group 1** **Randomised N:** 17 PU **Completed N:** 17 PU **Dropouts:** 0 **Age:** / **Gender (m/f): /** **Other relevant patient characteristics:** / **Group 2** **Randomised N:** 11 PU **Completed N:** 11PU **Dropouts:** 0 **Age:** / **Gender (m/f): /** **Other relevant patient characteristics:** / **Inclusion criteria:** no details **Exclusion criteria:** no details.	amounts of sterile buffered saline (pH=7.5) in a attempt to remove films of necrotic tissue. The ointment was applied directly to the decubitus ulcer and covered with a sterile gauze pad. Wound pH was determined regularly. Antiseptics containing heavy metal ions and hexachlorophene were not used. If bacteriologic studies showed contamination, polimyxin B-bacitracin-neomycin powder was applied locally.	**Outcome 4:** side effects	**Outcome 4:** **Group 1:** 1/17 (mild bleeding and a burning sensation) **Group 2:** 0/11 **Relative risk:** 2 **95% CI:**0.09-45.12 **P value:**	Ouchterlony plate method. **Notes:** /

measured by volume displacement in a graduated cylinder. These measurements were repeated weekly and at the end of the study when possible. **Multiple ulcers:** Ulcers were the unit of analysis					

Table 25 – Müller 2001

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Müller (2001)** Title: **Economic evaluation of collagenase-containing ointment and hydrocolloid dressing in the treatment of pressure ulcers.** Journal: **PharmacoEconomics , 19 (12); 1209-1216.** Study type: **randomized controlled trial** Sequence generation: **not reported.** Allocation concealment: **not**	**Patient group:** Hospitalized female patients with grade IV heel PUs. **All patients** **Randomised N:** 24 patients and 26 ulcers **Completed N:** 23 patients and 26 ulcers **Drop-outs:** 1 (failed treatment) **Group 1** **Randomised N:** 12 patients and 13 ulcers **Completed N:** 12 patients and 13 ulcers **Dropouts:** 0 **Age (mean years; range):** 74.6; 68-79	**Group 1:** Collagenase dressing (Novuxol®). Ulcers were cleansed with saline 0.9%. Ulcers were treated with collagenase-containing ointment, paraffin gauze (Jelonet®) and an absorbent bandage. Ulcers were treated once a day. **Group 2:** Hydrocolloid dressing (DuoDerm®). Ulcers were cleansed with saline 0.9% and covered with the dressing. Ulcers were treated twice a week. **Both groups:** Before randomization autolysis and surgical debridement was performed. Occasionally remaining necrosis was	**Outcome 1:** Proportion of patients completely healed **Outcome 2:** Time to achieve complete healing (mean weeks; range)	**Group 1:** 11/12 **Group 2:** 7/11 **P value:** <0.005 **Group 1:** 10; 6-12 **Group 2:** 14; 11-16 **P value:** <0.005	**Funding:** Unrestricted grant from Knoll AG, Ludwigshafen, Germany. **Limitations:**; no report on sequence allocation; no report on allocation concealment; no report on blinding; no ITT analysis; sample size calculation unclear; very small sample size; no measurement of

reported Blinding: **not reported** Addressing incomplete outcome data: **drop-out excluded.** Statistical analysis: **Log-rank for efficiency in terms of the rate of complete healing and the Wilcoxon test for time to achieve complete healing were calculated. Tests were two-sided with p <0.05** Baseline differences: **Difference not statistically measured.** Study power/sample size: **The sample size (n=12) was calculated for the parameter 'time to achieve compete healing' for a power of 80%.** Setting: **Naaldhorst hospital, Naaldwijk in the Netherlands** Length of study: **not reported. Complete healing was achieved at maximum 16 weeks.** Assessment of PUs: **PU classification not**	**Gender (m/f):** 0/12 **Group 2** **Randomised N:** 12 patients and 13 ulcers **Completed N:** 11 patients and 12 ulcers **Dropouts:** 1 (failed treatment) **Age (mean years; range):** 72.4; 65-78 **Gender (m/f):** 0/12 **Inclusion criteria:** Grade IV PU **Exclusion criteria:** life expectancy of less than 6 months	treated with collagenase.	statistical difference between groups; no information on PU classification; little information on PU assessment; no information on preventive measures **Additional outcomes:** Cost-effectiveness **Notes:** /

reported. **Ulcer size and depth was assessed weekly by a physician. Photographs were taken.** Multiple ulcers: **two patients had two ulcers**					

Table 26 – Parish 1979

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: Parish, 1979 **Title:** Decubitus ulcers: a comparative study **Journal:** Cutis; 23 (1): 106-110 **Study type:** Double-blinded study **Sequence generation:** Patients were assigned at random, but no randomization method was reported. **Allocation:** No details **Blinding:** Neither the principal investigator,	**Patient group:** Patients with pressure ulcers in a long-term care institution for the chronically ill and physically disabled. **All patients** **Randomised N:**Not reported **Completed N:**17 **Drop-outs:**Not reported **Group 1** **Randomised N:**Not reported **Completed N:**7	**Group 1:** Dextranomer powder is employed in the treatment of secreting skin lesions. Dextranomer (Debrisan, Pharmacia Laboratories) consists of beads of cross-linked dextran molecules 0.1 to 0.3 mm in diameter in a three-dimensional porous network. The beads are hydrophilic and each gm of dry beads has the capacity to absorb 4 ml of fluid. Experimental studies show dextranomer	**Outcome 1:** Proportion of PU improved for patients treated with dextranomer versus patients treated with collagenase (%) **Outcome 2:** Proportion of PU improved for patients treated with dextranomer versus patients treated with sugar and egg white	**Outcome 1:** **Group 1:**12/14 (85.7%) **Group 2:**5/11 (45.5%) **Relative risk:** 1.89 **95% CI:** 0.95-3.73 **P value:**<0.02 **Outcome 2:** **Group 1:**12/14 (85.7%) **Group 3:** 0/9 (0%) **Relative risk:** 16.67 **95% CI:** 1.11-250.76 **P value:**<0.0001	**Funding:**not reported **Limitations:** • No inclusion or exclusion criteria reported. • Small sample size • Blinding failed • Randomization method not reported • Six patients changed treatment during the study. No information was given if there was a washing-out period

nor the patients knew who was assigned to which treatment regimen. The authors state however that while the attempted to keep the study double-blinded, it became obvious which regimens were being used.

Addressing incomplete outcome data:

Not reported

Statistical analysis: A fisher exact test was used to evaluate the data. Average ulcer dimension= square root of surface area.

Baseline differences: Not reported.

Study power/sample size:

Not reported

Setting:

The Inglis House is a long-term care institution for the chronically ill and physically disabled. Patients in this institution have such

Dropouts: Not reported

Age:29-57

Gender (m/f): Not reported

Other relevant patient characteristics:

Number of ulcers (n=14)

Average ulcer dimension in cm = 4.5

Group 2

Randomised N:not reported

Completed N:5

Dropouts:1 (patient not responding to the collagenase treatment was switched to the dextranomer group).

Age:28-59

Gender (m/f):

Not reported

Other relevant patient characteristics:

Number of ulcers (n=11)

Average ulcer dimension in cm = 3.2

Group 3

Randomised N:not

capable of transporting bacteria, inflammatory mediators and debris away from the wound surface and into the bead layers. Patients paced on the dextranomer program were given saline soaks. Dextranomer was poured into the ulcer in a layer of at least 3mm deep and the sores were then covered with dry dressings. The dextranomer dressings were changed one to three times daily depending on the amount of wound exudate. The removal of the dextranomer beads was accomplished by saline irrigation.

Group 2: Patients receiving collagenase (Collagenase, Santyl, Knoll Pharmaceutical Co) were given a saline wash. Collagenase was then applied daily with a wooden applicator, and the ointment was covered with a dry dressing, as

Outcome 3:

Proportion of PU improved for patients treated with collagenase versus patients treated with sugar and egg white

Outcome 4:

Proportion of patients with ulcer closure for patients treated with dextranomer versus patients treated with collagenase

Outcome 5:

Proportion of patients with ulcer closure for patients treated with dextranomer versus patients treated with sugar and egg white

Outcome 6:

Proportion of patients with ulcers closure for patients treated with collagenase versus patients treated with sugar and egg white

Outcome 3:

Group 2:5/11 (45.5%)

Group 3: 0/9 (0%)

Relative risk: 9.17

95% CI: 0.57-146.40

P value: not significant

Outcome 4:

Group 1:4/7 (57%)

Group 2: 1/5 (20%)

Relative risk: 2.86

95% CI:0.44-18.48

P value: not significant

Outcome 5:

Group 1: 4/7 (57%)

Group 3: 0/5 (0%)

Relative risk: 6.75

95% CI:0.44-102.80

P value: <0.08

Outcome 6:

Group 2: 1/5 (20%)

Group 3: 0/5 (0%)

Relative risk: 3

95% CI:0.15-59.89

P value: not significant

Outcome 7:

Additional outcomes: All seven patients treated with dextranomer improved during the course of the study. In the collagenase group, two of five patients improved. None of the patients treated with sugar and egg white showed improvement. In four patients treated with dextranomer, improvement was observed within one week of the start of treatment and in two other patients improvement was seen within one month. In the collagenase group, none of the five patients improved within one week of treatment and two patients improved within one month of treatment.

All five patients who failed to respond to the sugar and egg white treatment were changed to either dextranomer or collagenase treatment. The four patients switched to dextranomer all improved, with three patients attaining complete closure of their ulcers (four ulcers). One patient with four decubitus ulcers was switched to the group

incapacitating disorders as paraplegia, quadriplegia, Parkinson's disease, rheumatoid arthritis, cerebral palsy, and multiple sclerosis. Of approximately three hundred residents, about 10 percent have decubitus ulcers at any one time. **Length of study:** The initial study was to have lasted four weeks, but many subjects were treated and observed for up to four months or longer. **Assessment of PUs:** Pressure ulcers were assessed as dry or moist. The authors believe that there is no purpose in further categorizing the ulcers. **Multiple ulcers:** All pressure ulcers of the included patients were treated and assessed.	reported **Completed N:**5 **Dropouts:**5 (patients not responding to the sugar and egg white treatment were switched to the dextranomer (n=4) or collagenase group (n=1)). **Age:**32-70 **Gender (m/f):** Not reported Other relevant patient characteristics: Number of ulcers (n=9) Average ulcer dimension in cm = 2.4 **Inclusion criteria:**not reported **Exclusion criteria:**not reported	recommended by the package insert. **Group 3:** Patients receiving sugar and egg white were also given a saline wash. The mixture was applied liberally to the area four times daily and allowed to dry. All groups: if a patient did not respond satisfactorily to any treatment at the end of four weeks, the regimen was changed to one of the two other treatments.	**Outcome 7:** Proportion of ulcer closed for patients treated with dextranomer versus patients treated with collagenase **Outcome 8:** Proportion of ulcer closed for patients treated with dextranomer versus patients treated with sugar and egg white **Outcome 9:** Proportion of ulcer closed for patients treated with collagenase versus patients treated with sugar and egg white **Outcome 10:** Proportion of patients improved treated with dextranomer versus patients treated with collagenase	**Group 1:** 6/14 (43%) **Group 2:** 1/11 (9%) **Relative risk:** 4.71 **95% CI:**0.66-33.61 **P value:** not significant **Outcome 8:** **Group 1:** 6/14 (43%) **Group 3:** 0/9 (0%) **Relative risk:** 8.67 **95% CI:**0.55-137.33 **P value:** <0.05 **Outcome 9:** **Group 2:** 1/11 (9%) **Group 3:** 0/9 (0%) **Relative risk:** 2.50 **95% CI:**0.11-54.87 **P value:**not significant **Outcome 10:** **Group 1:**7/7 **Group 2:**2/5 **Relative risk:** 2.25 **95% CI:**0.86-5.9 **P value:**	receiving collagenase. This patient improved, with one of four ulcers closing. One patient for whom collagenase treatment failed to produce an adequate response and who was crossed over into the dextranomer group also improved with one of two ulcers closing. The authors did not see any change in the progress of healing whether the patient was turned every two hours, as they had been initially or whether they were allowed to remain in the same position for many hours. Similarly, cleaning the patients and changing their linens frequently led to none but aesthetic improvements. All patients received the same diet as the other residents of the Inglis House. Sepsis did not develop during the course of the study. Bacteriologic cultures, both aerobic and anerobic were done before, during and after treatment, but no significant trends were noted.

Outcome 11: Proportion of PU closed treated with dextranomer versus collagenase after 1 week	**Outcome 11:** **Group 1:**6/14 **Group 2:**0/11 **Relative risk:** 10.40 **95% CI:**0.65-166.71 **P value:**	**Notes:**
Outcome 12: Proportion of PU closed treated with dextranomer versus collagenase after 1 month	**Outcome 12:** **Group 1:**8/14 **Group 2:**3/11 **Relative risk:** 2.10 **95% CI:**0.72-6.09 **P value:**	
Outcome 13: Proportion of PU closed treated with dextranomer versus collagenase after 2 months	**Outcome 13:** **Group 1:**8/14 **Group 2:**5/11 **Relative risk:** 1.89 **95% CI:**0.95-3.73 **P value:**	
Outcome 14: Proportion of PU closed treated with dextranomer versus collagenase after more than 2 months	**Outcome 14:** **Group 1:**12/14 **Group 2:**5/11 **Relative risk:** 1.89 **95% CI:**0.95-3.73 **P value:**	

	Outcome 15: Proportion patients improved treated with dextranomer versus patients treated with sugar and egg white	**Outcome 15:** **Group 1:**4/7 **Group 3:**0/5 **Relative risk:** 11.25 **95% CI:**0.79-160.81 **P value:**
	Outcome 16: Proportion of PU closed treated with dextranomer versus sugar and egg white after 1 week	**Outcome 16:** **Group 1:**6/14 **Group 3:**0/9 **Relative risk:** 8.67 **95% CI:**0.55-137.33 **P value:**
	Outcome 17: Proportion of PU closed treated with dextranomer versus sugar and egg white after 1 month	**Outcome 17:** **Group 1:**8/14 **Group 3:**0/9 **Relative risk:** 11.33 **95% CI:**0.73-175.10 **P value:**
	Outcome 18: Proportion of PU closed treated with dextranomer versus sugar and egg white	**Outcome 18:** **Group 1:**8/14 **Group 3:**0/9 **Relative risk:** 11.33 **95% CI:**0.73-175.10 **P value:**

			after 2 months	**Outcome 19:** **Group 1:**12/14 **Group 3:**0/9 **Relative risk:** 16.67 **95% CI:**1.11-250.76 **P value:**
			Outcome 19: Proportion of PU closed treated with dextranomer versus sugar and egg white after more than 2 months	**Outcome 20:** **Group 2:**2/5 **Group 3:**0/5 **Relative risk:** 5 **95% CI:**0.30-83.69 **P value:**
			Outcome 20: Proportion of patients improved treated with collagenase versus patients treated with sugar and egg white	**Outcome 21:** **Group 2:**0/11 **Group 3:**0/9 **Relative risk:** **95% CI:** **P value:**
			Outcome 21: Proportion of PU closed treated with collagenase versus sugar and egg white after 1 week	**Outcome 22:** **Group 2:**3/11 **Group 3:**0/9 **Relative risk:** 5.83 **95% CI:**0.34-100.03 **P value:**
			Outcome 22: Proportion of PU closed treated with collagenase versus sugar and egg white after 1 month	

						Outcome 23: **Group 2:**5/11 **Group 3:**0/9 **Relative risk:** 9.17 **95% CI:**0.57-146.40 **P value:**	
					Outcome 23: Proportion of PU closed treated with collagenase versus sugar and egg white after 2 months	**Outcome 24:** **Group 2:**5/11 **Group 3:**0/9 **Relative risk:** 9.17 **95% CI:**0.57-146.40 **P value:**	
					Outcome 24: Proportion of PU closed treated with collagenase versus sugar and egg white after more than 2 months	**Outcome 25:** **Group 1:** 0/7 **Group 2:**0/5 **Group 3:**0/5 **Relative risk:** **95% CI:** **P value:**	
					Outcome 25: Side effects		

Table 27 – Püllen 2002

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year:	**Patient group:**	**Group 1:** Twice-daily	**Outcome 1:**	**Outcome 1:**	**Funding:** none

Püllen, 2002 **Title:** Prospective randomized double-blind study of the wound-debriding effects of collagenase and fibrinolysin/deoxyribonuclease in pressure ulcers **Journal:** Age and Ageing, 2002; 31: 126-30 **Study type:** Prospective double-blind randomised controlled trial **Sequence generation:** No details **Allocation concealment:** No details **Blinding:** Outcome assessors were blinded for therapeutic assessment **Addressing incomplete outcome data:** No details **Statistical analysis:** Wilcoxon's test Intention to treat analysis including all patients who received study medication. This population was evaluated by end-point analysis.	Patients with pressure ulcers, Seiler stage 2,3 or 4, in the pelvic region with fibrinous and/or necrotic slough from 17 hospitals **All patients** **Randomised N:** 135 **Completed N:** 78 **Drop-outs:** 57 For 14 patients pictures of the wounds were not assessable. These were excluded from the intention to treat analysis. 16 patients from group 1 and 27 from group 2 were excluded from the per-protocol analysis because of protocol violations **Group 1** **Randomised N:** 66 **Completed N:** 44 **Dropouts:** 22 **Age:** 78.4 ± 8.9 **Gender (m/f):** **Other relevant patient characteristics:** Mean duration: 1.3 ± 0.6 Seiler decubitus stage (No. (%)): 2: 18 (27.3) 3: 44 (66.7)	treatment with collagenase (1.2 U/g) (Novuxal). **Group 2:** Twice-daily treatment fibrinolysin/DNAse (1 U Loomis and 666 Christensen/g) (Fibrolan) **Both groups:** The ointments were applied by nurses in a 2 mm layer to the ulcer and covered with gauze. They were not irrigated between treatments. The physician determined the type of mattress and frequency of repositioning	proportion of persons reporting adverse events **Outcome 2:** Proportion of serious adverse events reported	**Group 1:** 45/66 (68.2%) **Group 2:** 34/69 (49.3%) **Relative risk:** 1.38 **95% CI:**1.03-1.85 **P value:** **Outcome 2:** **Group 1:** 54/118 **Group 2:** 24/103 **Relative risk:** 1.96 **95% CI:** 1.31-2.93 **P value:**	mentioned **Limitations:** Underpowered Unclear randomization process Unclear allocation concealment **Additional outcomes:** No statistically significant difference between 2 groups with respect to change in necrotic wound area, wound environment*, wound margins*, wound depth*, pocketing*, area and slough*, and wound healing*. *no concrete data provided

Per-protocol analysis including only patients who met all criteria for inclusion and none for exclusion and who completed the study without major protocol violations. Patients who discontinued the trial prematurely and whose withdrawal was related to the therapy were included in the analysis. SAS software was used. **Baseline differences:** None **Study power/sample size:** Planning of the study was based on an estimated probability of 0.69 that collagenase reduces the necrotic wound surface to a greater extent than fibrinolysin/DNAse. A sample size of 50 patients per treatment arm was calculated in order to identify the supposed difference between the products with a 90% probability at a specified error probability of 5% using Wilcoxon's test. Taking an assumed drop-out rate of about 30% into account, the required sample size was set at 130 patients. **Setting:**	4: 4 (6.1) Support: Normal mattress: 18 (27.3) Extremely soft mattress: 12 (18.2) Other: 36 (54.5) Mean modified Norton scale: 18.6 ± 4.5 **Group 2** **Randomised N:** 69 **Completed N:** 34 **Dropouts:** 35 **Age:** 79.7 ± 8.1 **Gender (m/f):** Mean duration: 1.4 ± 1.0 Seiler decubitus stage (No. (%)): 2: 20 (29.0) 3: 43 (62.3) 4: 6 (8.7) Support: Normal mattress: 23 (33.3) Extremely soft mattress: 16 (23.2) Other: 30 (43.4) Mean modified Norton scale: 19.1 ± 4.7 **Inclusion criteria:** ➢ Seiler stage 2, 3 or	

17 hospitals in Germany providing acute care and rehabilitation services for elderly patients

Length of study:

4 weeks of treatment or until complete wound debridement whichever occurred first.

Assessment of PUs:

The treating physician took at least 12 photographs of the reference pressure ulcer under standard conditions at the beginning of the study and about every 4 days thereafter. The last photograph of the ulcer was taken within 2 days of the last application of study medication. A specific camera was used (Canon Eos 100 QD, Compact-Macro EF 50 mm lens, f/2.5) with a special flash (Canon Ringblitz Macro Ring Lit ML 3). Each physician was trained in the use of the camera. A scale displaying a range of colours was placed adjacent to the pressure ulcer to facilitate standardized evaluation of the lesions. An automatic distance meter ensured that photographs were always taken from the same distance.

3

- Fibrinous or necrotic slough
- Ulcers between 2 to 14.5 cm in diameter

Exclusion criteria:

- Alcohol or drug dependency
- End stage malignant disease
- Hypersensitivity to collagenase or fibrinolysin/DNAse
- Planned co-medication with local antiseptics, antibiotics, occlusive wound dressings, hydrogels or hydrocolloids
- Ulcers with black eshar only
- Ulcers that did not permit parallel positioning of the reference scale

The change of necrotic wound area was clinically assessed by 2 independent dermatologists (blinded to therapeutic assignment) by means of 13x18 cm photographs of the wound and classified into 5 categories:

- Marked increase by at least 100%
- Appreciable increase by at least 30%
- No appreciable increase
- Appreciable reduction by at least 25%
- Marked reduction by at least 50%

Additional efficacy criteria assessed were environment of the wound, wound margins, wound depth, pocketing area and wound healing.

Multiple ulcers:

If several pressure ulcers were present, the worst ulcer was chosen as the reference ulcer.

3.3.4.2. Maggots

Table 28 – Sherma 1975

Reference	Patient Characteristics	Intervention	Outcome measures	Effect sizes	Comments

Comparison					
Author and year: Sherman, 1995 **Title:** Maggot therapy for treating pressure ulcers in spinal cord injury patients **Journal:** The Journal of Spinal Cord Medicine, 18(2): 71-74. **Study type:** Prospective controlled study **Sequence generation:** patients were first followed for three-four weeks while still receiving treatments prescribed by their primary care teams. Patients were then treated with maggot therapy. **Allocation** concealment: Not applicable **Blinding:** No blinding **Addressing incomplete outcome data:**	**Patient group:** Patients with pressure ulcers for at least one month **All patients** **Randomised N:** 28 **Completed N:** 16 patients **Drop-outs:** 12(from the 20 patients treated with maggot therapy only 8 were first followed for three – four weeks while still receiving the wound treatment described by their primary care team). **Group 1** **Completed N:** 8 **Age:** 58 (44-68) **Gender (m/f): 8/0** **Other relevant patient characteristics:** Level of spinal injury (quadriplegic=1; paraplegic=7) Laboratory values (% ideal bodyweight = 118% (86-145); creatinine clearance =	**Group 1:** Fly larvae of the species Phaeniciasericata were sterilized by washing the eggs for eight minutes in 0.05 percent sodium hypochlorite and placing them in a sterile container to hatch. Within 24-48 hours after hatching they were ready to place on wounds. The young, 2mm long maggots were covered with porous sterile dressings, and left in place for 48-72 hours "cycles". One or two cycles were applied each week. In between cycles of maggot therapy, patients received either sodium hypochlorite (if their wounds were still necrotic) or normal saline (if their wounds were relatively clean) wet-to-dry gauze dressings every eight hours. **Group 2:** The treatment with the	**Outcome 1:**average change in surface area per week	**Group 1:**-22% **Group 2:** 21.8% **Relative risk:** **95% CI:** **P value**:<0.001	**Funding:**this research was supported in part by grants from the spinal cord research foundation of the paralysed veterans of America (1990) and the California paralyzed veterans of America (1991) **Limitations:** • No blinding • No details about baseline differences • Low patient number **Additional outcomes:** Of the ulcers with a 20 percent or larger necrotic base, none were more than half debrided by the time maggot therapy was initiated. All such ulcers were completely debrided within one – two weeks (average 1.4 weeks) afterwards. No complications resulted from the maggot therapy

No details **Statistical analysis:** no details **Baseline differences:** no details **Study power/sample size:** no **Setting:** Primary care and hospital setting in CA **Length of study:** Patients were followed up for three-four weeks prior to Maggot therapy **Assessment of PUs:** Ulcers were evaluated visually and photographically every week. Ulcer length, width, circumference and surface area were calculated precisely from each digitized photographic image, using the Image Analyst Software package (Automatrix, Inc.). Rate of wound healing was calculated as the percent change in surface area per week. Wound quality (i.e. necrosis, drainage, purulence) was also	104 (75-171); HGb = 13.0 (9.6-15.3); albumin = 3.54 (3.0-4.1) Cigarette smokers 3/8 (37.5%) Ulcer location: Sacrum (n=2); lateral foot (n=2); ischium (n=1); trochanter (n=1); heel (n=1); other (n=1) Ulcer stage: II (n=2), III (n=3); IV (n=3) Initial surface area= 13.0 sq cm (4.8-29.96) Necrotic tissue (% of initial surface area): 0-25% (n=5) en 51-100% (n=3) **Group 2** **Completed N:** 8 **Inclusion criteria:**all pressure ulcers existed for at least one month before patients were enrolled in this study. **Exclusion criteria:**Patients with underlying osteomyelitis or acute cellulitis were	conventional therapy group was chosen by patients' primary care providers in order to eliminate any potential investigator bias. Conventional treatment modalities included thrice daily sterile normal saline (n=2), 0.5 percent sodium hypochlorite (1/4 Dakin's solution) (n=2) or povidone iodine dressing combined with surgical debridement as needed (n=2), topical antimicrobial ointment (n=1) and daily dressing with Adaptic (Johnson & Johnson) (n=1) Both groups: any interventions that both groups received e.g debridement		treatment. Neither infection nor discomfort was reported. Occasionally larvae escaped from the dressings, producing some anxiety among the nursing staff. This reaction was usually short-lived and always unwarranted. **Notes:**

recorded. **Multiple ulcers:** No details	excluded.

Table 29 – Sherman 2002

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: Sherman, 2002 **Title:** Maggot versus conservative debridement therapy for the treatment of pressure ulcers **Journal:** Wound repair and regeneration, 10 (4): 208-214. **Study type:** Cohort study **Sequence generation:** patients were monitored for at least 2 weeks while continuing to receive the treatments prescribed by their primary care provider or hospital's wound care team (conventional therapy). If the wound did not improve, and if	**Patient group:** Between 1990 and 1995, our service followed 103 patients with 145 pressure ulcers. Sixty-one ulcers in 50 patients received maggot therapy at some point during their monitored course; 84 ulcers in 70 patients did not receive maggot therapy. Seventeen patients had one pressure ulcer treated with MDT and a second ulcer not treated with MDT. Two additional patients received only conventional therapy for their pressure ulcer while receiving MDT for a wound other than a pressure ulcer. **All patients** **Randomised** **N:**103	**Group 1:** Maggot therapy was administered by applying disinfected fly larvae (Phaeniciasericata) to the wound at a density offive to eight per cm2. The skin surrounding the ulcer wascovered with a hydrocolloid pad (Duoderm, Convatec, Princeton, NJ) out of which was cut a hole to match theulcer dimensions. This ring of hydrocolloid prevented the maggots from crawling on the intact skin surrounding the wound, and prevented the necrotic wound drainagefrom coming in direct contact with the skin. It also provided a foundation to	**Outcome 1:** Change in surface area during treatment (cm²) **Outcome 2:** Change in surface area per week **Outcome 3:** Proportion of wounds which decreased in surface area within 4 weeks	**Outcome 1:** **Group 1:**-7.3 (-10.4 to -4.2) **Group 2:**6.3 (2.5-10.1) **Relative risk:** **95% CI:** **P value:** **Outcome 2:** **Group 1:**-1.5 (-2.3 to -0.7) **Group 2:**1.4 (0.5-2.3) **Relative risk:** **95% CI:** **P value:** **Outcome 3:** **Group 1:**34/43 79% (63-94) **Group 2:**22/49 44% (27-61) **Relative risk:** 1.76	**Funding:** This work was supported, in part, by grants from the Spinal Cord Research Foundation of the Paralyzed Veterans of America (1990), the California Paralyzed Veterans of America (1991), and the Andrus Foundation of the American Association of Retired Persons (1992–1995). **Limitations:** • No details about blinding • High drop-outs • Baseline differences between groups • Incorrect figures in article:

the patient and primary care team consented to treatment, then maggot therapy was initiated. **Blinding:** No blinding **Addressing incomplete outcome data:** Wounds wit complex nonplanar topography, wounds photographed without scale markers and wounds followed for less than 2 weeks were omitted from the analysis. All wounds that received maggots were considered as ‘‘maggot-treated,’’ even when the maggots died in the dressings or were removed accidentally by the nursing staff. **Statistical analysis:** Normally distributed ordinal and interval data were analyzed using the Student’s t-test or logistic regression when variance was equal, and Welch’s t-test when variance was not equal. Ordinal and interval data not normally	patients with pressure ulcers 145 **Completed patients with pressure ulcers N:**50 61 **Drop-outs:** 51 patients in this cohort did not receive maggot therapy for any wound for the following reasons: the patients’ doctors did not consent to maggot therapy (11 patients); the wounds improved during the baseline observation period on conventional therapy alone (8); the patients (2) or their decision-making surrogates (2) did not consent to therapy. Twenty-four patients were being followed in anticipation of administering maggot therapy, but they were discharged, died, or were lost to follow-up before they could be treated. (Limited resources prevented us from treating more than four or five patients with MDT atany one time, and the maggot therapy program was	which the maggot dressings could be affixed securely. A porous sheet of Dacron_chiffon or a nylon stockingwas glued to the hydrocolloid ring such thatit covered the wound, creating a ‘‘cage’’ with the maggotsinside. This cage-like dressing was then topped with a light gauze pad to absorb the necrotic drainage. The top layer of gauze was replaced every 4 to 8 hours because it was quickly soiled by the profuse wound drainage, but the cage-dressing and maggots remained over the wound forcycles of about 48 hours. Two 48-hour cycles were appliedeach week; saline- or 0.125% sodium hypochlorite-moistenedgauze dressings were applied during the 1 to 4 daysbetween MDT cycles.	**Outcome 4:** Healing rate at 4 weeks **Outcome 5:** Healing rate at 8 weeks **Outcome 6:** Proportion of wounds that completely healed	(1.25-2.49) **95% CI:** **P value:** **Outcome 4:** **Group 1:**0.101 (0.061-0.141) **Group 2:** -0.038 (-0.847 to -0.008) **Relative risk:** **95% CI:** **P value:** **Outcome 5:** **Group 1:**0.096 (0.057-0.135) **Group 2:**-0.027 (-0.074-0.021) **Relative risk:** **95% CI:** **P value:** **Outcome 6:** **Group 1:**17/43 **Group 2:**10/49 **Relative risk:** 1.94 (1-3,77) **95% CI:** **P value:** 0.058	confidence interval of healing rate at 4 weeks for control group; change in surface area per week differs between text and table. **Additional outcomes:** Two of the 50 maggot-treated patientscomplained of pain during MDT; both had previouslycomplained of pain during conventional treatments aswell. Maggot-related anxiety was described by one patienttreated withMDT and by one patientwho declined maggottherapy. None of the seven recorded deaths occurred inpatients receiving maggot therapy. Maggot-treated wounds were debrided more quicklyand completely than were conventionally treated wounds. Eighty percent of maggot-treated

distributed were evaluated using the Mann–Whitney U-test. Nominal data were analyzed using Pearson's chi-square test. Changes in tissue quality and surface area over time were evaluated using repeated measures analysis of variance (ANOVA). Paired t-tests were used to compare pre-MDT outcomes with MDT associated outcomes in the same patients. The hypothesis of equality of means was discarded when the probability (p) of a type I error was <=5%. Analyses were performed with SPSS statistical software (SPSS, Inc., Chicago, Illinois). **Baseline differences:** Ulcers were almost 60% larger in the maggottreated group (p = 0.035). Also, maggot-treated patients were more often diabetic and spinal cord injured, with ahigher average serum albumin.	terminated in 1996 with many patients still awaiting therapy.) No reason was documented for four patients. **Group 1** **Completed N:** 43 pressure ulcers **Age:**62 (26-85) **Other relevant patient characteristics:** • Wound age in weeks = 37 (5-207) • wound surface in cm²= 22.1 (15.7-28.4) • necrotic tissue as a % of total surface area= 31% (21-41) • granulation tissue as a % of total surface area= 27% (16-38) • depth o Subcutaneous = 14 (33%) o Intramuscular = 11 (25%) o Down to bone = 15 (35%) o Into bone =3 (7%) • Anatomic locations o Foot and ankle =	**Group 2:**patients were monitored for at least 2 weeks while continuing to receive the treatment prescribed by their primary care provider or the hospital's wound care team. Conventional treatments included topical antimicrobial therapy (35%); acemannan and hydrogels (10%); chemical debriding agents (8%); saline-moistened or ''wet-to-dry'' dressings (8%); hydrocolloids and calcium alginates (6%); growth factors (4%); and multiple combinations of nonsurgical treatments (12%). Almost 17% of the conventionally treated group received bedside or intraoperative surgical debridement.	**Outcome 7:** Average time until wounds completely healed (weeks) **Outcome 8:** Proportion of wounds decreased during treatment	**Outcome 7:** **Group 1:**12.0 (7-17) **Group 2:**13.4 (8-19) **Relative risk:** **95% CI:** **P value:** **Outcome 8:** **Group 1:**36/43 84% **Group 2:**18/49 37% **Relative risk:** 2.28 (1.54-3.37) **95% CI:** **P value:**0.001	wounds were completely debrided in less than 5 weeks, while most (52%) non-maggot-treated wounds were stillnot completely debrided after 5.5 weeks of therapy(p = 0.021). Analysis of variance indicated no significant change in necrotic tissue for the conventionally treated wounds. Maggot treated wounds, however, were associatedwith a significant decrease in necrotic tissue (F [1.5, 49.1] = 15.02, p < 0.001), with an average decrease of3.7 cm² necrotic tissue within the first 2 weeks (p < 0.001). Maggot therapywas also associated with rapid growthof granulation tissue and rapid conversion of necrotic andstatic ulcers to a healthy wound bed which could appropriately be grafted or surgically closed. The averagemaggot-treated wound was not only debrided, but

Otherwise, there were nosignificant differences between the two treatment groups. **Study power/sample size:** No details **Setting:** Primary care setting and hospital care, California **Length of study:** Wounds were first followed for 2 to 8 weeks (average 4.8 weeks) while still receiving conventional therapy. Then the wounds were treated for 2 weeks or more (average 5.2 weeks) with maggot therapy. **Assessment of PUs:** Ulcer length, width, circumference, and surface area were calculated from digitized wound images and tracings,using the Image Analyst software package (Automatrix, Inc., Billerica, MA) or Mocha (Jandell Scientific, San Rafael, CA). Patient	11(25%) o Leg, knee, thigh = 5 (12%) o Sacrum, ischium, trochanter = 25 (58%) o Other = 2 (5%) • Underlying medical conditions o Spinal cord injury, paraplegia = 44% o Diabetes = 37% o Peripheral venous or arterial disease = 24% o Cerebral vascular accident = 24% o Incontinence of bowel and /or bladder = 83% o Cigarette smoker = 29% o % ideal body weight (range)= 101% (65-179) o Albumin (g/dl)= 3.3 o Hemoglobin (g/dl)=11.1 **Group 2** **Completed N:** 49 pressure ulcers **Age:**66 (32-91) Other relevant patient characteristics: • Wound age in		covered60% by healthy granulation tissue within 3 weeks. Twice as many maggot-treated wounds were over 50% covered by healthy granulation tissue during the course of treatment (49% vs. 18%, p = 0.002). Analysis of variance (with granulation tissue as the within-subjects factor)indicated no significant change in granulation tissue for the conventionally treated wounds. Maggot treated wounds,however, were associated with a rapid spread of granulation tissue (F [1.89, 56.6] = 25.5, p < 0.001), where 25% ofthe wound surface was covered by new granulation tissue within the first 2 weeks of therapy (p < 0.001). No single factor was associated with successful debridement except treatment with maggot therapy (Pearson's chi-square [8.380; 1], p = 0.004). Among the maggottreated patients,

and wound histories were collecteddirectly from patients or their medical records. The wound healing rate, based on studies by Gilman (1990) and Margolis et al., (1993) was defined as the change in surface area divided by the mean circumference over time. **Multiple ulcers:** Quantification of debridement and wound healing was evaluated for the first two ulcers per patient, where those ulcers could be measured reliably from photographs or tracings.	weeks = 34 (4-208) • wound surface in cm²= 14.0 (9.7-18.2) • necrotic tissue as a % of total surface area= 34% (23-45) • granulation tissue as a % of total surface area= 31% (19-42) • depth o Subcutaneous = 28 (57%) o Intramuscular = 17 (35%) o Down to bone = 4 (8%) o Into bone = 0 • Anatomic locations o Foot and ankle = 10 (21%) o Leg, knee, thigh = 3 (6%) o Sacrum, ischium, trochanter = 34 (69%) o Other = 2 (4%) • Underlying medical conditions o Spinal cord injury, paraplegia = 19% o Diabetes = 17% o Peripheral venous or arterial disease = 15% o Cerebral vascular accident = 32%		failure to achieve adequate debridement(that is, failure ofMDTto debride at least 95% of thewoundbase) was not associated with wound size, patient age,nutritional status, diabetes, or cigarette smoking. The amount of necrotic tissue at the beginning ofconventional and maggot therapy was equal (5.6 cm² and 5.4 cm², respectively); but by the end of therapy, conventional therapy had debrided very little necrotic tissue (1.0 cm²) compared to MDT (4.2 cm² necrotic tissuedebrided; p = 0.003). Patient willingness to undergo maggot therapy wasassessed by evaluating consent data. All of the 50 patientstreated with MDT gave written consent. Of the 53 patientsin this cohort who received no maggot therapy, 19 gavewritten or verbal consent, 4 declined

	o Incontinence of bowel and /or +bladder = 87% o Cigarette smoker = 26% o % ideal body weight (range)= 90% (50-162) o Albumin (g/dl)= 2.9 o Hemoglobin (g/dl)=11.0 **Inclusion criteria:** Patients with non-healing wounds **Exclusion criteria:** Patients with underlying osteomyelitis or rapidly advancing infection in need of urgent surgical resection.				therapy, and 30 were not asked. Thus, only 4 (5%) of 73 patients or theirconservators declined maggot therapy. Twenty of thequestioned patients were unable to give informed consent, so consent was solicited from next of kin or the patients' conservators. Two (10%) of these surrogate decision makers did not consent to maggot therapy. In contrast,only 2 (4%) of the 53 patients whowere themselves capableof giving informed consent declined therapy. **Notes:**

Table 30 – Wang 2010

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: Wang, 2010 **Title:** Clinical research on the	**Patient group:** Patients with pressure ulcers after spinal cord injury treated in the	**Group 1:** Eggs were collected from the eyes of scomberomorusniphonius	**Outcome 1:** Time to wound healing (days)	**Group 1:**18.7 +-10.4 **Group 2:**30.6 +-12.2 **Relative risk:** **95% CI:**	**Funding:**The present study was supported by grants from the National Natural Science

bio-debridement effect of maggot therapy for treatment of chronically infected lesions. **Journal:** Orthopaedic surgery, 2 (3): 201-206 **Study type:** A retrospective study **Sequence generation:** Patients who were agreeable to maggot therapy, received it, and were accordingly allocated to the study group. Patients who were not agreeable to maggot therapy were treated by a traditional dressing method, and were accordingly allocated to the control group. **Blinding:** No blinding **Addressing incomplete outcome data:** No details **Statistical analysis:** all the presented data were expressed as mean +- SD and their statistical significance analysed by	hospital **All patients** **Randomised N:**/ **Completed N:**18 **Drop-outs:**/ **Group 1** **Randomised N:**/ **Completed N:**10 **Dropouts:**/ **Age:**48.4 +-4.9 (34-53) **Gender (m/f):** 7/3 **Other relevant patient characteristics:** Wound area (cm²)=28.3 +-5.5 (9-45) Infective bacteria Staphylococcus aureus (n=7); pseudomonas aeruginosa (n=3) **Group 2** **Randomised N:**/ **Completed N:**8 **Dropouts:**/ **Age:**47.4+-4.9 (34-53) **Gender (m/f):** 5/3 **Other relevant patient characteristics:** Wound area (cm²)=27.6	and disinfected in 1% sodium sulfite solution for 3 min, and subsequently in 3% Lysol brand disinfectant for 5 min. The disinfected eggs were then transferred to sterile vials to clone. Third stage larvae of Luciliasericata were selected to be placed in 3.5% formalin for 5 min, 2% hydrogen peroxide solution for 3 min and then 5% dilute hydrochloric acid solution for 5 min. After the two-step disinfection, the larvae remined vigorous. A hundred randomly selected larvae were proven to be aseptic by bacterial culture test. After two-step disinfection, disinfected larvae were applied to the lesion. In case where the lesion was dry, gauze soaked in hypertonic saline was placed on it in order to keep it moist and accommodate the larvae's preferences. The skin around the lesion was covered with sterile saline gauze with a hole cut in the middle to match	**P value:**0.039	Foundation of China **Limitations:** • Selection bias: patients chose intervention • No blinding • **Additional outcomes:** The time taken to achieve bacterial negativity, granulation and wound healing in the maggot therapy group was significantly shorter than in the control group (p<0.05). **Notes:**

independent sample t-test using SPSS 12.0 software. A p-value of less than 0.05 was considered to be statistically significant. **Baseline differences:** No significant differences. **Study power/sample size:** No details **Setting:** Hospital, China **Length of study:** All patients were followed up for 2 to 6 months (mean 3.5 months). **Assessment of PUs:** No details **Multiple ulcers:** No details	+-5.2 (7-42) Infective bacteria Staphylococcus aureus (n=5); pseudomonas aeruginosa (n=3) **Inclusion criteria:** Before treatment, all the lesions were evaluated by four experienced orthopedic surgeons to make sure they could be treated with either maggot therapy or a traditional dressing method. **Exclusion criteria:** • Symptoms of systemic infections • Positive blood bacterial cultures • Gangrene in the area of the local lesion.	its dimensions. The larvae were placed on the lesion through the hole at a density of five to ten per cm² and the number of larvae delivered was recorded. Then a disinfected nylon cage which was slightly larger than the gauze and lesion was fixed to the skin surrounding the wound by medical adhesive. Finally the cage was lightly covered with a gauze wrap to absorb the draining exudates without obstructing the flow of air. Every day the dressing and larvae were changed, the lesions checked and the number of larvae documented. This procedure was continued until the lesions had healed. **Group 2:** A dressing was applied daily with normal saline only and if necessary surgical debridement was performed. Both groups: The exudates from the lesions in both groups	

	were cultured every time. Other ancillary measures for ulcers were the same in both groups. No systemic antibiotics were used for the duration of treatment. In the pressure ulcers patients, a soft pad was inserted between the patient's back and the bed to make a local depression.	

4. TOPICAL AGENTS

4.1. Review protocol

Table 31 – Review protocol topical agents

Protocol	Topical agents
Protocol	**Topical agents**
Review question	What are the most clinically effective topical agents for the treatment of pressure ulcers?
Population	Individuals of all ages, with at least one pressure ulcer of any category/stage
Intervention	Topical agents (cleansers, moisturizers, protective agents, antiseptic agents, antibiotics, anti-inflammatory agents, anti-fungal agents)
Comparison	• No topical agent • Comparison between topical agents • Placebo • Other type of therapy for pressure ulcer treatment
Outcomes	**Critical outcome for decision-making** • Time to complete healing (time to event data) • Rate of healing (continuous data) • Rate of reduction in size and volume of pressure ulcer (absolute and relative) (continuous data) • Reduction in size and volume of pressure ulcer (absolute and relative) (continuous data) • Proportion of patients completely healed within trial period (dichotomous) **Important outcomes** • Wound related pain • Health-related quality of life o Short-form health survey (SF36) o Manchester Short Assessment of Quality of Life o EQ-5D o WHOQOL-BREF

	○ Cardiff HRQoL tool ○ HUI ○ Pressure ulcer quality of life (Gorecki) • Acceptability of treatment (e.g. compliance, tolerance) • Time in hospital (continuous data) • Side effects (infection, health skin damage, healthy tissue damage, maceration, treatment related pain, skin irritation, allergic reaction, itching, odour, bleeding, rash, toxicity.
Study design	• High quality systematic reviews of RCT's or RCT's only. • Cochrane reviews will be included if they match the inclusion criteria and have appropriate assumptions for missing data such as available case analysis or ITT (with the appropriate assumptions) • Cohort studies will be considered if no RCTs are available.
Exclusion	• Studies with another population, intervention, comparison or outcome • Non-English, non-French, non-Dutch language papers
Search strategy	**The electronic databases to be searched are:** • Medline (OVID interface), Cinahl (EBSCO-interface), Embase, Library of the Cochrane Collaboration • All years • Search strategy see Appendix I
Review strategy	**How will individual PICO characteristics be combined across studies)** • Population – any population will be combined except those specified in the strata. Must have active pressure ulcers at time of enrolment. • Intervention – any type of topical agent will be combined for meta-analysis. • Comparison – any comparison which fits the inclusion criteria will be meta-analysed • Outcomes – same outcomes will be combined for meta-analysis. • Blinding – Blinded and unblinded studies will be meta-analysed together. • Unit of analysis – patients, individual pressure ulcers • Minimum follow up = no minimum. • Minimum total size = no minimum • Use authors data. If there is a 10% differential or higher between the groups or if the missing data is higher than the event rate downgrade on risk of bias. If authors use ACA and ITT, ACA is preferable over ITT. • MIDs: 0.75 to 1.25 for dichotomous variables and 0.5 x standard deviation for continuous variables.

Analysis	**The following groups will be considered separately if data are present:** • ICU patients, spinal cord patients, palliative patients, paediatric patients and adults (if not in other subgroup); **Subgroups:** The following groups will be considered separately as subgroups if data are present: • Different categories of pressure ulcers (from category 2 upwards where outcomes are reported separately) • Different locations of pressure ulcers: sacral, heel and others

4.2. Search strategy

4.2.1. Search filters

Table 32 – Search filters in OVID Medline

Search strategy	Topical agents	Results
Date	12/11/2012	
Database	Medline-Ovid	
Search strategy	1. Pressure Ulcer/	9271
	2. Decubit*.ti,ab	4048
	3. (pressure adj (sore* or ulcer* or damage)).ti,ab	6394
	4. (bedsore* or bed-sore*).ti,ab	521
	5. ((friction or shear) adj2 (sore* or ulcer* or damage or wound* or inju* or lesion*)).ti,ab	259
	6. OR/1 – 5	13757
	7. Topic$ agent$.tw	1401
	8. Topic$ preparation$.tw	587
	9. Topic$ therap$.tw	2279
	10. Topic$ treatment$.tw	4769
	11. Wound$ cleans$.tw	195
	12. Wound$ irrigation.tw	241
	13. Wound$ solution$.tw	4
	14. Exp Administration, topical/	63290
	15. past$.tw	236689
	16. salve$.tw	1147
	17. cream$.tw	12404
	18. unguent$.tw	89

Search strategy	Topical agents	Results
	19. balm$.tw	475
	20. unction$.tw	27
	21. emollient/	1248
	22. emollient$.tw	990
	23. exp ointments/	10717
	24. ointment$.tw	8863
	25. barrier$.tw	141583
	26. no-sting barrier$.tw	12
	27. exp sodium chloride/	51417
	28. exp sodium hypochlorite/	3219
	29. exp anti-infective agents/	1197744
	30. exp saline solution, hypertonic/	4623
	31. exp iodophors/	2472
	32. exp chlorhexidine/	5669
	33. exp detergents/	27407
	34. exp hydrogen peroxide/	39401
	35. exp benzoyl peroxide/	881
	36. exp gentian violet/	1747
	37. exp alcohols/	533156
	38. exp solutions/	101262
	39. exp hydrotherapy/	16776
	40. exp baths	3992
	41. (normal saline or hypochlorite$ or iodophor$ or Povidone or iodine or chlorhexidine or hibitane or betadine or antiseptic$ or disinfectant$ or detergent$ or soap$ or hydrogen peroxide or benzoyl peroxide or gentian violet or eusol or dakin$ or permanganate or water or alcohol$ or solution$).mp	1121992
	42. (wash$ or scrub$ or swab$ or shower$ or bath$ or soak$ or irrigate$ or whirlpool).mp	168120
	43. OR/7 – 42	3091895
	44. randomized controlled trial.pt.	341981
	45. controlled clinical trial.pt.	85650
	46. randomi#ed.tw.	308554
	47. placebo.ab.	141394
	48. randomly.tw.	187724
	49. trial.ti	110775
	50. Clinical Trials as topic.sh.	163571
	51. OR/44 – 50	837678
	52. AND/6, 43, 51	228

Search strategy	Topical agents	Results
	53. Limit language: 'English, Dutch, Flemish, French'	212
Notes		

Table 33 – Search filters in Embase

Search strategy	Topical agents	Results
Date	12/11/2012	
Database	Embase-OVID	
Search strategy	1. 'decubitus'/exp	16116
	2. Decubit*:ab,ti	5533
	3. (pressure NEAR/1 (sore* or ulcer* or damage)):ab,ti	4967
	4. (bed NEAR/2 sore*):ab,ti or bedsore*:ab,ti	743
	5. ((friction or shear) NEAR/2 (sore* or ulcer* or damage or wound* or injur* or lesion*)):ab,ti	313
	6. OR/1 – 5	17723
	7. 'topical agent'/exp	2637
	8. 'Topic* near/1 agent*':ti,ab	1961
	9. 'Topic* near/1 preparation*':ti,ab	947
	10. 'Topic* near/1 therap*':ti,ab	3439
	11. 'Topical treatment'/exp	8092
	12. 'Topic* near/1 treatment*':ti,ab	6995
	13. 'Wound* near/1 cleans*':ti,ab	250
	14. 'wound irrigation'/exp	1288
	15. 'Wound* near/1 irrigation':ti,ab	266
	16. 'Wound* near/1 solution*':ti,ab	10
	17. 'Paste'/exp	7739
	18. 'past*':ti,ab	291379
	19. 'salve'/exp	536
	20. 'salve*':ti,ab	1442
	21. 'cream'/exp	18911
	22. 'cream*':ti,ab	17653
	23. 'unguent*':ti,ab	264
	24. 'balm*':ti,ab	629
	25. 'unction*':ti,ab	150
	26. 'emollient agent'/exp	3276

Search strategy	Topical agents	Results
	27. 'emollient*':ti,ab	1574
	28. 'ointments'/exp	12578
	29. 'ointment*':ti,ab	12881
	30. 'barrier*':ti,ab	163841
	31. 'no-sting barrier*':ti,ab	20
	32. sodium chloride/exp	115886
	33. anti-infective agents/exp	2039622
	34. detergent/exp	15172
	35. soap/exp	3187
	36. water/exp	255865
	37. alcohol/exp	169262
	38. solution and solubility/exp	155363
	39. wound irrigation/exp	1174
	40. bath/exp	6477
	41. hydrotherapy/exp	3379
	42. (normal saline or hypochlorite$ or iodophor$ or Povidone or iodine or chlorhexidine or hibitane or betadine or antiseptic$ or disinfectant$ or detergent$ or soap$ or hydrogen peroxide or benzoyl peroxide or gentian violet or eusol or dakin$ or permanganate or water or alcohol$ or solution$):ti,ab	895842
	43. (wash$ or scrub$ or swab$ or shower$ or bath$ or soak$ or irrigate$ or whirlpool).ti,ab	54784
	44. OR/7 – 43	3640506
	45. 'clinical trial'/exp	1055206
	46. 'clinical trial (as topic)'/exp	48856
	47. random*:ti,ab	767572
	48. factorial*:ti,ab	20214
	49. (crossover* or cross over*):ti,ab	122670
	50. ((doubl* or singl*) adj blind*):ti,ab	13
	51. (assign* or allocat* or volunteer* or placebo*):ti,ab	592083
	52. 'crossover procedure'/exp	35675
	53. 'single blind procedure'/exp	16044
	54. 'double blind procedure'/exp	111427
	55. OR/45 – 54	1917209
	56. AND/7, 44, 55	517
	57. Limit language: 'English, Dutch, French'	456
Notes		

Table 34 – Search filters in CINAHL

Search strategy	Topical agents	Results
Date	12/11/2012	
Database	CINAHL	
Search strategy	26. MH “Pressure Ulcer”	7865
	27. Bedsore* or bed-sore*	159
	28. Pressure n1 sore* or pressure n1 ulcer* or pressure n1 damage*	8648
	29. Decubit*	486
	30. ((friction or shear) and (sore* or ulcer* or damage or wound* or injur* or lesion*))	814
	31. OR/1 – 5	9511
	32. MH “administration, topical+”	6311
	33. “Topic* agent*”	231
	34. “Topic* preparation*”	62
	35. “Topic* therap*”	508
	36. “Topic* treatment*”	320
	37. “Wound* cleans*”	133
	38. “Wound* irrigation*”	56
	39. “Wound* solution*”	1
	40. “past*”	31852
	41. “salve*”	38
	42. “cream*”	2290
	43. “unguent*”	2
	44. “balm*”	147
	45. “unction*”	22
	46. “MH “emollients+”	813
	47. “emollient*”	713
	48. MH “ointments”	851
	49. “barrier*”	27059
	50. “no-sting barrier*”	15
	51. MH “sodium chloride”	1180
	52. MH “sodium hypochlorite”	295
	53. MH “saline solution, hypertonic”	366
	54. MH “antiinfective agents+”	51273
	55. MH “Povidone-iodine”	368
	56. MH “detergents+”	755
	57. MH ‘soaps”	519

Search strategy	Topical agents	Results
	58. MH “hydrogen peroxide”	616
	59. MH “gentian violet”	61
	60. MH “water+”	3190
	61. MH “alcohols+”	13623
	62. MH “solutions+”	5064
	63. MH “irrigation”	1821
	64. MH “bathing and baths”	1516
	65. (normal saline or hypochlorite* or iodophor* or povidone or iodine or chlorhexidine or hibitane or betadine or antiseptic* or disinfectant* or detergent* or soap* or hydrogen peroxide or benzoyl peroxide or gentian violet or eusol or dakin* or permanganate or water or alcohol* or solution*)	45411
	66. (wash* or scrub* or swab* or shower* or bath* or soak* or irrigate* or whirlpool)	20199
	67. OR/7 – 41	184806
	68. MH "Clinical Trials+"	109448
	69. “trial*”	140517
	70. “randomi#ed”	68152
	71. “randomly”	25686
	72. “randomized controlled trial”	9331
	73. PT “randomized controlled trial”	11971
	74. PT “clinical trial”	51706
	75. OR/43 - 49	171882
	76. AND/6, 42, 50	124
	77. Limit language=’English, Dutch, French’	120
Notes		

Table 35 – Search filters in Cochrane

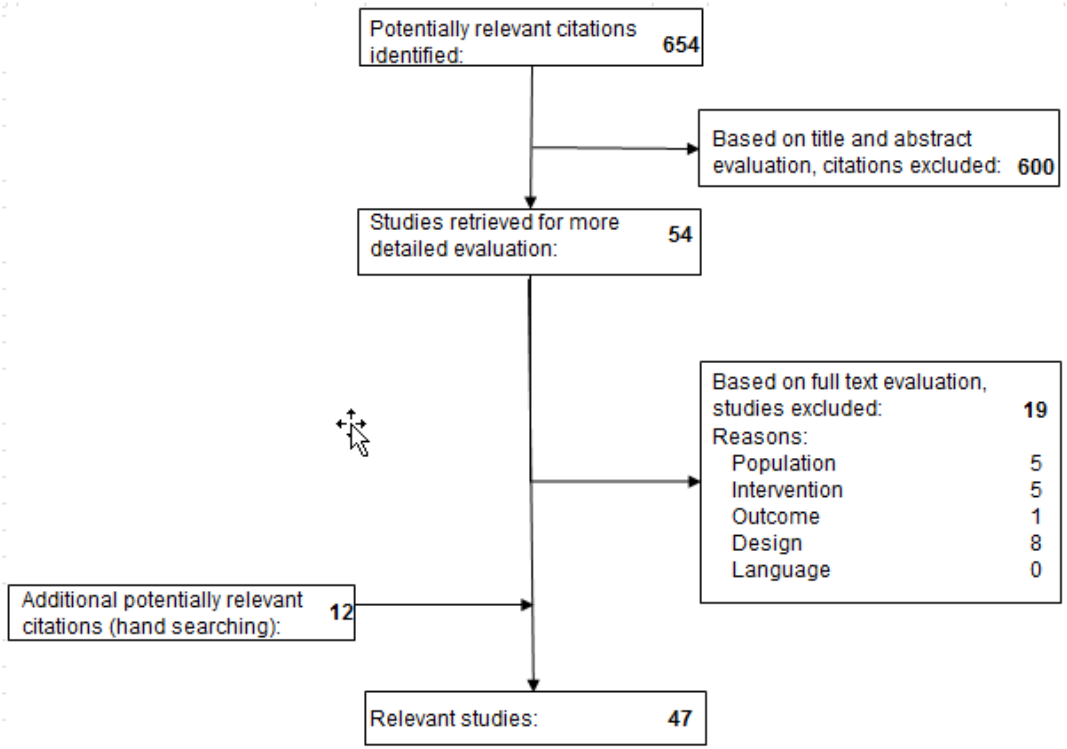
Search strategy	Topical agents	Results
Date	12/11/2012	
Database	Cochrane (- CDSR [3/2012]; DARE; Central [3/2012]; NHS EED; HTA)	
Search strategy	1. “Pressure ulcer”[MeSH]	490
	2. Decubit*:ti,ab,kw	353
	3. (pressure near/2 (sore* or ulcer* or damage*)):ti,ab,kw	870
	4. (bedsore* or bed-sore*):ti,ab,kw	34
	5. ((friction or shear) near/2 (sore* or ulcer* or damage or wound* or injur* or lesion*)):ti,ab,kw	3

Search strategy	Topical agents	Results
	6. OR/1 – 5	1153
	7. (Topic* agent*):ti,ab,kw	19815
	8. (Topic* preparation*):ti,ab,kw	3426
	9. (Topic* therap*):ti,ab,kw	25567
	10. (Topic* treatment*):ti,ab,kw	40009
	11. (Wound* cleans*):ti,ab,kw	114
	12. (Wound* irrigation*):ti,ab,kw	244
	13. (Wound* solution*):ti,ab,kw	632
	14. "Administration, topical"[MeSH]	11735
	15. (past*):ti,ab,kw	4472
	16. (salve*):ti,ab,kw	8
	17. (cream*):ti,ab,kw	4008
	18. (unguent*):ti,ab,kw	28
	19. (balm*):ti,ab,kw	28
	20. (unction*):ti,ab,kw	3
	21. "emollients"[MeSH]	258
	22. (emollient*):ti,ab,kw	439
	23. "ointments"[MeSH]	1583
	24. (ointment*):ti,ab,kw	3109
	25. (barrier*):ti,ab,kw	3799
	26. (no-sting barrier*):ti,ab,kw	11
	27. "sodium chloride" [MeSH]	1895
	28. "sodium hypochlorite" [MeSH]	253
	29. "Saline solution, hypertonic" [MeSH]	347
	30. "Iodophors" [MeSH]	406
	31. "chlorhexidine"[MeSH]	1194
	32. "anti-infective agents" [MeSH]	20582
	33. "disinfectants"[MeSH]	456
	34. "detergents"[MeSH]	276
	35. "Soaps"[MeSH]	162
	36. "Hydrogen peroxide"[MeSH]	354
	37. "Benzoyl violet"[MeSH]	140
	38. "Water"[]MeSH]	30
	39. "Alcohols"[MeSH]	1520
	40. "Solutions"[MeSH]	28025
	41. "Baths"[MeSH]	5441

Search strategy	Topical agents	Results
	42. "Hydrotherapy"[MeSH]	232
	43. (normal saline or hypochlorite* or iodophor* or povidone or iodine or chlorhexidine or hibitane or betadine or antiseptic* or disinfectant* or detergent* or soap* or hydrogen peroxide or benzoyl peroxide or gentian violet or eusol or dakin* or permanganate or water or alcohol* or solution*)	34901
	44. (wash* or scrub* or swab* or shower* or bath* or soak* or irrigate* or whirlpool)	14210
	45. OR/7 – 44	145052
	46. "Clinical Trial" [publication type]	335463
	47. "Randomized Controlled Trial" [publication type]	314204
	48. "clinical trial" as topic	51645
	49. (trial):ti,ab,kw	349494
	50. (randomi#ed):ti,ab,kw	1
	51. (randomly):ti,ab,kw	862222
	52. (group):ti,ab,kw	274705
	53. OR/46 – 52	519638
	54. AND/6, 45, 53	250
Notes		

4.2.2. Selection of articles

Figure 33 – Flow chart topical agents



4.2.3. Excluded clinical studies

Table 36 – Excluded studies topical agents

Reference	Reason of exclusion
No author - Does metronidazole help leg ulcers and pressure sores?	No original study
Baker 1981	No RCT
Burke 1998	Hydrotherapy
Cutler 1994	No original study
Dealey 1995	Not treatment
Flock 2003	Study on analgesic
Gerber 1979	No outcome of interest
Griffiths 2001	PU not reported separately
Gray 2004	Incontinence associated dermatitis
Ho 2012	Hydrotherapy
Janssens 1989	PU not reported separately
Konya 2005	No RCT
Le Vasseur 1991	No RCT
Maas-Irslinger 2003	No original data
Naviau 1964	No RCT
Prentice 2004	No PU
Romanelli 2008	PU not reported separately
Saji 1995	No RCT
Tytgat 1988	PU not reported separately
Zeppetella 2003	Study on analgesic

4.3. Clinical evidence

A Cochrane review on wound cleansing for pressure ulcer by Moore and Cowan (2011)[44] and a meta-analysis[45] on traditional Chinese medicine were identified and used as reference for this review. The Cochrane review by Moore and Cowan (2011) [44] included three RCT's[46-48], of which two were excluded because they didn't meet the inclusion criteria of our review. One was excluded as it was a study on hydrotherapy[47] and will therefore be included in the debridement review. The other study did not separately reported on outcomes for patients with pressure ulcers.[48] The meta-analysis by Zhang et al. (2012) [45] included 10 RCT's, which were all included in this review.[49-58] Forty-seven randomized controlled trials were included in this review[46, 49-91]. The authors of the review on traditional Chinese medicine[45] meta-analysed different types of Chinese ointments (intervention) with different types of comparisons such as iodophor and saline. In this review only studies with the same intervention and outcome were meta-analysed together and therefore results will be presented differently from the review of Zhang et al. (2012). [45]

4.3.1. Summary of included studies

Table 37 – Summary included studies - topical agents

Study	Intervention/comparator	Population	Outcome	Study length
Agren 1985[59]	Zinc oxide Streptokinase-streptodornase ointment	Geriatric patients with necrotic PUs	Reduction in ulcer area Side effects	Eight weeks of treatment
Alm 1989[60]	Saline Hydrocolloid	Long-term care patients with PUs	Reduction in ulcer area Side effects	Six weeks of treatment and additional 3 and 6 weeks of follow-up
Bao 2006[49]	JiFu FuYuan ointment Gentamicin 80 000 U	Patients with stage II to IV PUs	Proportion of patients completely healed Proportion of patients improved Proportion of patients not changed or worsened	14 days of treatment
Bellingeri 2004[46]	Aloe vera, silver chloride and decyl glucoside Saline	Elderly home care patients with a grade II to IV PU (NPUAP classification)	Reduction in PSST score	14 days of treatment
Chang 1998[61]	Saline	Inpatients with a stage II or III	Reduction in ulcer area	Eight weeks of treatment or

	Hydrocolloid	PU	Side effects	until complete healing
Chuansuwanich 2011[92]	Silver sulfadiazine cream Silver dressing	In- and outpatients with a stage III or IV PU (NPUAP classification)	Rate of healing Reduction in PUSH score Side effects	Eight weeks of treatment
Chen 2008[50]	ShenJuYuHong ointment 0.9% NaCl	Patients with stage III and IV PUs	Proportion of patients completely healed Proportion of patients improved Proportion of patients not changed or worsened	Not reported
Gerding 1992[62]	Oxyquinoline A&D® -Petrolatum based ointment	Palliative care patients with a stage II or III PU (NPUAP classification)	Proportion of ulcers completely healed Proportion of ulcers improved Proportion of ulcers not changed Proportion of ulcers worsened Healing rate	28 days of treatment or until complete healing
Günes 2007[63]	Ethoxydiaminoacridine plus nitrofurazone Honey	Hospitalized patients older than 18 years with a stage II or III PU (AHCPR classification)	Proportion of ulcers completely healed Reduction in PUSH score Reduction in ulcer size Side effects	Five weeks of treatment or until complete healing

Hirshberg 2003[64]	Growth factors Placebo	Inpatients with a stage III or IV PU (NPUAP classification)	Proportion of ulcers completely healed Reduction in ulcer area Reduction in ulcer volume	16 weeks or until complete healing
Hollisaz 2004[65]	Phenytoin cream Saline Hydrocolloid	Patients with a spinal cord injury and a stage I or II PU (NPUAP or Shea classification)	Proportion of ulcers completely healed Proportion of ulcers improved Proportion of ulcers worsened Proportion of patients completely healed	Eight weeks of treatment
Jing 2005[51]	FuFangDahuang ding Chloramphenicol and sulfadiazine silver powder	Not reported	Proportion of patients completely healed Proportion of patients improved Proportion of patients not changed or worsened	Mean duration of 27.2 days (G1) and 56.5 days (G2)
Kaya 2005[66]	Povidone-iodine Hydrogel	Hospitalized patients with a spinal cord injury and a grade I to III PU (NPUAP classification)	Healing rate	Not reported
Kim 1996[67]	Povidone Hydrocolloid	Patients with a stage I or II PU (NPUAP classification)	Proportion of patients completely healed Healing rate Healing speed	Mean duration of 18.9 days and 24.3 in group 1 and 2 respectively

			Side effects	
Knudsen 1982[68]	Dialysate Placebo	Patients with a spinal cord injury and a PU	Decrease in ulcer size Healing half-time Side effects	Three weeks of treatment
Kraft 1993[69]	Saline Foam dressing	Male veterans with a stage II or III PU (Enterstomal Therapy definition)	Proportion of patients completely healed	24 days of treatment
Kucan 1981[70]	5. Povidone-iodine 6. Silver sulfazidine cream	Hospitalized patients with an infected PU	Proportion of patient clinically responding Bacterial levels	Three weeks of treatment or until the ulcer was deemed microbiologically clean, clinically ready for closure or the medical regimen was considered a failure
Kuflik 2001[71]	Ointment (Resurflix®) Petrolatum	Elderly patients with a stage I or II PU (AHCPR classification)	Proportion of ulcers completely healed Proportion of ulcers improved Proportion of ulcers not changed Proportion of ulcers worsened	Six weeks of treatment
Landi 2003[72]	Nerve growth factor Placebo	Nursing home patients with a stage II to V foot PU (Yarkony classification)	Proportion of patients completely healed Proportion of patients improved in PU stage Reduction in ulcer area Side effects	Six weeks of treatment or until complete healing

Ljungberg 2009[73]	Saline Dextranomer	Male patients with a spinal cord injury and exudative PUs (Eltorai classification)	Proportion of ulcers improved Side effects	14 days of treatment
Li 2007A[53]	RuYiZhuHuang ointment Iodophor	Patients with a stage III PUs	Proportion of patients completely healed Proportion of patients improved Proportion of patients not changed or worsened	Mean duration of 14.5 days (G1) and 26.6 days (G2)
Li 2007B[54]	RuYiZhuHuang ointment Iodophor + antibacterial	Patients with a stage IV PUs	Proportion of patients completely healed Proportion of patients improved Proportion of patients not changed or worsened	Mean duration of 36.9 days (G1) and 71.2 days (G2)
Li 2008[52]	SanHuanfZhang Yu Yousha Nitrofurazone	Not reported	Proportion of patients completely healed Proportion of patients improved Proportion of patients not changed or worsened	Duration between 7 and 660 days
Luo 1998[55]	RuYiZhuHuang ointment Iodophor	Patients with a stage I and III	Proportion of patients completely healed Proportion of patients improved Proportion of patients not changed or worsened	Mean duration of 3.4 days (G1) and 8.2 days (G2)

Matzen 1999[74]	Saline Hydrocolloid dressing	Patients with a stage III or IV PU (Lowthian classification)	Proportion of patients completely healed Reduction in ulcer volume Side effects	12 weeks of treatment or until complete healing
Moberg 1983[75]	Iodine Standard treatment	Hospitalized patients with an deep or superficial PU	Proportion of ulcers reduced with 50% Reduction in ulcer area	Three weeks of treatment
Mustoe 1994[76]	Growth factors Placebo	Patients with a stage III or IV PU	Proportion of patients completely healed Ulcer volume	29 days of treatment and up to five months of follow-up
Neill 1989[77]	Saline Hydrocolloid dressing	Patients with a grade II or III PU (Shea classification)	Proportion of ulcers completely healed Proportion of patients worsened Reduction in ulcer area Side effects	Eight weeks of treatment
Oleske 1986[78]	Saline Polyurethane dressing	Inpatients with a stage I or II PU (Enis and Sarmiento classification)	Proportion of ulcers completely healed Proportion of ulcers worsened Reduction in ulcer area	10 days of treatment
Payne 2001[79]	Growth factors Placebo	Inpatients with a grade III or IV PU	Proportion of patients completely healed Proportion of patients worsened	35 days of treatment and 1 year of follow-up

Payne 2009[80]	Saline Foam dressing	Patients with a stage II PU (NPUAP classification)	Proportion of patients completely healed Time to healing	Four weeks of treatment or until complete healing
Rees 1999[81]	Growth factor Placebo	Patients with a stage III or IV PU (NPUAP classification)	Proportion of patients completely healed Proportion of patients healed ≥ 90% Reduction in ulcer volume Side effects	16 weeks of treatment or until complete healing
Rhodes 2001[82]	Phenytoin Triple antibiotics Hydrocolloid	Nursing home patients with a stage II PU (AHCPR classification)	Healing time Side effects Pain	Not reported
Robson 1992a[85]	Growth factors Placebo	Inpatients with denervated ulcers and a grade III or IV PU	Proportion of patients healed > 70% Reduction in ulcer volume	30 days of treatment and 5 months of follow-up
Robson 1992b[93]	Growth factors Placebo	Inpatients with denervated ulcers and a grade III or IV PU	Proportion of patients completely healed Reduction in ulcer depth Side effects	Four weeks of treatment and five months of follow-up
Robson 1994[83]	Growth factors Placebo	Inpatients with denervated ulcers and a grade III or IV PU	Proportion of patients completely healed Reduction in ulcer area	28 days of treatment and three months of follow-up

Robson 2000[84]	Growth factors Placebo	Inpatients with a grade III or IV PU	Reduction in ulcer area	35 days of treatment
Shamimi 2008[86]	Herbal extract (Semelil) Standard treatment	Hospitalized patients with a PU	Proportion of patients healed > 80%, 50-80%, 20-50%, < 20% Reduction in ulcer area Healing rate Side effects	Two months of treatment
Sipponen 2008[87]	Resin salve Hydrofibre	Hospitalized patients with a grade II to IV PU (NPUAP classification)	Proportion of patients completely healed Proportion of ulcers completely healed Proportion of ulcers improved Proportion of ulcers worsened Reduction in ulcer width and depth Healing speed Side effects	Six months of treatment
Subbanna 2007[88]	Phenytoin Saline	Patients with a spinal cord injury and a grade II PU (NPUAP classification)	Reduction in ulcer size Reduction in ulcer volume Reduction in PUSH score Side effects	15 days of treatment

Tao 2008[56]	FuChunSanYi Hao ointment Iodophor	Patients with a stage II to IV PU	Proportion of patients completely healed Proportion of patients improved Proportion of patients not changed or worsened	20 days of treatment
Thomas 1998[94]	Saline Hydrogel	Patients with a stage II, III or IV PU	Proportion of patients completely healed Proportion of patients worsened Reduction in ulcer area Time to healing	Ten weeks of treatment or until complete healing
Van Ort 1976[95]	Insuline Standard treatment	Nursing home patients with a pressure ulcer	Healing rate	15 days of treatment
Xakellis 1992[90]	Saline Hydrocolloid dressing	Long term care patients with a stage II or III (Shea classification)	Proportion of patients completely healed Time to healing	Six months of treatment
Yastrub 2004[91]	Antibiotic ointment Foam dressing	Long term care patient with a stage II PU (AHCPR classification)	Proportion of patients improved PUSH score	Four weeks of treatment
Zhang 2010[57]	ShenJi ointment Antibacterial	Patients with a stage III and IV PU	Proportion of patients completely healed Proportion of patients improved Proportion of patients not	60 days of treatment

			changed or worsened	
Zhao 2010[58]	ShenJi ointment Iodophor	Patients with a stage III and IV PU	Proportion of patients completely healed Proportion of patients improved Proportion of patients not changed or worsened	15 to 60 days of treatment

6.1.1. Clinical evidence GRADE-tables

Table 38 – Saline versus hydrocolloid dressing

Quality assessment							No of patients/ulcers		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Saline	Hydro-colloid	Relative (95% CI)	Absolute		
Proportion of patients completely healed – general population and patients with a spinal cord injury – stage I and above – Lowthian and Shea classification[m]												
3 Hollisaz (2004); Matzen (1999); Xakellis (1992)	randomised trials	very serious[a,b,c]	very serious[h]	no serious indirectness	Serious[d]	none	26/63 (41.3%)	41/63 (65.1%)	RR 0.50 (0.14 to 1.74)	325 fewer per 1000 (from 560 fewer to 482 fewer)	⊕OOO VERY LOW	CRITICAL OUTCOME
								71.4%		357 fewer per 1000 (from 614 fewer to 528 fewer)		
Proportion of patients completely healed – general population – stage I and above – Lowthian and Shea classification												
2 Matzen (1999); Xakellis (1992)	randomised trials	very serious[a,c]	very serious[h]	no serious indirectness	Serious[d]	none	18/36 (50%)	21/35 (60%)	RR 0.38 (0.01 to 10.16)	372fewer per 1000 (from 594 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								59.2%		367 fewer per 1000 (from 586 fewer to 1000 more)		

Proportion of patients completely healed - Patients with a spinal cord injury – stage I and II – Shea classification												
1 Hollisaz (2004)	randomised trials	Serious[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/27 (29.6%)	20/28 (71.4%)	RR 0.41 (0.22 to 0.78)	421 fewer per 1000 (from 157 fewer to 557 fewer)	⊕⊕⊕O MODERATE	CRITICAL OUTCOME
								71.4%		421 fewer per 1000 (from 157 fewer to 557 fewer)		
Proportion of ulcers completely healed (all sites) - general population and patients with a spinal cord injury – stage I to III – Shea classification												
2 Hollisaz (2004); Neill (1989)	randomised trials	very serious[b,e]	Serious[f]	no serious indirectness	Serious[d]	none	18/75 (24%)	36/73 (49.3%)	RR 0.50 (0.25 to 0.98)	RD 280 fewer (from 660 fewer to 100 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								52.6%		-		
Proportion of ulcers completely healed (all sites) - General population – stage II and III – Shea classification												
1 Neill (1989)	randomised trials	very serious[e]	no serious inconsistency	no serious indirectness	very serious[g]	none	10/45 (22.2%)	13/42 (31%)	RR 0.72 (0.35 to 1.46)	RD 90 fewer (from 270 fewer to 110 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								31%		-		
Proportion of ulcers completely healed (all sites) - Patients with a spinal cord injury – stage I and II – Shea classification												
1 Hollisaz (2004)	randomised trials	Serious[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/30 (26.7%)	23/31 (74.2%)	RR 0.36 (0.19 to 0.67)	RD 480 fewer (from 700 fewer to 250 fewer)	⊕⊕⊕O MODERATE	CRITICAL OUTCOME
								74.2%		-		
Proportion of ulcers completely healed (all sites) - Patients with a spinal cord injury – stage I - Shea classification												
1 Hollisaz (2004)	randomised trials	Serious[b]	no serious inconsistency	no serious indirectness	Serious[d]	none	5/11 (45.5%)	11/13 (84.6%)	RR 0.54 (0.27 to 1.07)	RD 390 fewer (from 750 more to 40 fewer)	⊕⊕OO LOW	CRITICAL OUTCOME
								84.6%		-		
Proportion of ulcers completely healed (all sites) - general population and patients with a spinal cord injury – stage II - Shea classification												
2 Hollisaz (2004); Neill	randomised	very	no serious	no serious	no serious	none	6/53	23/43	RR 0.22 (0.1	RD 410 fewer (from 580 fewer	⊕⊕OO	CRITICAL

(1989)	trials	serious[b,e]	inconsistency	indirectness	imprecision		(11.3%)	(53.5%)	to 0.48)	to 240 fewer)	LOW	OUTCOME
								55.3%		-		
Proportion of ulcers completely healed (all sites) - General population – - stage II - Shea classification												
1 Neill (1989)	randomised trials	very serious[e]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/34 (8.8%)	11/25 (44%)	RR 0.2 (0.06 to 0.64)	RD 350 fewer (from 570 fewer to 140 fewer)	⊕⊕OO LOW	CRITICAL OUTCOME
								44%		-		
Proportion of ulcers completely healed (all sites) - Patients with a spinal cord injury – stage II - Shea classification												
1 Hollisaz (2004)	randomised trials	Serious[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/19 (15.8%)	12/18 (66.7%)	RR 0.24 (0.08 to 0.7)	RD 510 fewer (from 780 fewer to 240 fewer)	⊕⊕⊕O MODERATE	CRITICAL OUTCOME
								66.7%		-		
Proportion of ulcers completely healed (all sites) - General population – stage III - Shea classification												
1 Neill (1989)	randomised trials	very serious[e]	no serious inconsistency	no serious indirectness	very serious[g]	none	1/11 (9.1%)	2/17 (11.8%)	RR 0.77 (0.08 to 7.54)	RD 30 fewer (from 260 fewer to 200 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								11.8%		-		
Proportion of ulcers completely healed (sacral area) - Patients with a spinal cord injury – stage I and II – Shea classification												
1 Hollisaz (2004)	randomised trials	Serious[b]	no serious inconsistency	no serious indirectness	serious[d]	none	4/8 (50%)	0/7 (0%)	OR 10.87 (1.19-99.73)	RD 100 fewer (from 650 fewer to 450 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								0%		-		
Proportion of ulcers improved - Patients with a spinal cord injury – stage I and II – Shea classification												
1 Hollisaz (2004)	randomised trials	Serious[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	29/60 (48.3%)	27/31 (87.1%)	RR 0.55 (0.41 to 0.75)	392 fewer per 1000 (from 218 fewer to 514 fewer)	⊕⊕⊕O MODERATE	CRITICAL OUTCOME
								87.1%		392 fewer per 1000 (from 218 fewer to 514 fewer)		

Proportion of ulcers worsened - general population and patients with a spinal cord injury – stage I to III – Shea classification												
2 Hollisaz (2004); Neill (1989)	randomised trials	very serious[b,e]	very serious[h]	no serious indirectness	Serious[d]	none	24/75 (32%)	16/73 (21.9%)	RR 1.88 (0.41 to 8.68)	193 more per 1000 (from 129 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								19.9%		175 more per 1000 (from 117 fewer to 1000 more)		
Proportion of ulcers worsened - General population – stage II and III – Shea classification												
1 Neill (1989)	randomised trials	very serious[e]	no serious inconsistency	no serious indirectness	very serious[g]	none	15/45 (33.3%)	14/42 (33.3%)	RR 1 (0.55 to 1.81)	0 fewer per 1000 (from 150 fewer to 270 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								33.3%		0 fewer per 1000 (from 150 fewer to 270 more)		
Proportion of ulcers worsened - Patients with a spinal cord injury – stage I and II – Shea classification												
1 Hollisaz (2004)	randomised trials	Serious[b]	no serious inconsistency	no serious indirectness	very serious[g]	none	9/30 (30%)	2/31 (6.5%)	RR 4.65 (1.09 to 19.78)	235 more per 1000 (from 6 more to 1000 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								6.5%		237 more per 1000 (from 6 more to 1000 more)		
Proportion of ulcers worsened - General population – stage II– Shea classification												
1 Neill (1989)	randomised trials	very serious[e]	no serious inconsistency	no serious indirectness	very serious[g]	none	11/34 (32.4%)	7/25 (28%)	RR 1.16 (0.52 to 2.56)	45 more per 1000 (from 134 fewer to 437 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								28%		45 more per 1000 (from 134 fewer to 437		

										more)		
Proportion of ulcers worsened - General population – stage III – Shea classification												
1 Neill (1989)	randomised trials	very serious[e]	no serious inconsistency	no serious indirectness	very serious[g]	none	4/11 (36.4%)	7/17 (41.2%)	RR 0.88 (0.34 to 2.32)	49 fewer per 1000 (from 272 fewer to 544 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								41.2%		49 fewer per 1000 (from 272 fewer to 544 more)		
Mean percentage reduction in ulcer area – general population – stage II and III – classification method not reported												
1 Chang (1998)	randomised trials	very serious[i]	no serious inconsistency	no serious indirectness	Serious[d]	none	-9 (SD 102.45)	34 (SD 102.45)	-	MD 43 lower (111.87 lower to 25.87 higher)	⊕OOO VERY LOW	CRITICAL OUTCOME
Mean percentage reduction in ulcer volume – general population – stage III and IV – Lowthian classification												
1 Matzen (1999)	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	64 (SD 16)	26 (SD 20)	-	MD 38 higher (28.61 to 47.39 higher)	⊕⊕OO LOW	CRITICAL OUTCOME
Median percentage reduction in ulcer area – long-term care patients – PU stage not reported – classification method not reported												
1 Alm (1989)	randomised trials	very serious[j]	no serious inconsistency	no serious indirectness	very serious[k]	none	85.7 (n=21)	100 (n=29)	-	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME
Median percentage reduction in ulcer size - General population – stage II– Shea classification												
1 Neill (1989)	randomised trials	very serious[e]	no serious inconsistency	no serious indirectness	very serious[k]	none	48 (n=34)	91 (n=25)	p>0.05	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME
Median percentage reduction in ulcer size - General population – stage III – Shea classification												
1 Neill (1989)	randomised trials	very serious[e]	no serious inconsistency	no serious indirectness	very serious[k]	none	30 (n=11)	(0.3) (n=17)	p>0.05	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME
Median days to healing – long-term care patients – stage II and III – Shea classification												
1 Xakellis	randomised	very	no serious	no serious	very serious[k]	none	11	9	p=0.12	not pooled	⊕OOO	CRITICAL

(1992)	trials	serious[c]	inconsistency	indirectness			(n=21)	(n=18)			VERY LOW	OUTCOME
Healing distribution function – long-term care patients – PU stage not reported – classification method not reported												
1 Alm (1989)	randomised trials	very serious[j]	no serious inconsistency	no serious indirectness	very serious[12]	none	n=21	n=29	p=0.15 (favours hydrocolloid)	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME
Proportion of patients with pain at dressing removal – general population – stage II and III – classification method not reported												
1 Chang (1998)	randomised trials	very serious[i]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/17 (0%)	7/17 (41.2%)	OR 0.09 (0.02 to 0.45)	352 fewer per 1000 (from 172 fewer to 398 fewer)	⊕⊕OO LOW	IMPORTANT OUTCOME
								41.2%		353 fewer per 1000 (from 172 fewer to 398 fewer)		
Median pain score during treatment (scoring system not reported) – general population – stage III and IV – Lowthian classification												
1 Matzen (1999)	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[k]	none	2.0 (range: 1-3) (n=15)	2.0 (range: 1-4) (n=17)	-	not pooled	⊕OOO VERY LOW	IMPORTANT OUTCOME
Proportion of patients with discomfort at dressing removal – general population – stage II and III – classification method not reported												
1 Chang (1998)	randomised trials	very serious[i]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/17 (0%)	9/17 (52.9%)	OR 0.07 (0.02 to 0.32)	456 fewer per 1000 (from 265 fewer to 507 fewer)	⊕⊕OO LOW	IMPORTANT OUTCOME
								52.9%		456 fewer per 1000 (from 265 fewer to 507 fewer)		
Median comfort score during treatment (scoring system not reported) – general population – stage III and IV – Lowthian classification												
1 Matzen (1999)	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[k]	none	3.0 (range: 2-4)	4.0 (range: 3-4)	-	not pooled	⊕OOO VERY LOW	IMPORTANT OUTCOME

							(n=15)	(n=17)				
Proportion of patients with an infection – general population – stage II and III – classification method not reported												
1 Chang (1998)	randomised trials	very serious[i]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/17 (0%)	0/17 (0%)	not pooled	RD 0 fewer (from 110 fewer to 110 more)	⊕⊕OO LOW	IMPORTANT OUTCOME
								0%		-		
Median smell score during treatment (scoring system not reported) – general population – stage III and IV – Lowthian classification												
1 Matzen (1999)	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[k]	none	2.0 (range: 1-4) (n=15)	2.0 (range: 1-3) (n=17)	-	not pooled	⊕OOO VERY LOW	IMPORTANT OUTCOME
Proportion of patients with skin irritation - General population – stage II and III – Shea classification												
1 Neill (1989)	randomised trials	very serious[e]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/50 (0%)	9/50 (18%)	OR 0.11 (0.03 to 0.44)	156 fewer per 1000 (from 92 fewer to 173 fewer)	⊕OOO VERY LOW	IMPORTANT OUTCOME
								18%		156 fewer per 1000 (from 92 fewer to 173 fewer)		

a Matzen (1999): no report or insufficient information on sequence generation, allocation concealment and blinding; no log-transformation of data
b Hollisaz (2004): only blinding of outcome assessor
c Xakellis (1992): no report on sequence generation and blinding
d Confidence interval crossed one MID point
e Neill (1989): no report on sequence generation, allocation concealment and blinding; no ITT analysis; no log-transformation of data
f Different populations and high heterogeneity (> 50%) but p-value > 0.1
g Confidence interval crossed both MID points
h Different populations and high heterogeneity (> 50%) and p-value < 0.1
i Chang (1998): no report on sequence generation, allocation concealment and blinding; no log-transformation of data
j Alm (1989): no report on sequence generation; allocation concealment by stratification according to Norton score; only blinding of outcome assessor; no log-transformation of data
k No standard deviation; unknown if sample size was sufficient
l Only p-value reported
m Matzen (1999): Lowthian classification; Xakellis (1992) and Hollisaz (2004): Shea classification

Table 39 – Saline versus hydrogel dressing

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Saline	Hydrogel	Relative (95% CI)	Absolute		
Proportion of patients completely healed – general population – stage II to IV – classification method not reported												
1 Thomas (1998)	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	9/14 (64.3%)	10/16 (62.5%)	RR 1.03 (0.6 to 1.77)	19 more per 1000 (from 250 fewer to 481 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								62.5%		19 more per 1000 (from 250 fewer to 481 more)		
Proportion of patients worsened – general population – stage II to IV – classification method not reported												
1 Thomas (1998)	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/19 (5.3%)	1/22 (4.5%)	RR 1.16 (0.08 to 17.28)	7 more per 1000 (from 42 fewer to 740 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								4.6%		7 more per 1000 (from 42 fewer to 749 more)		
Percentage healing rate – general population – stage II to IV – classification method not reported												
1 Thomas (1998)	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	64 (n=14)	63 (n=16)	-	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME
Mean weeks to healing – general population – stage II to IV – classification method not reported												
1 Thomas (1998)	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	5.2 (SD 2.4)	5.3 (SD 2.3)	-	MD 0.1 lower (1.79 lower to 1.59 higher)	⊕OOO VERY LOW	CRITICAL OUTCOME

a No report on sequence generation, allocation concealment and blinding; no log-transformation of data
b Confidence interval crossed both MID points
c No standard deviation; unknown if sample size was sufficient

Table 40 – Saline versus foam dressing

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Saline	Foam	Relative (95% CI)	Absolute		
Proportion of patients completely healed – general population – stage II and III – Enterostomal Therapy and NPUAP classification[d]												
2 Kraft (1993); Payne (2009)	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	9/30 (30%)	20/44 (45.5%)	RR 0.64 (0.34 to 1.22)	164 fewer per 1000 (from 300 fewer to 100 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								45.8%		165 fewer per 1000 (from 302 fewer to 101 more)		
Median days to healing of 50% of the patients – general population – stage II – NPUAP classification												
1 Payne (2009)	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	28 (n=16)	28 (n=20)	-	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME

1 No report on sequence generation, allocation concealment and blinding
2 Confidence interval crossed one MID point
3 No standard deviation; unknown if sample size was sufficient
d Kraft (1993): Enterostomal Therapy classification; Payne (2009): NPUAP classification

Table 41 – Saline versus polyurethane dressing

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Saline	Poly-urethane	Relative (95% CI)	Absolute		
Proportion of ulcers completely healed – general population – stage I and II – Ernis and Sarmiento classification												
1 Oleske (1986)	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	0/10 (0%)	1/9 (11.1%)	OR 0.12 (0 to 6.14)	96 fewer per 1000 (from 111 fewer to 323 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								11.1%		96 fewer per 1000 (from 111 fewer to		

										323 more)		
Proportion of ulcers worsened – general population – stage I and II – Ernis and Sarmiento classification												
1 Oleske (1986)	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	2/10 (20%)	1/9 (11.1%)	RR 1.8 (0.19 to 16.66)	89 more per 1000 (from 90 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								11.1%		89 more per 1000 (from 90 fewer to 1000 more)		
Mean percentage reduction in ulcer area – general population – stage I and II – Ernis and Sarmiento classification												
1 Oleske (1986)	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	2.5 (n=10)	42.9 (n=9)	-	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME

a No report on sequence generation, allocation concealment and blinding; no log-transformation
b Confidence interval crossed both MID points
c No standard deviation; unknown if sample size was sufficient

Table 42 – Saline versus dextranomer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Saline	Dextranomer	Relative (95% CI)	Absolute		
Proportion of ulcers improved – patients with a spinal cord injury - stage II to IV – Eltotai classification												
1 Ljungberg (2009)	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/15 (13.3%)	11/15 (73.3%)	RR 0.18 (0.05 to 0.68)	601 fewer per 1000 (from 235 fewer to 697 fewer)	⊕⊕OO LOW	CRITICAL OUTCOME
								73.3%		601 fewer per 1000 (from 235 fewer to 696 fewer)		
Proportion of patients with adverse events – patients with a spinal cord injury - stage II to IV – Eltotai classification												
1 Ljungberg (2009)	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/15 (0%)	0/15 (0%)	not pooled	RD 0 fewer (from 120 fewer to 120 more)	⊕⊕OO LOW	IMPORTANT OUTCOME
								0%		-		

a No report on sequence generation, allocation concealment and blinding

Table 43 – Phenytoin versus saline

Quality assessment							No of patients/ulcers		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phenytoin	Saline	Relative (95% CI)	Absolute		
Proportion of patients completely healed – patients with a spinal cord injury – stage I and II PU – NPUAP classification												
1 Hollisaz 2004	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	11/28 (39.3%)	8/27 (29.6%)	RR 1.33 (0.63 to 2.78)	98 more per 1000 (from 110 fewer to 527 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								29.6%		98 more per 1000 (from 110 fewer to 527 more)		
Proportion of ulcers completely healed (all sites) – patients with a spinal cord injury – stage I and II PU – NPUAP classification												
1 Hollisaz 2004	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	12/30 (40%)	8/30 (26.7%)	RR 1.5 (0.72 to 3.14)	133 more per 1000 (from 75 fewer to 571 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								26.7%		134 more per 1000 (from 75 fewer to 571 more)		
Proportion of ulcers completely healed (all sites) – patients with a spinal cord injury - stage I – NPUAP classification												
1 Hollisaz 2004	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	2/9 (22.2%)	5/11 (45.5%)	RR 0.49 (0.12 to 1.95)	232 fewer per 1000 (from 400 fewer to 432 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								45.5%		232 fewer per 1000 (from 400 fewer to 432 more)		
Proportion of ulcers completely healed (all sites) – patients with a spinal cord injury – stage II – NPUAP classification												
1 Hollisaz 2004	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	Serious[c]	none	10/21 (47.6%)	3/19 (15.8%)	RR 3.02 (0.97 to 9.35)	319 more per 1000 (from 5 fewer to 1000 more)	⊕⊕OO LOW	CRITICAL OUTCOME
								15.8%		319 more per 1000 (from 5 fewer to 1000 more)		

Proportion of ulcers completely healed (sacral) – patients with a spinal cord injury – stage I and II PU – NPUAP classification												
1 Hollisaz 2004	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	2/5 (40%)	4/8 (50%)	RR 0.8 (0.22 to 2.87)	100 fewer per 1000 (from 390 fewer to 935 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								50%		100 fewer per 1000 (from 390 fewer to 935 more)		
Proportion of ulcers improved – patients with a spinal cord injury – stage I and II PU – NPUAP classification												
1 Hollisaz 2004	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	16/30 (53.3%)	13/30 (43.3%)	RR 1.23 (0.73 to 2.09)	100 more per 1000 (from 117 fewer to 472 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								43.3%		100 more per 1000 (from 117 fewer to 472 more)		
Proportion of ulcers worsened – patients with a spinal cord injury – stage I and II PU – NPUAP classification												
1 Hollisaz 2004	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	Serious[c]	none	2/30 (6.7%)	9/30 (30%)	RR 0.22 (0.05 to 0.94)	234 fewer per 1000 (from 18 fewer to 285 fewer)	⊕⊕OO LOW	CRITICAL OUTCOME
								30%		234 fewer per 1000 (from 18 fewer to 285 fewer)		
Mean percentage reduction in ulcer size – spinal cord injury patients – grade II PU – NPUAP classification												
1 Subbanna 2007	randomised trials	very serious[d]	no serious inconsistency	no serious indirectness	Serious[c]	none	47.83 (SD 20.94)	36.03 (SD 17.63)	-	MD 11.8 higher (3.22 lower to 26.82 higher)	⊕OOO VERY LOW	CRITICAL OUTCOME
Mean percentage reduction in ulcer volume – spinal cord injury patients – grade II PU – NPUAP classification												
1 Subbanna 2007	randomised trials	very serious[d]	no serious inconsistency	no serious indirectness	very serious[b]	none	53.94 (SD 31.2)	55.76 (SD 27.75)	-	MD 1.82 lower (24.69 lower to 21.05 higher)	⊕OOO VERY LOW	CRITICAL OUTCOME
Mean percentage reduction in PUSH score – spinal cord injury patients – grade II PU – NPUAP classification												

1 Subbanna 2007	randomised trials	very serious[d]	no serious inconsistency	no serious indirectness	very serious[b]	none	19.53 (SD 17.7)	11.39 (SD 11.09)	-	MD 8.14 higher (3.44 lower to 19.72 higher)	⊕OOO VERY LOW	CRITICAL OUTCOME
Proportion of patients with treatment related adverse events – spinal cord injury patients – grade II PU – NPUAP classification												
1 Subbanna 2007	randomised trials	very serious[d]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/12 (0%)	0/14 (0%)	not pooled	RD 0 fewer (from 140 fewer to 140 more)	⊕⊕OO LOW	IMPORTANT OUTCOME
								0%		-		

a No blinding of patients and nurses
b Confidence interval crossed both MID points
c Confidence interval crossed one MID point
d No report on allocation concealment and blinding; no ITT analysis; no log-transformation of data

Table 44 – Phenytoin versus hydrocolloid

Quality assessment							No of patients/ulcers		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Phenytoin**	**Hydrocolloid**	**Relative (95% CI)**	**Absolute**		
Proportion of patients completely healed – patients with a spinal cord injury – stage I and II PU – NPUAP classification												
1 Hollisaz 2004	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	11/28 (39.3%)	20/28 (71.4%)	RR 0.55 (0.33 to 0.92)	321 fewer per 1000 (from 57 fewer to 479 fewer)	⊕⊕OO LOW	CRITICAL OUTCOME
								71.4%		321 fewer per 1000 (from 57 fewer to 478 fewer)		
Proportion of ulcers completely healed (all sites) – patients with a spinal cord injury – stage I and II PU – NPUAP classification												
1 Hollisaz 2004	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	12/30 (40%)	23/31 (74.2%)	RR 0.54 (0.33 to 0.88)	341 fewer per 1000 (from 89 fewer to 497 fewer)	⊕⊕OO LOW	CRITICAL OUTCOME
								74.2%		341 fewer per		

										1000 (from 89 fewer to 497 fewer)		
Proportion of ulcers completely healed (all sites) – patients with a spinal cord injury - stage I – NPUAP classification												
1 Hollisaz 2004	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	2/9 (22.2%)	11/13 (84.6%)	RR 0.26 (0.08 to 0.91)	626 fewer per 1000 (from 76 fewer to 778 fewer)	⊕⊕OO LOW	CRITICAL OUTCOME
								84.6%		626 fewer per 1000 (from 76 fewer to 778 fewer)		
Proportion of ulcers completely healed (all sites) – patients with a spinal cord injury – stage II – NPUAP classification												
1 Hollisaz 2004	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	10/21 (47.6%)	12/18 (66.7%)	RR 0.71 (0.41 to 1.24)	193 fewer per 1000 (from 393 fewer to 160 more)	⊕⊕OO LOW	CRITICAL OUTCOME
								66.7%		193 fewer per 1000 (from 394 fewer to 160 more)		
Proportion of ulcers completely healed (sacral) – patients with a spinal cord injury – stage I and II PU – NPUAP classification												
1 Hollisaz 2004	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	4/8 (50%)	4/7 (57.1%)	RR 0.88 (0.34 to 2.25)	69 fewer per 1000 (from 377 fewer to 714 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								57.1%		69 fewer per 1000 (from 377 fewer to 714 more)		
Proportion of ulcers improved – patients with a spinal cord injury – stage I and II PU – NPUAP classification												
1 Hollisaz	randomised	Serious[a]	no serious	no serious	Serious[b]	none	16/30	27/31	RR 0.61 (0.43	340 fewer per 1000 (from 105	⊕⊕OO	CRITICAL

2004	trials		inconsistency	indirectness			(53.3%)	(87.1%)	to 0.88)	fewer to 496 fewer)	LOW	OUTCOME
								87.1%		340 fewer per 1000 (from 105 fewer to 496 fewer)		
Proportion of ulcers worsened– patients with a spinal cord injury – stage I and II PU – NPUAP classification												
1 Hollisaz 2004	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	2/30 (6.7%)	2/31 (6.5%)	RR 1.03 (0.16 to 6.87)	2 more per 1000 (from 54 fewer to 379 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								6.5%		2 more per 1000 (from 55 fewer to 382 more)		
Mean days to healing – nursing home patients – stage II PU - (AHCPR classification												
1 Rhodes 2001	randomised trials	very serious[d]	no serious inconsistency	no serious indirectness	Serious[b]	none	35.3 (SD 14.3)	51.8 (SD 19.6)	-	MD 16.5 lower (29.38 to 3.62 lower)	⊕OOO VERY LOW	CRITICAL OUTCOME
Proportion of patients with pain – nursing home patients – stage II PU - AHCPR classification												
1 Rhodes 2001	randomised trials	very serious[d]	no serious inconsistency	no serious indirectness	very serious[e]	none	-	-	Minimal pain was reported in both groups	not pooled	⊕OOO VERY LOW	IMPORTANT OUTCOME
								0%		not pooled		
Proportion of patients with treatment related adverse events – nursing home patients – stage II PU -AHCPR classification												
1 Rhodes 2001	randomised trials	very serious[d]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/15 (0%)	0/13 (0%)	not pooled	RD 0 fewer (from 130 fewer to 130 more)	⊕⊕OO LOW	IMPORTANT OUTCOME
								0%		-		

a No blinding of patients and nurses
b Confidence interval crossed one MID point
c Confidence interval crossed both MID points
d No report on allocation concealment, sequence generation and blinding; no ITT analysis
e No figures reported, no p-value

Table 45 – Phenytoin versus triple antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phenytoin	Triple antibiotics	Relative (95% CI)	Absolute		
Mean days to healing – nursing home patients – stage II PU - AHCPR classification												
1 Rhodes 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	35.3 (SD 14.3)	53.8 (SD 8.5)	-	MD 18.5 lower (27.31 to 9.69 lower)	⊕⊕OO LOW	CRITICAL OUTCOME
Proportion of patients with pain – nursing home patients – stage II PU - AHCPR classification												
1 Rhodes 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	-	-	Minimal pain was reported in both groups	not pooled	⊕OOO VERY LOW	IMPORTANT OUTCOME
								0%		not pooled		
Proportion of patients with treatment related adverse events – nursing home patients – stage II PU - AHCPR classification												
1 Rhodes 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/15 (0%)	0/11 (0%)	not pooled	RD 0 fewer (from 140 fewer to 140 more)	⊕⊕OO LOW	IMPORTANT OUTCOME
								0%		-		

a No report on allocation concealment, sequence generation and blinding; no ITT analysis
b No figures reported; no p-value

Table 46 – Aloe vera, silver chloride and decyl glucoside versus saline

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aloe vera	Saline	Relative (95% CI)	Absolute		
Mean percentage reduction in PSST – elderly patients – grade II to IV – NPUAP classification												
1 Bellingeri 2004	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	22.7 (SD 31.3) (n=?)	20.5 (SD 24.1) (n=?)	-	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME

a No report on allocation concealment, sequence generation and blinding; no ITT analysis
b Unclear on how many patients the analysis was performed

Table 47 – Dialysate (Solcoseryl®) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dialysate	Placebo	Relative (95% CI)	Absolute		
Mean ml reduction in ulcer area - patients with a spinal cord injury – PU stage not reported – classification method not reported												
1 Knudsen 1982	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	13.4 (SD 10.02)	6.57 (SD 4.88)	-	MD 6.83 higher (3.54 lower to 17.2 higher)	⊕OOO VERY LOW	CRITICAL OUTCOME
Mean percentage reduction in ulcer area at day 10 - patients with a spinal cord injury – PU stage not reported – classification method not reported												
1 Knudsen 1982	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	39 (n=5)	28 (n=3)	-	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME
Mean percentage reduction in ulcer area at day 20 - patients with a spinal cord injury – PU stage not reported – classification method not reported												
1 Knudsen 1982	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	80 (n=5)	59 (n=3)	-	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME

Mean healing half-time (days) patients with a spinal cord injury – PU stage not reported – classification method not reported												
1 Knudsen 1982	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	8.52 (2.36)	24 (SD 18.43)	-	MD 15.48 lower (36.44 lower to 5.48 higher)	⊕OOO VERY LOW	CRITICAL OUTCOME
Proportion of patients with treatment related adverse events patients with a spinal cord injury – PU stage not reported – classification method not reported												
1 Knudsen 1982	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/5 (0%)	0/3 (0%)	not pooled	RD 0 fewer (from 390 fewer to 390 more)	⊕⊕OO LOW	IMPORTANT OUTCOME
								0%		-		

a No report on allocation concealment and sequence generation; double-blinded, but no further information; no ITT analysis; no log-transformation of data
b Confidence interval crossed one MID point

Table 48 – Petrolatum ointment versus petrolatum (base component)

Quality assessment							No of ulcers		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical ointment with petrolatum	Petrolatum (base component)	Relative (95% CI)	Absolute		
Proportion of ulcers completely healed – elderly patients – stage I and II – AHCPR classification												
1 Kuflik 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	5/10 (50%)	2/9 (22.2%)	RR 2.30 (0.73 to 7.29)	RD 360 more (from 30 fewer to 750 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								16.7%		-		
Proportion of ulcers completely healed - Stage I – elderly patients – AHCPR classification												
1 Kuflik 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	4/5 (80%)	2/6 (33.3%)	RR 2.40 (0.71 to 8.08)	RD 470 more (from 50 fewer to 980 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								33.3%		-		
Proportion of ulcers completely healed - Stage II – elderly patients – AHCPR classification												
1 Kuflik 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/5 (20%)	0/3 (0%)	OR 4.95 (0.09 to	RD 200 more (from 270 fewer	⊕OOO VERY	CRITICAL OUTCOME

									283.86)	to 670 more)	LOW	
								0%		-		
Proportion of ulcers improved – elderly patients – stage I and II – AHCPR classification												
1 Kuflik 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	4/10 (40%)	0/9 (0%)	OR 9.27 (0.96 to 89.09)	RD 360 more (from 20 fewer to 750 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								0%		-		
Proportion of ulcers improved - Stage I – elderly patients – AHCPR classification												
1 Kuflik 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/5 (20%)	0/6 (0%)	OR 9.03 (0.18 to 462.31)	RD 200 more (from 200 fewer to 600 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								0%		-		
Proportion of ulcers improved - Stage II – elderly patients – AHCPR classification												
1 Kuflik 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	3/5 (60%)	0/3 (0%)	OR 9.39 (0.59 to 149.25)	RD 600 more (from 90 fewer to 1110 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								0%		-		
Proportion of ulcers not changed – elderly patients – stage I and II – AHCPR classification												
1 Kuflik 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/10 (10%)	1/9 (11.1%)	RR 0.88 (0.13 to 6.09)	RD 20 fewer (from 380 fewer to 340 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								8.3%		-		
Proportion of ulcers not changed - Stage I – elderly patients – AHCPR classification												
1 Kuflik 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	0/5 (0%)	1/6 (16.7%)	OR 0.16 (0 to 8.19)	RD 170 fewer (from 540 fewer to 210 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								16.7%		-		
Proportion of ulcers not changed - Stage II – elderly patients – AHCPR classification												
1 Kuflik 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/5 (20%)	0/3 (0%)	OR 4.95 (0.09 to 283.86)	RD 20 more (from 380 fewer to 340 more)	⊕OOO VERY	CRITICAL OUTCOME

								0%		-	LOW	
Proportion of ulcers worsened – elderly patients – stage I and II – AHCPR classification												
1 Kuflik 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/10 (0%)	6/9 (66.7%)	OR 0.05 (0.01 to 0.34)	RD 70 fewer (from 1070 fewer to 340 fewer)	⊕⊕OO LOW	CRITICAL OUTCOME
								75%		-		
Proportion of ulcers worsened - Stage I – elderly patients – AHCPR classification												
1 Kuflik 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	0/5 (0%)	3/6 (50%)	OR 0.1 (0.01 to 1.28)	RD 500 fewer (from 930 fewer to 70 fewer)	⊕OOO VERY LOW	CRITICAL OUTCOME
								50%		-		
Proportion of ulcers worsened - Stage II – elderly patients– AHCPR classification												
1 Kuflik 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/5 (0%)	3/3 (100%)	OR 0.02 (0 to 0.38)	RD 1000 fewer (from 1390 fewer to 610 more)	⊕⊕OO LOW	CRITICAL OUTCOME
								100%				

1 Insufficient information on sequence generation; no report on allocation concealment and blinding of outcome assessor
2 Confidence interval crossed both MID points

Table 49 – Herbal extract (Semelil) versus standard treatment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Herbal extract	Standard treatment	Relative (95% CI)	Absolute		
Proportion of patients healed > 80% - general population – stage not reported – classification method not reported												
1 Shamimi 2008	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/9 (66.7%)	0/9 (0%)	OR 17 (2.53 to 114.21)	RD 670 more (from 340 more to 990 more)	⊕⊕OO LOW	CRITICAL OUTCOME
								0%		-		

Proportion of patients healed 50-80% - general population – stage not reported – classification method not reported												
1 Shamimi 2008	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	3/9 (33.3%)	1/9 (11.1%)	RR 3 (0.38 to 23.68)	222 more per 1000 (from 69 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								11.1%		222 more per 1000 (from 69 fewer to 1000 more)		
Proportion of patients healed 20-50% - general population – stage not reported – classification method not reported												
1 Shamimi 2008	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/9 (0%)	0/9 (0%)	not pooled	RD 890 fewer (from 1150 fewer to 630 fewer)	⊕⊕OO LOW	CRITICAL OUTCOME
								0%		-		
Proportion of patients healed < 20% - general population – stage not reported – classification method not reported												
1 Shamimi 2008	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/9 (0%)	8/9 (88.9%)	OR 0.03 (0.01 to 0.2)	695 fewer per 1000 (from 274 fewer to 815 fewer)	⊕⊕OO LOW	CRITICAL OUTCOME
								88.9%		695 fewer per 1000 (from 273 fewer to 815 fewer)		
Mean cm² reduction in ulcer area - general population – stage not reported – classification method not reported												
1 Shamimi 2008	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[c]	none	48.2 (SD 85.3)	2.8 (SD 6.2)	-	MD 45.4 higher (10.48 lower to 101.28 higher)	⊕OOO VERY LOW	CRITICAL OUTCOME
Mean percentage rate of healing - general population – stage not reported – classification method not reported												
1 Shamimi 2008	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	78.3 (SD 12.5)	6.3 (SD 227)	-	MD 72 higher (55.07 to 88.93 higher)	⊕⊕OO LOW	CRITICAL OUTCOME
Proportion of patients with treatment related adverse events - general population – stage not reported – classification method not reported												
1 Shamimi 2008	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/9 (0%)	0/9 (0%)	not pooled	RD 0 more (from 190 fewer to 190	⊕⊕OO	IMPORTANT OUTCOME

										more)	LOW	
								0%		-		

a No report on allocation concealment and blinding; no log-transformation of data
b Confidence interval crossed both MID points
c Confidence interval crossed one MID point

Table 50 – Zinc oxide versus streptokinase-streptodornase

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Zinc oxide	Streptokinase-streptodornase	Relative (95% CI)	Absolute		
Median percentage reduction in ulcer area – elderly patients – necrotic PU - classification method not reported												
1 Agren 1985	randomised trials	very serious[c]	no serious inconsistency	no serious indirectness	very serious[b]	none	24 (n=14)	-18.7 (n=14)	-	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME
Proportion of patients with an infection – elderly patients – necrotic PU - classification method not reported												
1 Agren 1985	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	0/14 (0%)	1/14 (7.1%)	OR 0.14 (0 to 6.82)	61 fewer per 1000 (from 71 fewer to 273 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								7.1%		60 fewer per 1000 (from 71 fewer to 272 more)		
Proportion of patients with skin reaction – elderly patients – necrotic PU - classification method not reported												
1 Agren 1985	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	0/14 (0%)	1/14 (7.1%)	OR 0.14 (0 to 6.82)	61 fewer per 1000 (from 71 fewer to 273 more)	⊕OOO VERY LOW	IMPORTANT OUTCOME
								7.1%		60 fewer per 1000 (from 71 fewer to 272 more)		

a Sequence generation by matched pairs; no report on allocation concealment and no blinding of patient and nurses; no log-transformation of data
b No standard deviation reported; small sample size
c Confidence interval crossed both MID points

Table 51 – Phenol versus A&D® -Petrolatum based ointment treatment

Quality assessment							No of ulcers		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phenol	A&D treatment	Relative (95% CI)	Absolute		
Proportion of ulcers completely healed (all stages) – palliative care patients – stage I and II PU – NPUAP classification												
1 Gerding 1993	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	43/86 (50%)	21/51 (41.2%)	RR 1.21 (0.82 to 1.79)	86 more per 1000 (from 74 fewer to 325 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								41.2%		87 more per 1000 (from 74 fewer to 325 more)		
Proportion of ulcers completely healed– palliative care patients – stage I – NPUAP classification												
1 Gerding 1993	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	23/41 (56.1%)	16/28 (57.1%)	RR 0.98 (0.65 to 1.49)	11 fewer per 1000 (from 200 fewer to 280 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								57.1%		11 fewer per 1000 (from 200 fewer to 280 more)		
Proportion of ulcers completely healed– palliative care patients – stage II – NPUAP classification												
1 Gerding 1993	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	20/45 (44.4%)	5/23 (21.7%)	RR 2.04 (0.88 to 4.74)	226 more per 1000 (from 26 fewer to 813 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								21.7%		226 more per 1000 (from 26 fewer to 812 more)		
Proportion of ulcers improved after 15 days– palliative care patients – stage I – NPUAP classification												
1 Gerding 1993	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	15/41 (36.6%)	6/28 (21.4%)	RR 1.71 (0.76 to 3.86)	152 more per 1000 (from 51 fewer to 613 more)	⊕OOO VERY	CRITICAL OUTCOME

								21.4%		152 more per 1000 (from 51 fewer to 612 more)	LOW	
Proportion of ulcers improved after 22 days– palliative care patients –stage II – NPUAP classification												
1 Gerding 1993	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	19/45 (42.2%)	8/23 (34.8%)	RR 1.21 (0.63 to 2.34)	73 more per 1000 (from 129 fewer to 466 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								34.8%		73 more per 1000 (from 129 fewer to 466 more)		
Proportion of ulcers not changed on day 15– palliative care patients – stage I – NPUAP classification												
1 Gerding 1993	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	4/41 (9.8%)	4/28 (14.3%)	RR 0.68 (0.19 to 2.51)	46 fewer per 1000 (from 116 fewer to 216 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								14.3%		46 fewer per 1000 (from 116 fewer to 216 more)		
Proportion of ulcers not changed on day 22– palliative care patients – stage II – NPUAP classification												
1 Gerding 1993	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	5/45 (11.1%)	7/23 (30.4%)	RR 0.37 (0.13 to 1.02)	192 fewer per 1000 (from 265 fewer to 6 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								30.4%		192 fewer per 1000 (from 264 fewer to 6 more)		
Proportion of ulcers worsened on day 15– palliative care patients – stage I – NPUAP classification												
1 Gerding 1993	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	0/41 (0%)	2/28 (7.1%)	OR 0.08 (0 to 1.41)	65 fewer per 1000 (from 71 fewer to 26 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								7.1%		65 fewer per 1000 (from 71 fewer to 26		

										more)		
Proportion of ulcers worsened on day 22– palliative care patients – stage II – NPUAP classification												
1 Gerding 1993	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	1/45 (2.2%)	3/23 (13%)	RR 0.17 (0.02 to 1.55)	108 fewer per 1000 (from 128 fewer to 72 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								13%		108 fewer per 1000 (from 127 fewer to 71 more)		
Mean days to complete healing– palliative care patients – stage I and II PU – NPUAP classification												
1 Gerding 1993	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	7.23 (SD 4.15)	8.62 (SD 5.16)	-	MD 1.39 lower (3.06 lower to 0.28 higher)	⊕OOO VERY LOW	CRITICAL OUTCOME
Mean days to complete healing– palliative care patients – stage I – NPUAP classification												
1 Gerding 1993	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	6.75 (SD 3.9)	7.25 (SD 4.8)	-	MD 0.5 lower (2.64 lower to 1.64 higher)	⊕OOO VERY LOW	CRITICAL OUTCOME
Mean days to complete healing– palliative care patients –stage II – NPUAP classification												
1 Gerding 1993	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7.8 (SD 4.47)	13 (SD 3.94)	-	MD 5.2 lower (7.27 to 3.13 lower)	⊕⊕OO LOW	CRITICAL OUTCOME

a No report on allocation concealment; only blinding of outcome assessor
b Confidence interval crossed one MID point
c Confidence interval crossed both MID points

Table 52 – Ethoxy-diaminoacridine plus nitrofuazone versus honey

Quality assessment							No of patients/ulcers		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ethoxy-diaminoacridine plus nitrofuazone	Honey	Relative (95% CI)	Absolute		
Proportion of ulcers completely healed – general population – stage II and III PU – AHCPR classification												
1 Günes 2007	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/25 (0%)	5/25 (33.3%)	OR 0.11 (0.02 to 0.71)	173 fewer per 1000 (from 49 fewer to 195 fewer)	⊕⊕OO LOW	CRITICAL OUTCOME
								33.3%		272 fewer per 1000 (from 28 fewer to 323 fewer)		
Mean percentage reduction in PUSH score – general population – stage II and III PU – AHCPR classification												
1 Günes 2007	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12.9 (SD 28.92)	56.3 (SD 28.92)	-	MD 43.4 lower (59.43 to 27.37 lower)	⊕⊕OO LOW	CRITICAL OUTCOME
Mean percentage reduction in ulcer size – general population – stage II and III PU – AHCPR classification												
1 Günes 2007	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13 (SD 29.39)	56 (SD 29.39)	-	MD 43 lower (59.29 to 26.71 lower)	⊕⊕OO LOW	CRITICAL OUTCOME
Proportion of patients with treatment related adverse events – general population – stage II and III PU – AHCPR classification												
1 Günes 2007	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/11 (0%)	0/15 (0%)	not pooled	RD 0 more (from 140 fewer to 140 more)	⊕⊕OO LOW	IMPORTANT OUTCOME
								0%		-		

a No report on allocation concealment, sequence generation and blinding; no ITT analysis; no log-transformation of data

Table 53 – Povidone-iodine versus hydrocolloid

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Povidone-iodine	Hydrocolloid	Relative (95% CI)	Absolute		
Proportion of patients completely healed – general population – stage I and II PU – NPUAP classification												
1 Kim 1996	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	14/18 (77.8%)	21/26 (80.8%)	RR 0.96 (0.71 to 1.31)	32 fewer per 1000 (from 234 fewer to 250 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								80.8%		32 fewer per 1000 (from 234 fewer to 250 more)		
Percentage rate of healing – general population – stage I and II PU – NPUAP classification												
1 Kim 1996	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	77.8 (n=18)	80.8 (n=26)	-	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME
Mean speed of healing (mm²/day) – general population – stage I and II PU – NPUAP classification												
1 Kim 1996	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[d]	none	7.9 (SD 4.7)	9.1 (SD 5.4)	-	MD 1.2 lower (4.2 lower to 1.8 higher)	⊕OOO VERY LOW	CRITICAL OUTCOME
Proportion of patients with hypergranulation – general population – stage I and II PU – NPUAP classification												
1 Kim 1996	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	0/18 (0%)	3/26 (11.5%)	OR 0.17 (0.02 to 1.79)	94 fewer per 1000 (from 113 fewer to 74 more)	⊕OOO VERY LOW	IMPORTANT OUTCOME
								11.5%		93 fewer per 1000 (from 112 fewer to 74 more)		

a No report on allocation concealment, sequence generation and blinding; no log-transformation of data
b Confidence interval crossed both MID points
c No standard deviation reported; unclear if sample size was sufficient
d Confidence interval crossed one MID point

Table 54 – Povidone-iodine versus hydrogel

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Povidone-iodine	Hydrogel	Relative (95% CI)	Absolute		
Mean cm²/day to healing – patients with a spinal cord injury – stage I to III – NPUAP classification												
1 Kaya 2005	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	0.09 (SD 0.05)	0.12 (SD 0.16)	-	MD 0.03 lower (0.1 lower to 0.04 higher)	⊕OOO VERY LOW	CRITICAL OUTCOME

a No report on allocation concealment, sequence generation and blinding; no ITT analysis; no log-transformation of data; b Confidence interval crossed one MID point

Table 55 – Cadexomer iodine versus standard treatment

Quality assessment							No of ulcers		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cadexomer iodine	Standard treatment	Relative (95% CI)	Absolute		
Proportion of ulcers reduced with 50% - general population – superficial or deep PU – classification method not reported												
1 Moberg 1983	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/16 (50%)	1/18 (5.6%)	RR 9 (1.26 to 64.33)	444 more per 1000 (from 14 more to 1000 more)	⊕⊕OO LOW	CRITICAL OUTCOME
								5.6%		448 more per 1000 (from 15 more to 1000 more)		
Mean cm² reduction in ulcer area - general population – superficial or deep PU – classification method not reported												
1 Moberg 1983	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2.9 (SD 5.2)	2.5 (SD 4.67)	-	MD 0.4 higher (2.94 lower to 3.74 higher)	⊕⊕OO LOW	CRITICAL OUTCOME
Mean percentage reduction in ulcer area - general population – superficial or deep PU – classification method not reported												
1 Moberg 1983	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30.9 (SD 46)	19.6 (SD 83.16)	-	MD 11.3 higher (33.24 lower to	⊕⊕OO LOW	CRITICAL OUTCOME

										55.84 higher)		

a No report on allocation concealment and blinding; no ITT analysis; no log-transformation of data

Table 56 – Povidone-iodine versus silver sulfazidine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Povidone-iodine	Silver sulfazidine	Relative (95% CI)	Absolute		
Proportion of patients clinically responding within three weeks – general population – stages not reported – classification method not reported												
1 Kucan 1981	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	n=11	n=15	p≤0.022 (favour silver sulfazidine)	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME
								0%		not pooled		
Mean values of bacterial levels – general population – stages not reported – classification method not reported												
1 Kucan 1981	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	n=11	n=15	p<0.01 (favour silver sulfazidine)	not pooled	⊕OOO VERY LOW	IMPORTANT OUTCOME

a No report on allocation concealment and blinding; no ITT analysis
b Only p-value reported

Table 57 – Silver sulfazidine cream versus silver dressing

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Silver sulfazidine	Silver dressing	Relative (95% CI)	Absolute		
Mean percentage reduction in ulcer area – in- and outpatients – stage IV – NPUAP classification												
1 Chuagsuwanich (2011)	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	25.06 (SD 56.13)	36.95 (SD 56.13)	-	MD 11.89 lower (46.68 lower to 22.9 higher)	⊕OOO VERY LOW	CRITICAL OUTCOME
Percentage reduction in PUSH score – in- and outpatients – stage IV – NPUAP classification												

1 Chuagsuwanich (2011)	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	34.51 (n=20)	28.15 (SD 20)	P=0.473	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME
Proportion of patients with adverse events – in- and outpatients – stage IV – NPUAP classification												
1 Chuagsuwanich (2011)	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/20 (0%)	0/20 (0%)	not pooled	RD 0 more (from 90 fewer to 90 more)	⊕⊕OO LOW	IMPORTANT OUTCOME
								0%		-		

a No report on sequence generation, allocation concealment and blinding; no log-transformation of data
b Confidence interval crossed both MID points
c No standard deviation; unknown if sample size was sufficient

Table 58 – Resin salve versus hydrofibre

Quality assessment							No of patients/ulcers		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resin salve	Hydrofibre	Relative (95% CI)	Absolute		
Proportion of patients completely healed – general population – grade II to IV PU – NPUAP classification												
1 Sipponen 2008	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	12/13 (92.3%)	4/9 (44.4%)	RR 2.08 (0.98 to 4.38)	480 more per 1000 (from 9 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								44.4%		480 more per 1000 (from 9 fewer to 1000 more)		
Proportion of ulcers completely healed – general population – grade II to IV PU – NPUAP classification												
1 Sipponen 2008	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	17/18 (94.4%)	4/11 (36.4%)	RR 2.6 (1.18 to 5.72)	582 more per 1000 (from 65 more to 1000 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								36.4%		582 more per 1000 (from 66 more to 1000 more)		
Proportion of ulcers improved – general population – grade II to IV PU – NPUAP classification												

1 Sipponen 2008	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	18/18 (100%)	10/11 (90.9%)	RR 1.11 (0.89 to 1.4)	100 more per 1000 (from 100 fewer to 364 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								90.9%		100 more per 1000 (from 100 fewer to 364 more)		
Proportion of ulcers worsened – general population – grade II to IV PU – NPUAP classification												
1 Sipponen 2008	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	0/18 (0%)	1/11 (9.1%)	OR 0.07 (0.00 to 4.07)	84 fewer per 1000 (from 91 fewer to 198 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								9.1%		84 fewer per 1000 (from 91 fewer to 198 more)		
Mean percentage reduction in ulcer width – general population – grade II to IV PU – NPUAP classification												
1 Sipponen 2008	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[d]	none	93.75 (n=18)	57.14 (n=11)	-	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME
Mean percentage reduction in ulcer depth – general population – grade II to IV PU – NPUAP classification												
1 Sipponen 2008	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[d]	none	88.46 (n=18)	-1.89 (n=11)	-	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME
Speed of healing (days) – general population – grade II to IV PU – NPUAP classification												
1 Sipponen 2008	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[e]	none	(n=18)	(n=11)	p=0.013 (log-rank-test) (favour resin salve)	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME
Proportion of patients with allergic skin reactions – general population – grade II to IV PU – NPUAP classification												
1 Sipponen 2008	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	1/21 (4.8%)	0/16 (0%)	OR 5.82 (0.11 to 304.33)	RD 50 more (from 80 fewer to 180 more)	⊕OOO VERY LOW	IMPORTANT OUTCOME
								0%		-		

a No blinding; no ITT analysis; no log-transformation of data
b Confidence interval crossed one MID point
c Confidence interval crossed both MID points
d No standard deviation reported; small sample size
e Only p-value reported

Table 59 – Antibiotic ointment versus foam dressing

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic	foam dressing	Relative (95% CI)	Absolute		
Proportion of patients completely healed – institutionalized elderly patients – stage II PU – NPUAP classification												
1 Yastrub (2004)	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	15/23 (65.2%)	18/21 (85.7%)	RR 2.43 (0.74 to 7.99)	1000 more per 1000 (from 223 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								85.7%		1000 more per 1000 (from 223 fewer to 1000 more)		
Mean PUSH score at end of treatment – institutionalized elderly patients – stage II PU – NPUAP classification												
1 Yastrub (2004)	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	1.61 (n=19)	3.24 (n=23)	p>0.05	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME

a No report on sequence generation, allocation concealment and blinding
b Confidence interval crossed both MID points
c No standard deviation; unknown if sample size was sufficient

Table 60 – FuChunSanYi Hao ointmentd versus iodophor

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FuChunSanYi Hao ointment	Iodophor	Relative (95% CI)	Absolute		
Proportion of patients completely healed – stage II to IV PU												
1 Tao 2008	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	14/24 (58.3%)	10/24 (41.7%)	RR 1.4 (0.78 to 2.5)	167 more per 1000 (from 92 fewer to 625 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								41.7%		167 more per 1000 (from 92 fewer to 625 more)		
Proportion of patients improved – stage II to IV PU												
1 Tao 2008	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	23/24 (95.8%)	18/24 (75%)	RR 1.28 (1 to 1.63)	210 more per 1000 (from 0 more to 472 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								75%		210 more per 1000 (from 0 more to 472 more)		
Proportion of patients not changed or worsened – stage II to IV PU												
1 Tao 2008	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	1/24 (4.2%)	6/24 (25%)	RR 0.17 (0.02 to 1.28)	207 fewer per 1000 (from 245 fewer to 70 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								25%		207 fewer per 1000 (from 245 fewer to 70 more)		

a No report on sequence generation, allocation concealment, and blinding.
b Confidence interval crossed one MID point
c Confidence interval crossed both MID points
d Formulation ointment: Rhizoma Coptidis, Cortex Phellodendri, Radix Scutellariae, Borneolum Syntheticum, Myrrha, Sesame Oil

Table 61 – RuYiZhuHuang ointmentc versus iodophor

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RuYiZhuHuang ointment	Iodophor	Relative (95% CI)	Absolute		
Proportion of patients completely healed – stage I to IV												
3 Li 2007a; Li 2007b; Luo 1998	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	114/125 (91.2%)	57/123 (46.3%)	RR 1.97 (1.61 to 2.4)	450 more per 1000 (from 283 more to 649 more)	⊕⊕OO LOW	CRITICAL OUTCOME
								47.7%		463 more per 1000 (from 291 more to 668 more)		
Proportion of patients improved – stage I to IV												
3 Li 2007a; Li 2007b; Luo 1998	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	117/125 (93.6%)	97/123 (78.9%)	RR 1.18 (1.07 to 1.31)	142 more per 1000 (from 55 more to 244 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								76.3%		137 more per 1000 (from 53 more to 237 more)		
Proportion of patients not changed or worsened – stage I to IV												
3 Li 2007a; Li 2007b;	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/125 (0.8%)	26/123 (21.1%)	OR 0.13 (0.06 to	178 fewer per 1000 (from 142 fewer to	⊕⊕OO LOW	CRITICAL OUTCOME

Luo 1998									0.28)	196 fewer)		
								23.7%		198 fewer per 1000 (from 157 fewer to 219 fewer)		

a Li 2007a: no report on allocation concealment, sequence generation and blinding; Li 2007b: no report on blinding; Luo 1998: no report on allocation concealment and blinding
b Confidence interval crossed one MID point
c Ointment formulation: Rhizoma Curcumae Longae, Radix et Rhizoma Rhei, Cortex Phellodendri, Rhizoma Atractylodis, Cortex Magnoliae Officinalis, Pericarpium Citri Reticulatae, Radix Glycyrrhizae, Rhizoma Arisaematis, Radix Angelicae Dahuricae, Radix Trichosanthis, Sesame Oil.

Table 62 – ShenJi ointmentc versus iodophor

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ShenJi oinment	Iodophor	Relative (95% CI)	Absolute		
Proportion of patients completely healed – stage III and IV												
1 Zhao 2010	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/22 (86.4%)	7/22 (31.8%)	RR 2.71 (1.44 to 5.12)	544 more per 1000 (from 140 more to 1000 more)	⊕⊕OO LOW	CRITICAL OUTCOME
								31.8%		544 more per 1000 (from 140 more to 1000 more)		
Proportion of patients improved – stage III and IV												
1 Zhao 2010	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	21/22 (95.5%)	13/22 (59.1%)	RR 1.62 (1.13 to 2.31)	366 more per 1000 (from 77 more to 774 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								59.1%		366 more per 1000 (from 77 more to 774 more)		

Proportion of patients not changed or worsened – stage III and IV												
1 Zhao 2010	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	1/22 (4.5%)	9/22 (40.9%)	RR 0.11 (0.02 to 0.8)	364 fewer per 1000 (from 82 fewer to 401 fewer)	⊕OOO VERY LOW	CRITICAL OUTCOME
								40.9%		364 fewer per 1000 (from 82 fewer to 401 fewer)		

a No report on allocation concealment and blinding
b Confidence interval crossed one MID point
c Ointment formulation: Crinis Carbonisatus, Tortoise plastron, Radix Angelicae Sinensis, Radix Rehmanniae Recens, Gypsum, Galamina, Yellow Wax, Sesame Oil

Table 63 – JiFuYuan ointmentc versus gentamicin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JiFuYuan ointment	Gentamicin	Relative (95% CI)	Absolute		
Proportion of patients completely healed – stage II to IV												
1 Bao 2006	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/23 (78.3%)	4/23 (17.4%)	RR 4.5 (1.8 to 11.25)	609 more per 1000 (from 139 more to 1000 more)	⊕⊕OO LOW	CRITICAL OUTCOME
								17.4%		609 more per 1000 (from 139 more to 1000 more)		
Proportion of patients improved – stage II to IV												
1 Bao 2006	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	22/23 (95.7%)	15/23 (65.2%)	RR 1.47 (1.07 to 2)	307 more per 1000 (from 46 more to 652 more)	⊕OOO VERY LOW	CRITICAL OUTCOME

								65.2%		306 more per 1000 (from 46 more to 652 more)		
Proportion of patients not changed or worsened – stage II to IV												
1 Bao 2006	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	1/23 (4.3%)	8/23 (34.8%)	RR 0.12 (0.02 to 0.92)	306 fewer per 1000 (from 28 fewer to 341 fewer)	⊕OOO VERY LOW	CRITICAL OUTCOME
								34.8%		306 fewer per 1000 (from 28 fewer to 341 fewer)		

a No report on sequence generation, allocation concealment and blinding
b Confidence interval crossed one MID point
c Ointment formulation: Radix Scutellariae, Cortex Phellodendri, Borneolum Syntheticum, Radix Angelicae Sinensis, Radix et Rhizoma Rhei, Sanguis Draconis, Sesame Oil

Table 64 – FuFangDahuang Dingc versus Chloramphenicol and sulfazidine silver powder

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FuFangDahuang Ding	Chloramphenicol and sulfazidine silver powder	Relative (95% CI)	Absolute		
Proportion of patients completely healed – stage not reported												
1 Jing 2006	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	23/30 (76.7%)	13/25 (52%)	RR 1.47 (0.96 to 2.26)	244 more per 1000 (from 21 fewer to 655 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								52%		244 more per 1000 (from 21 fewer to 655		

										more)		
Proportion of patients improved – stage not reported												
1 Jing 2006	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	30/30 (100%)	19/25 (76%)	RR 1.31 (1.05 to 1.65)	236 more per 1000 (from 38 more to 494 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								76%		236 more per 1000 (from 38 more to 494 more)		
Proportion of patients not changed or worsened – stage not reported												
1 Jing 2006	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/30 (0%)	6/25 (24%)	OR 0.09 (0.02 to 0.48)	212 fewer per 1000 (from 108 fewer to 234 fewer)	⊕⊕OO LOW	CRITICAL OUTCOME
								24%		212 fewer per 1000 (from 108 fewer to 234 fewer)		

a No report on sequence generation and blinding
b Confidence interval crossed one MID point
c Ointment formulation: Radix et Rhizoma Rhei (150 g), Rhizoma Polygoni Cuspidati (150 g), Natrii Sulfas (10 g), Borneolum Syntheticum (10 g), Fresh Aloe (200 g).

Table 65 – ShenJiYuHong ointmentc versus saline

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ShenJiYuHong ointment	Saline	Relative (95% CI)	Absolute		
Proportion of patients completely healed – stage III and IV												
1 Chen 2008	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/18 (66.7%)	2/17 (11.8%)	RR 5.67 (1.48 to 21.69)	549 more per 1000 (from 56 more to 1000 more)	⊕⊕OO LOW	CRITICAL OUTCOME
								11.8%		551 more per 1000 (from 57 more to 1000 more)		
Proportion of patients improved – stage III and IV												
1 Chen 2008	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	18/18 (100%)	10/17 (58.8%)	RR 1.67 (1.12 to 2.48)	394 more per 1000 (from 71 more to 871 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								58.8%		394 more per 1000 (from 71 more to 870 more)		
Proportion of patients not changed or worsened – stage III and IV												
1 Chen 2008	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/18 (0%)	7/17 (41.2%)	OR 0.08 (0.02 to 0.42)	359 fewer per 1000 (from 185 fewer to 398 fewer)	⊕⊕OO LOW	CRITICAL OUTCOME
								41.2%		359 fewer per 1000 (from 185 fewer to 398 fewer)		

a No report on sequence generation, allocation concealment and blinding
b Confidence interval crossed one MID point
c Ointment formulation: Radix Angelicae Sinensis, Radix Angelicae Dahuricae, White Wax, Radix Glycyrrhizae, Radix Lithospermi, Sanguis Draconis, Sesame Oil.

Table 66 – ShenJi ointmentc versus antibacterial

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ShenJi ointment	Antibacterial	Relative (95% CI)	Absolute		
Proportion of patients completely healed – stage III and IV												
1 Zhang 2010	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	20/57 (35.1%)	11/52 (21.2%)	RR 1.66 (0.88 to 3.12)	140 more per 1000 (from 25 fewer to 448 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								21.2%		140 more per 1000 (from 25 fewer to 449 more)		
Proportion of patients improved – stage III and IV												
1 Zhang 2010	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	53/57 (93%)	40/52 (76.9%)	RR 1.21 (1.02 to 1.43)	162 more per 1000 (from 15 more to 331 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								76.9%		161 more per 1000 (from 15 more to 331 more)		
Proportion of patients not changed or worsened – stage III and IV												
1 Zhang 2010	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	4/57 (7%)	12/52 (23.1%)	RR 0.3 (0.1 to 0.88)	162 fewer per 1000 (from 28 fewer to 208 fewer)	⊕OOO VERY LOW	CRITICAL OUTCOME

								23.1%		162 fewer per 1000 (from 28 fewer to 208 fewer)		

a No report on allocation concealment and blinding
b Confidence interval crossed one MID point
c Ointment formulation: Rhizoma Coptidis, Cortex Phellodendri, Rhizoma Curcumae Longae, Radix Angelicae Sinensis, Radix Rehmanniae Recens, Sesame Oil.

Table 67 – SanHuangZhang Yu YouSha ointmentc versus nitrofurazone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SanHuangZhang Yu YouSha	Nitrofurazone	Relative (95% CI)	Absolute		
Proportion of patients completely healed – stage not reported												
1 Li 2008	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	84/200 (42%)	22/108 (20.4%)	RR 2.06 (1.37 to 3.1)	216 more per 1000 (from 75 more to 428 more)	⊕⊕OO LOW	CRITICAL OUTCOME
								20.4%		216 more per 1000 (from 75 more to 428 more)		
Proportion of patients improved – stage not reported												
1 Li 2008	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	188/200 (94%)	80/108 (74.1%)	RR 1.27 (1.13 to 1.43)	200 more per 1000 (from 96 more to 319 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								74.1%		200 more per 1000 (from 96 more to 319 more)		

Proportion of patients not changed or worsened – stage not reported												
1 Li 2008	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/200 (6%)	28/108 (25.9%)	RR 0.23 (0.12 to 0.44)	200 fewer per 1000 (from 145 fewer to 228 fewer)	⊕⊕OO LOW	CRITICAL OUTCOME
								25.9%		199 fewer per 1000 (from 145 fewer to 228 fewer)		

a No report on sequence generation, allocation concealment and blinding
b Confidence interval crossed one MID point
c Ointment formulation: Rhizoma Coptidis (350 g), Cortex Phellodendri (150 g), Radix Scutellariae (100 g), Rhizoma Polygoni Cuspidati (150 g), Radix Sanguisorbae (100 g), Sesame Oil (2000 g).

Table 68 – Insulin versus standard treatment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Insulin	Placebo	Relative (95% CI)	Absolute		
Mean rate of healing - nursing home patients – stage not reported – PU definition was reported[c]												
1 Van Ort (1976)	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	n=6	n=8	p=0.05 (favour insulin group)	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME

a No report on allocation concealment and blinding
b Only p-value reported
c PU were defined as a break in skin continuity as evidenced by epidermal or dermal injury involving erythema, pallor, cyanosis, and superficial erosion

Table 69 – Different growth factors versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Growth factors	Placebo	Relative (95% CI)	Absolute		
Proportion of patients completely healed – general population and denervated patients – stage II and above – NPUAP and Yarkony classification[i]												
Hirshberg 2003; Landi 2003; Mustoe 1994; Payne 2001; Rees 1999; Robson 1992b, 1994	randomised trials	very serious[a]	very serious[b]	no serious indirectness	very serious[d]	none	54/222 (24.3%)	12/94 (12.8%)	RR 2.33 (0.54 to 10.02)	170 more per 1000 (from 59 more to 1000 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								0%		-		
Proportion of patients completely healed - TGF-β3[j] versus placebo – inpatients – stage III and IV – NPUAP classification												
Hirshberg 2003	randomised trials	very serious[c]	no serious inconsistency	no serious indirectness	very serious[d]	none	1/9 (11.1%)	0/5 (0%)	OR 4.74 (0.08 to 283.15)	-	⊕OOO VERY LOW	CRITICAL OUTCOME
								0%		-		
Proportion of patients completely healed (foot ulcers) - mNGF[j] versus placebo – nursing home patients – stage II and above - Yarkony classification												
Landi 2003	randomised trials	Serious[e]	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/18 (44.4%)	1/18 (5.6%)	RR 8.00 (1.11 to 57.57)	389 more per 1000 (from 6 more to 1000 more)	⊕⊕⊕O MODERATE	CRITICAL OUTCOME
								5.6%		392 more per 1000 (from 6 more to 1000 more)		
Proportion of patients completely healed - rPDGF-BB[j] versus placebo – general population and denervated patients – stage III and IV – NPUAP classification[i]												
Mustoe 1994; Rees 1999; Robson 1992b	randomised trials	very serious[f]	no serious inconsistency	no serious indirectness	very serious[d]	none	18/136 (13.2%)	1/52 (1.9%)	RR 2.55 (0.56 to 11.65)	30 more per 1000 (from 8 more to 205 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								0%		-		

Proportion of patients completely healed - bFGF or GM-CSF[j] versus placebo – inpatients – stage III and IV – classification system not reported												
Payne 2001	randomised trials	very serious[g]	no serious inconsistency	no serious indirectness	very serious[d]	none	27/41 (65.9%)	10/13 (76.9%)	RR 0.86 (0.59 to 1.24)	108 fewer per 1000 (from 315 fewer to 185 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								76.9%		108 fewer per 1000 (from 315 fewer to 185 more)		
Proportion of patients completely healed - rIL-1β[j] versus placebo – denervated patients – stage III and IV – classification system not reported												
Robson 1994	randomised trials	very serious[h]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/18 (0%)	0/6 (0%)	not pooled	RD 0 more (from 200 fewer to 200 more)	⊕⊕OO LOW	CRITICAL OUTCOME
								0%		-		

a Hirshberg (2003): no report on sequence generation and allocation concealment and report of blinding, but no further information; Landi (2003): allocation according to age, group, sex and ulcer area and blinding of nurses and outcome assessor, but no blinding of patient; Mustoe (1994), Payne (2001) and Robson (1994): no report on sequence generation, allocation concealment and report of double blinding, but no further information; Rees (1999): no report on sequence generation, allocation concealment and blinding; Robson (1992b): no report on sequence generation, unequal allocation and only blinding of outcome assessor
b Heterogeneity: p-value < 0.1 and I^2 > 50%
c Hirshberg (2003): no report on sequence generation and allocation concealment and report of blinding, but no further information
d Confidence interval crossed both MID points
e Landi (2003): allocation according to age, group, sex and ulcer area and blinding of nurses and outcome assessor, but no blinding of patient
f No explanation was provided
g Payne (2001): no report on sequence generation, allocation concealment and report of double blinding, but no further information
h Robson (1994): no report on sequence generation, allocation concealment and report of double blinding, but no further information
I Hirshberg (2003) and Rees (1999): NPUAP classification; Landi (2003): Yarkony classification; Mustoe (1994), Robson (1992b and 1994), and Payne (2001): classification system not reported
j TGF-β3: topical growth factor; mNGF: S murine nerve growth factor; rPDGF-BB: recombinant platelet-derived growth factor –BB; bFGF: basic fibroblast growth factor; GM-CSF: granulocyte-macrophage/colony-stimulating factor; rIL-1β: rhu- interleukin

Table 70 – Topical growth factor – beta 3 (1.0µg/cm²) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TGF-β3 (1.0ug/cm²)	Placebo	Relative (95% CI)	Absolute		
Proportion of patients completely healed – inpatients – stage III and IV – NPUAP classification												
Hirshberg 2003	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/4 (0%)	0/5 (0%)	not pooled	not pooled	⊕⊕OO LOW	CRITICAL OUTCOME
								0%		not pooled		
Mean percentage reduction in ulcer area – inpatients – stage III and IV – NPUAP classification												
Hirshberg 2003	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	70 (n=4)	30 (n=5)	-	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME
Mean percentage reduction in ulcer volume – inpatients – stage III and IV – NPUAP classification												
Hirshberg 2003	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	75 (n=4)	20 (n=5)	-	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME

a Hirshberg (2003): no report on sequence generation and allocation concealment and report of blinding, but no further information; no log-transformation of data
b No standard deviation; small sample size

Table 71 – Topical growth factor – beta 3 (1.0µg/cm²) versus topical growth factor – beta 3 (2.5µg/cm²)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TGF-β3 (1.0ug/cm²)	TGF-β3 (2.5ug/cm²)	Relative (95% CI)	Absolute		
Proportion of patients completely healed – inpatients – stage III and IV – NPUAP classification												
Hirshberg 2003	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	0/4 (0%)	1/5 (20%)	OR 0.17 (0 to 8.54)	159 fewer per 1000 (from 200 fewer to 481 more)	⊕OOO VERY	CRITICAL OUTCOME

								20%		159 fewer per 1000 (from 200 fewer to 481 more)	LOW	
Mean percentage reduction in ulcer area – inpatients – stage III and IV – NPUAP classification												
Hirshberg 2003	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	70 (n=4)	60 (n=5)	-	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME
Mean percentage reduction in ulcer volume – inpatients – stage III and IV – NPUAP classification												
Hirshberg 2003	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	75 (n=4)	60 (n=5)	-	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME

a Hirshberg (2003): no report on sequence generation and allocation concealment and report of blinding, but no further information; no log-transformation of data
b Confidence interval crossed both MID points
c No standard deviation; small sample size

Table 72 – Topical growth factor – beta 3 (2.5µg/cm²) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TGF-β3 (2.5ug/cm²)**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Proportion of patients completely healed – inpatients – stage III and IV – NPUAP classification												
Hirshberg 2003	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/5 (20%)	0/5 (0%)	OR 7.39 (0.15 to 372.38)	RD 200 more (from 210 fewer to 610 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								0%		-		
Mean percentage reduction in ulcer area – inpatients – stage III and IV – NPUAP classification												
Hirshberg 2003	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	60 (n=5)	30 (n=5)	-	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME
Mean percentage reduction in ulcer volume – inpatients – stage III and IV – NPUAP classification												
Hirshberg	randomised	very	no serious	no serious	very	none	60	20	-	not pooled	⊕OOO	CRITICAL

2003	trials	serious[a]	inconsistency	indirectness	serious[c]		(n=5)	(n=5)			VERY LOW	OUTCOME

a Hirshberg (2003): no report on sequence generation and allocation concealment and report of blinding, but no further information; no log-transformation of data
b Confidence interval crossed both MID points
c No standard deviation; small sample size

Table 73 – Nerve growth factor (2.5 S murine) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NGF	Placebo	Relative (95% CI)	Absolute		
Proportion of patients completely healed (foot ulcers) – nursing home patients – stage II and above - Yarkony classification												
Landi 2003	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	8/18 (44.4%)	1/18 (5.6%)	RR 8 (1.11 to 57.57)	389 more per 1000 (from 6 more to 1000 more)	⊕⊕OO LOW	CRITICAL OUTCOME
								5.6%		392 more per 1000 (from 6 more to 1000 more)		
Proportion of patients improved by 3 or more stages (foot ulcers) – nursing home patients – stage II and above - Yarkony classification												
Landi 2003	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	5/18 (27.8%)	0/18 (0%)	OR 9.56 (1.48 to 61.61)	RD 280 more (from 60 more to 490 more)	⊕⊕⊕O MODERATE	CRITICAL OUTCOME
								0%		-		
Proportion of patients improved by 2 stages (foot ulcers) – nursing home patients – stage II and above - Yarkony classification												
Landi 2003	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/18 (77.8%)	2/18 (11.1%)	RR 7 (1.85 to 26.46)	667 more per 1000 (from 94 more to 1000 more)	⊕⊕⊕O MODERATE	CRITICAL OUTCOME
								11.1%		666 more per 1000 (from 94 more to 1000 more)		

Proportion of patients improved by 1 stages (foot ulcers) – nursing home patients – stage II and above - Yarkony classification												
Landi 2003	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/18 (100%)	8/18 (44.4%)	RR 2.18 (1.31 to 3.61)	524 more per 1000 (from 138 more to 1000 more)	⊕⊕⊕O MODERATE	CRITICAL OUTCOME
								44.4%		524 more per 1000 (from 138 more to 1000 more)		
Mean mm² reduction in ulcer area (foot ulcers) – nursing home patients – stage II and above - Yarkony classification												
Landi 2003	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	738 (SD 393)	485 (SD 384)	-	MD 253 higher (0.83 lower to 506.83 higher)	⊕⊕OO LOW	CRITICAL OUTCOME
Mean mm² reduction in ulcer (foot ulcers) – nursing home patients – stage II and above - Yarkony classification												
Landi 2003	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	6.5 (SD 0.3)	5.9 (SD 0.3)	-	MD 0.6 higher (0.4 to 0.8 higher) (adjusted for baseline ulcer area, location and duration)	⊕⊕⊕O MODERATE	CRITICAL OUTCOME
Proportion of patients with adverse events (foot ulcers) – nursing home patients – stage II and above - Yarkony classification												
Landi 2003	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/18 (0%)	0/18 (0%)	not pooled	RD 0 more (from 100 fewer to 100 more)	⊕⊕⊕O MODERATE	CRITICAL OUTCOME
								0%		-		

a Landi (2003): allocation according to age, group, sex and ulcer area and blinding of nurses and outcome assessor, but no blinding of patient
b Confidence interval crossed one MID point

Table 74 – Recombinant platelet-derived growth factor-BB (100µg/ml) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rPDGF-BB (100ug/ml)	Placebo	Relative (95% CI)	Absolute		
Proportion of patients completely healed – general population and denervated patients – stage III and IV – NPUAP classification[e]												
Mustoe 1994;; Robson 1992b	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Very serious[b]	none	8/29 (27.6%)	2/21 (9.5%)	RR 2.68 (0.74 to 9.74)	160 more per 1000 (from 25 fewer to 832 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								7.1%		119 more per 1000 (from 18 fewer to 621 more)		
Ulcer volume (g) at end of treatment – general population – stage III and IV – classification system not reported												
Mustoe 1994	randomised trials	very serious[c]	no serious inconsistency	no serious indirectness	very serious[d]	none	1.75 (n=16)	3.5 (n=14)	-	not pooled (adjusted for initial volume)	⊕OOO VERY LOW	CRITICAL OUTCOME

a Mustoe (1994): no report on sequence generation, allocation concealment and report of double blinding, but no further information; Robson (1992b): no report on sequence generation, unequal allocation and only blinding of outcome assessor
b Confidence interval crossed both MID points
c Mustoe (1994): no report on sequence generation, allocation concealment and report of double blinding, but no further information
d No standard deviation; small sample size
e Mustoe (1994): classification system not reported; Robson (1992b): NPUAP classification

Table 75 – Recombinant platelet-derived growth factor-BB (100µg/ml) versus recombinant platelet-derived growth factor-BB (300µg/ml)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rPDGF-BB (100ug/ml)	rPDGF-BB (300ug/ml)	Relative (95% CI)	Absolute		
Proportion of patients completely healed – general population – stage III and IV – classification system not reported												
Mustoe 1994	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	6/16 (37.5%)	3/12 (25%)	RR 1.5 (0.47 to 4.82)	125 more per 1000 (from 132 fewer to 955 more)	⊕OOO VERY	CRITICAL OUTCOME

								25%		125 more per 1000 (from 132 fewer to 955 more)	LOW	
Ulcer volume (g) at end of treatment – general population – stage III and IV – classification system not reported												
Mustoe 1994	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	1.75 (n=16)	2.0 (n=12)	-	not pooled (adjusted for initial volume)	⊕OOO VERY LOW	CRITICAL OUTCOME

1 Mustoe (1994): no report on sequence generation, allocation concealment and report of double blinding, but no further information
2 Confidence interval crossed both MID points
3 No standard deviation; small sample size

Table 76 – Recombinant platelet-derived growth factor-BB (300µg/ml) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**rPDGF-BB (300ug/ml)**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Proportion of patients completely healed – general population – stage III and IV – classification system not reported												
Mustoe 1994	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	3/12 (25%)	2/14 (14.3%)	RR 1.75 (0.35 to 8.79)	107 more per 1000 (from 93 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								14.3%		107 more per 1000 (from 93 fewer to 1000 more)		
Ulcer volume (g) at end of treatment – general population – stage III and IV – classification system not reported												
Mustoe 1994	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	2.0 (n=12)	3.5 (n=14)	-	not pooled (adjusted for initial volume)	⊕OOO VERY LOW	CRITICAL OUTCOME

a Mustoe (1994): no report on sequence generation, allocation concealment and report of double blinding, but no further information
b Confidence interval crossed both MID points
c No standard deviation; small sample size

Table 77 – Granulo-macrophage/colony-stimulating factor (2.0µg/cm²) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rGM-CSF (2.0ug/cm²)	Placebo	Relative (95% CI)	Absolute		
Proportion of patients completely healed (after 1 year) – inpatients – stage III and IV – classification not reported												
Payne 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	8/14 (57.1%)	10/13 (76.9%)	RR 0.74 (0.43 to 1.28)	200 fewer per 1000 (from 438 fewer to 215 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								76.9%		200 fewer per 1000 (from 438 fewer to 215 more)		
Proportion of patients worsened (after 1 year) – inpatients – stage III and IV – classification not reported												
Payne 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	2/14 (14.3%)	0/13 (0%)	OR 7.43 (0.44 to 125.76)	RD 140 more (from 70 fewer to 360 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								0%		-		
Mean percentage reduction in ulcer area – inpatients – stage III and IV – classification not reported												
Robson 2000	randomised trials	very serious[a,d]	no serious inconsistency	no serious indirectness	Very serious[b]	none	67 (SD 24)	71 (SD 11)	-	MD 4 lower (17.36 lower to 9.36 higher)	⊕OOO VERY LOW	CRITICAL OUTCOME
Median percentage reduction in ulcer area – inpatients – stage III and IV – classification not reported												
Robson 2000	randomised trials	very serious[a,d]	no serious inconsistency	no serious indirectness	very serious[c]	none	70 (range: 3-93) (n=15)	72 (range: 39-84) (n=15)	-	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME

a No report on sequence generation, allocation concealment and report of double blinding, but no further information
b Confidence interval crossed both MID points
c No standard deviation; small sample size
d No log-transformation of data

Table 78 – Granulo-macrophage/colony-stimulating factor (2.0µg/cm²) versus basic fibroblast growth factor (5.0µg/cm²)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rGM-CSF (2.0ug/cm²)	rBFGF (5.0ug/cm²)	Relative (95% CI)	Absolute		
Proportion of patients completely healed (after 1 year) – inpatients – stage III and IV – classification not reported												
Payne 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	8/14 (57.1%)	10/14 (71.4%)	RR 0.8 (0.46 to 1.4)	143 fewer per 1000 (from 386 fewer to 286 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								71.4%		143 fewer per 1000 (from 386 fewer to 286 more)		
Proportion of patients worsened (after 1 year) – inpatients – stage III and IV – classification not reported												
Payne 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	2/14 (14.3%)	4/14 (28.6%)	RR 0.5 (0.11 to 2.3)	143 fewer per 1000 (from 254 fewer to 371 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								28.6%		143 fewer per 1000 (from 255 fewer to 372 more)		
Mean percentage reduction in ulcer area – inpatients – stage III and IV – classification not reported												
Robson 2000	randomised trials	very serious[a,e]	no serious inconsistency	no serious indirectness	Serious[c]	none	67 (SD 24)	75 (SD 19)	-	MD 8 lower (23.49 lower to 7.49 higher)	⊕OOO VERY LOW	CRITICAL OUTCOME
Median percentage reduction in ulcer area – inpatients – stage III and IV – classification not reported												
Robson 2000	randomised trials	very serious[a,e]	no serious inconsistency	no serious indirectness	very serious[d]	none	70 (range:3-93) (n=15)	79 (range:42-99) (n=15)	-	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME

a No report on sequence generation, allocation concealment and report of double blinding, but no further information
b Confidence interval crossed both MID points
c Confidence interval crossed one MID point
d No standard deviation; small sample size
e No log-transformation of data

Table 79 – Granulo-macrophage/colony-stimulating factor (2.0µg/cm²) versus granulo-macrophage/colony-stimulating factor (2.0µg/cm²) and basic fibroblast growth factor (5.0µg/cm²)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rGM-CSF	rGM-CSF/rBFGF	Relative (95% CI)	Absolute		
Proportion of patients completely healed (after 1 year) – inpatients – stage III and IV – classification not reported												
Payne 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	8/14 (57.1%)	9/13 (69.2%)	RR 0.83 (0.46 to 1.48)	118 fewer per 1000 (from 374 fewer to 332 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								69.2%		118 fewer per 1000 (from 374 fewer to 332 more)		
Proportion of patients worsened (after 1 year) – inpatients – stage III and IV – classification not reported												
Payne 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	2/14 (14.3%)	1/13 (7.7%)	RR 1.86 (0.19 to 18.13)	66 more per 1000 (from 62 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								7.7%		66 more per 1000 (from 62 fewer to 1000 more)		
Mean percentage reduction in ulcer area – inpatients – stage III and IV – classification not reported												
Robson 2000	randomised trials	very serious[a,d]	no serious inconsistency	no serious indirectness	very serious[b]	none	67 (SD 24)	68 (SD 21)	-	MD 1 lower (16.92 lower to 14.92 higher)	⊕OOO VERY LOW	CRITICAL OUTCOME
Median percentage reduction in ulcer area – inpatients – stage III and IV – classification not reported												
Robson 2000	randomised trials	very serious[a,d]	no serious inconsistency	no serious indirectness	very serious[c]	none	70 (range: 3-93)	73 (range:29-	-	not pooled	⊕OOO VERY	CRITICAL OUTCOME

							(n=15)	98) (n=16)			LOW	

a No report on sequence generation, allocation concealment and report of double blinding, but no further information; b Confidence interval crossed both MID points
c No standard deviation; small sample size
d No log-transformation of data

Table 80 – Basic fibroblast growth factor (5.0µg/cm²) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rBFGF	Placebo	Relative (95% CI)	Absolute		
Proportion of patients completely healed (after 1 year) – inpatients – stage III and IV – classification not reported												
Payne 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	10/14 (71.4%)	10/13 (76.9%)	RR 0.93 (0.59 to 1.45)	54 fewer per 1000 (from 315 fewer to 346 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								76.9%		54 fewer per 1000 (from 315 fewer to 346 more)		
Proportion of patients worsened (after 1 year) – inpatients – stage III and IV – classification not reported												
Payne 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[c]	none	4/14 (28.6%)	0/13 (0%)	OR 8.85 (1.1 to 71.2)	RD 290 more (from 30 fewer to 540 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								0%		-		
Mean percentage reduction in ulcer area – inpatients – stage III and IV – classification not reported												
Robson 2000	randomised trials	very serious[a,e]	no serious inconsistency	no serious indirectness	Serious[c]	none	79 (SD 19)	71 (SD 11)	-	MD 4 higher (7.11 lower to 15.11 higher)	⊕OOO VERY LOW	CRITICAL OUTCOME
Median percentage reduction in ulcer area – inpatients – stage III and IV – classification not reported												
Robson 2000	randomised trials	very serious[a,e]	no serious inconsistency	no serious indirectness	very serious[d]	none	79 (range:42-99)	72 (range:39-84)	-	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME

							(n=15)	(n=15)				

a No report on sequence generation, allocation concealment and report of double blinding, but no further information
b Confidence interval crossed both MID points
c Confidence interval crossed one MID point
d No standard deviation; small sample size
e No log-transformation of data

Table 81 – Basic fibroblast growth factor (5.0µg/cm²) versus granulo-macrophage/colony-stimulating factor (2.0µg/cm²) and basic fibroblast growth factor (5.0µg/cm²)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rBFGF	rGM-CSF/rBFGF	Relative (95% CI)	Absolute		
Proportion of patients completely healed (after 1 year) – inpatients – stage III and IV – classification not reported												
Payne 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	10/14 (71.4%)	9/13 (69.2%)	RR 1.03 (0.63 to 1.69)	21 more per 1000 (from 256 fewer to 478 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								69.2%		21 more per 1000 (from 256 fewer to 477 more)		
Proportion of patients worsened (after 1 year) – inpatients – stage III and IV – classification not reported												
Payne 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	4/14 (28.6%)	1/13 (7.7%)	RR 3.71 (0.47 to 29.06)	208 more per 1000 (from 41 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								7.7%		209 more per 1000 (from 41 fewer to 1000 more)		
Mean percentage reduction in ulcer area – inpatients – stage III and IV – classification not reported												
Robson 2000	randomised trials	very serious[a,e]	no serious inconsistency	no serious indirectness	Serious[c]	none	75 (SD 19)	68 (SD 21)	-	MD 7 higher (7.08 lower to 21.08 higher)	⊕OOO VERY LOW	CRITICAL OUTCOME
Median percentage reduction in ulcer area – inpatients – stage III and IV – classification not reported												

Robson 2000	randomised trials	very serious[a,e]	no serious inconsistency	no serious indirectness	very serious[d]	none	79 (range: 42-99 (n=15)	73 (range: 29-98) (n=16)	-	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME

a No report on sequence generation, allocation concealment and report of double blinding, but no further information; b Confidence interval crossed both MID point; c Confidence interval crossed one MID point; d No standard deviation; small sample size
e No log-transformation of data

Table 82 – Granulo-macrophage/colony-stimulating factor (2.0µg/cm²) and basic fibroblast growth factor (5.0µg/cm²) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rGM-CSF/rBFGF	Placebo	Relative (95% CI)	Absolute		
Proportion of patients completely healed (after 1 year) – inpatients – stage III and IV – classification not reported												
Payne 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	9/13 (69.2%)	10/13 (76.9%)	RR 0.9 (0.56 to 1.44)	77 fewer per 1000 (from 338 fewer to 338 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								76.9%		77 fewer per 1000 (from 338 fewer to 338 more)		
Proportion of patients worsened (after 1 year) – inpatients – stage III and IV – classification not reported												
Payne 2001	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/13 (7.7%)	0/13 (0%)	OR 7.39 (0.15 to 372.38)	RD 80 more (from 110 fewer to 270 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								0%		-		
Mean percentage reduction in ulcer area – inpatients – stage III and IV – classification not reported												
Robson 2000	randomised trials	very serious[a,d]	no serious inconsistency	no serious indirectness	very serious[b]	none	168 (SD 21)	71 (SD 11)	-	MD 3 lower (14.7 lower to 8.7 higher)	⊕OOO VERY LOW	CRITICAL OUTCOME
Median percentage reduction in ulcer area – inpatients – stage III and IV – classification not reported												
Robson	randomised	very	no	serious	no	serious	very	none	73	72	-	not pooled	⊕OOO	CRITICAL

2000	trials	serious[a,d]	inconsistency	indirectness	serious[c]		(range:29-98) (n=16)	(range:39-84) (n=15)			VERY LOW	OUTCOME

a No report on sequence generation, allocation concealment and report of double blinding, but no further information
b Confidence interval crossed both MID points
c No standard deviation; small sample size
d No log-transformation of data

Table 83 – Recombinant platelet-derived growth factor-BB (100.0µg/g) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rPDGF-BB	Placebo	Relative (95% CI)	Absolute		
Proportion of patients completely healed – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/31 (22.6%)	0/31 (0%)	OR 9.19 (1.93 to 43.75)	RD 230 more (from 70 more to 380 more)	⊕⊕OO LOW	CRITICAL OUTCOME
								0%		-		
Proportion of patients healed 90% or higher – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	18/31 (58.1%)	9/31 (29%)	RR 2 (1.07 to 3.74)	290 more per 1000 (from 20 more to 795 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								29%		290 more per 1000 (from 20 more to 795 more)		
Median percentage reduction in ulcer volume – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	99.6 (n=31)	99.1 (n=31)	p=0.013	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME
Proportion of patients with osteomyelitis – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[d]	none	2/31 (6.5%)	1/31 (3.2%)	RR 2 (0.19 to 20.93)	32 more per 1000 (from 26 fewer to 643	⊕OOO VERY	IMPORTANT OUTCOME

										more)	LOW	
								3.2%		32 more per 1000 (from 26 fewer to 638 more)		
Proportion of patients with infection – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[d]	none	0/31 (0%)	1/31 (3.2%)	OR 0.14 (0 to 6.82)	28 fewer per 1000 (from 32 fewer to 153 more)	⊕OOO VERY LOW	IMPORTANT OUTCOME
								3.2%		27 fewer per 1000 (from 32 fewer to 152 more)		
Proportion of patients with sepsis – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/31 (0%)	0/31 (0%)	not pooled	RD 0 more (from 60 fewer to 60 more)	⊕⊕OO LOW	IMPORTANT OUTCOME
								0%		-		
Proportion of patients with adverse events other than osteomyelitis, infection and sepsis – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[d]	none	2/31 (6.5%)	2/31 (6.5%)	RR 1 (0.15 to 6.66)	0 fewer per 1000 (from 55 fewer to 365 more)	⊕OOO VERY LOW	IMPORTANT OUTCOME
								6.5%		0 fewer per 1000 (from 55 fewer to 368 more)		

a Rees (1999): no report on sequence generation, allocation concealment and blinding; no log-transformation of data
b Confidence interval crossed one MID point
c No standard deviation; unknown if sample size was sufficient
d Confidence interval crossed both MID points

Table 84 – Recombinant platelet-derived growth factor-BB (100.0µg/g) versus recombinant platelet-derived growth factor-BB (300.0µg/g) alternated with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rPDGF-BB (100ug/g)	rPDGF-BB (300ug/g) alternated with placebo	Relative (95% CI)	Absolute		
Proportion of patients completely healed – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	7/31 (22.6%)	6/32 (18.8%)	RR 1.2 (0.46 to 3.18)	38 more per 1000 (from 101 fewer to 409 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								18.8%		38 more per 1000 (from 102 fewer to 410 more)		
Proportion of patients healed 90% or higher – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	18/31 (58.1%)	19/32 (59.4%)	RR 0.98 (0.65 to 1.48)	12 fewer per 1000 (from 208 fewer to 285 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								59.4%		12 fewer per 1000 (from 208 fewer to 285 more)		
Median percentage reduction in ulcer volume – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	99.6 (n=31)	99.7 (n=32)	-	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME
Proportion of patients with osteomyelitis – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	2/31 (6.5%)	1/32 (3.1%)	RR 2.06 (0.2 to 21.63)	33 more per 1000 (from 25 fewer to 645 more)	⊕OOO VERY LOW	IMPORTANT OUTCOME
								3.1%		33 more per 1000		

										(from 25 fewer to 640 more)		
Proportion of patients with infection – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/31 (0%)	0/32 (0%)	not pooled	RD 0 more (from 60 fewer to 60 more)	⊕⊕OO LOW	IMPORTANT OUTCOME
								0%		-		
Proportion of patients with sepsis – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	0/31 (0%)	1/32 (3.1%)	OR 0.14 (0 to 7.04)	27 fewer per 1000 (from 31 fewer to 154 more)	⊕OOO VERY LOW	IMPORTANT OUTCOME
								3.1%		27 fewer per 1000 (from 31 fewer to 153 more)		
Proportion of patients with adverse events other than osteomyelitis, infection and sepsis – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	2/31 (6.5%)	3/32 (9.4%)	RR 0.69 (0.12 to 3.84)	29 fewer per 1000 (from 83 fewer to 266 more)	⊕OOO VERY LOW	IMPORTANT OUTCOME
								9.4%		29 fewer per 1000 (from 83 fewer to 267 more)		

a Rees (1999): no report on sequence generation, allocation concealment and blinding; no log-transformation of data
b Confidence interval crossed both MID points
c No standard deviation; unknown if sample size was sufficient

Table 85 – Recombinant platelet-derived growth factor-BB (100.0µg/g) versus recombinant platelet-derived growth factor-BB (300.0µg/g)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rPDGF-BB (100ug/g)	rPDGF-BB (300ug/g)	Relative (95% CI)	Absolute		
Proportion of patients completely healed – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	7/31 (22.6%)	1/30 (3.3%)	RR 6.77 (0.89 to 51.8)	192 more per 1000 (from 4 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								3.3%		190 more per 1000 (from 4 fewer to 1000 more)		
Proportion of patients healed 90% or higher – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	18/31 (58.1%)	12/30 (40%)	RR 1.45 (0.85 to 2.47)	180 more per 1000 (from 60 fewer to 588 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								40%		180 more per 1000 (from 60 fewer to 588 more)		
Median percentage reduction in ulcer volume – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	99.6 (n=31)	98.6 (n=30)	-	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME
Proportion of patients with osteomyelitis – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[d]	none	2/31 (6.5%)	0/30 (0%)	OR 7.4 (0.45 to 121.11)	RD 60 more (from 40 fewer to 170 more)	⊕OOO VERY LOW	IMPORTANT OUTCOME
								0%		-		

Proportion of patients with infection – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[d]	none	0/31 (0%)	1/30 (3.3%)	OR 0.13 (0 to 6.6)	29 fewer per 1000 (from 33 fewer to 152 more)	⊕OOO VERY LOW	IMPORTANT OUTCOME
								3.3%		29 fewer per 1000 (from 33 fewer to 151 more)		
Proportion of patients with sepsis – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[d]	none	0/31 (0%)	0/30 (0%)	not pooled	RD 0 more (from 60 fewer to 60 more)	⊕OOO VERY LOW	IMPORTANT OUTCOME
								0%		-		
Proportion of patients with adverse events other than osteomyelitis, infection and sepsis – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[d]	none	2/31 (6.5%)	2/30 (6.7%)	RR 0.97 (0.15 to 6.44)	2 fewer per 1000 (from 57 fewer to 363 more)	⊕OOO VERY LOW	IMPORTANT OUTCOME
								6.7%		2 fewer per 1000 (from 57 fewer to 364 more)		

a Rees (1999): no report on sequence generation, allocation concealment and blinding; no log-transformation of data
b Confidence interval crossed one MID point
c No standard deviation; unknown if sample size was sufficient
d Confidence interval crossed both MID points

Table 86 – Recombinant platelet-derived growth factor-BB (300.0µg/g) alternated with placebo versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rPDGF-BB (300ug/g) alternated with placebo	Placebo	Relative (95% CI)	Absolute		
Proportion of patients completely healed – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/32 (18.8%)	0/31 (0%)	OR 8.51 (1.6 to	RD 190 more (from 50 more to	⊕⊕OO	CRITICAL OUTCOME

									45.18)	330 more)	LOW	
								0%		-		
Proportion of patients healed 90% or higher – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	19/32 (59.4%)	9/31 (29%)	RR 2.05 (1.1 to 3.8)	305 more per 1000 (from 29 more to 813 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								29%		304 more per 1000 (from 29 more to 812 more)		
Median percentage reduction in ulcer volume – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	99.7 (n=32)	99.1 (n=31)	p=0.011	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME
Proportion of patients with osteomyelitis – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[d]	none	2/31 (6.5%)	1/31 (3.2%)	RR 2 (0.19 to 20.93)	32 more per 1000 (from 26 fewer to 643 more)	⊕OOO VERY LOW	IMPORTANT OUTCOME
								3.2%		32 more per 1000 (from 26 fewer to 638 more)		
Proportion of patients with infection – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[d]	none	0/32 (0%)	1/31 (3.2%)	OR 0.13 (0 to 6.61)	28 fewer per 1000 (from 32 fewer to 148 more)	⊕OOO VERY LOW	IMPORTANT OUTCOME
								3.2%		28 fewer per 1000 (from 32 fewer to 147 more)		
Proportion of patients with sepsis – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[d]	none	1/32 (3.1%)	0/31 (0%)	OR 7.16 (0.14 to	RD 30 more (from 50 fewer to 110	⊕OOO VERY	IMPORTANT OUTCOME

									361.11)	more)	LOW	
								0%		-		
Proportion of patients with adverse events other than osteomyelitis, infection and sepsis – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[d]	none	3/32 (9.4%)	2/31 (6.5%)	RR 1.45 (0.26 to 8.11)	29 more per 1000 (from 48 fewer to 459 more)	⊕OOO VERY LOW	IMPORTANT OUTCOME
								6.5%		29 more per 1000 (from 48 fewer to 462 more)		

a Rees (1999): no report on sequence generation, allocation concealment and blinding; no log-transformation of data
b Confidence interval crossed one MID point
c No standard deviation; unknown if sample size was sufficient
d Confidence interval crossed both MID points

Table 87 – Recombinant platelet-derived growth factor-BB (300.0µg/g) alternated with placebo versus recombinant platelet-derived growth factor-BB (300.0µg/g

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rPDGF-BB (300ug/g) alternated with placebo	rPDGF-BB (300ug/g)	Relative (95% CI)	Absolute		
Proportion of patients completely healed – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	6/32 (18.8%)	1/30 (3.3%)	RR 5.62 (0.72 to 44.03)	154 more per 1000 (from 9 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								3.3%		152 more per 1000 (from 9 fewer to 1000 more)		
Proportion of patients healed 90% or higher – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[c]	none	19/32 (59.4%)	12/30 (40%)	RR 1.48 (0.88 to	192 more per 1000 (from 48	⊕OOO VERY	CRITICAL OUTCOME

									2.51)	fewer to 604 more)	LOW	
								40%		192 more per 1000 (from 48 fewer to 604 more)		
Median percentage reduction in ulcer volume – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[d]	none	99.7 (n=32)	98.6 (n=30)	-	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME
Proportion of patients with osteomyelitis – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/32 (3.1%)	0/30 (0%)	OR 6.94 (0.14 to 350.54)	RD 30 more (from 50 fewer to 120 more)	⊕OOO VERY LOW	IMPORTANT OUTCOME
								0%		-		
Proportion of patients with infection – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	0/32 (0%)	1/30 (3.3%)	OR 0.13 (0 to 6.39)	29 fewer per 1000 (from 33 fewer to 147 more)	⊕OOO VERY LOW	IMPORTANT OUTCOME
								3.3%		29 fewer per 1000 (from 33 fewer to 146 more)		
Proportion of patients with sepsis – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/32 (3.1%)	0/30 (0%)	OR 6.94 (0.14 to 350.54)	RD 30 more (from 50 fewer to 120 more)	⊕OOO VERY LOW	IMPORTANT OUTCOME
								0%		-		
Proportion of patients with adverse events other than osteomyelitis, infection and sepsis – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	3/32 (9.4%)	2/30 (6.7%)	RR 1.41 (0.25 to	27 more per 1000 (from 50 fewer to	⊕OOO VERY	IMPORTANT OUTCOME

									7.84)	456 more)	LOW	
								6.7%		27 more per 1000 (from 50 fewer to 458 more)		

a Rees (1999): no report on sequence generation, allocation concealment and blinding; no log-transformation of data
b Confidence interval crossed both MID points
c Confidence interval crossed one MID point
d No standard deviation; unknown if sample size was sufficient

Table 88 – Recombinant platelet-derived growth factor-BB (300.0µg/g) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rPDGF-BB (300ug/g)	Placebo	Relative (95% CI)	Absolute		
Proportion of patients completely healed – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/30 (3.3%)	0/31 (0%)	OR 7.64 (0.15 to 385.21)	RD 30 more (from 50 fewer to 120 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								0%		-		
Proportion of patients healed 90% or higher – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	12/30 (40%)	9/31 (29%)	RR 1.38 (0.68 to 2.78)	110 more per 1000 (from 93 fewer to 517 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								29%		110 more per 1000 (from 93 fewer to 516 more)		
Median percentage reduction in ulcer volume – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	98.6 (n=30)	99.1 (n=31)	-	not pooled	⊕OOO VERY	CRITICAL OUTCOME

											LOW	
Proportion of patients with osteomyelitis – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	0/30 (0%)	1/31 (3.2%)	OR 0.14 (0 to 7.05)	28 fewer per 1000 (from 32 fewer to 158 more)	⊕OOO VERY LOW	IMPORTANT OUTCOME
								3.2%		27 fewer per 1000 (from 32 fewer to 157 more)		
Proportion of patients with infection – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/30 (3.3%)	1/31 (3.2%)	RR 1.03 (0.07 to 15.78)	1 more per 1000 (from 30 fewer to 477 more)	⊕OOO VERY LOW	IMPORTANT OUTCOME
								3.2%		1 more per 1000 (from 30 fewer to 473 more)		
Proportion of patients with sepsis – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/30 (0%)	0/31 (0%)	not pooled	RD 0 more (from 60 fewer to 60 more)	⊕⊕OO LOW	IMPORTANT OUTCOME
								0%		-		
Proportion of patients with adverse events other than osteomyelitis, infection and sepsis – general population – stage III and IV – NPUAP classification												
Rees 1999	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	2/30 (6.7%)	2/31 (6.5%)	RR 1.03 (0.16 to 6.87)	2 more per 1000 (from 54 fewer to 379 more)	⊕OOO VERY LOW	IMPORTANT OUTCOME
								6.5%		2 more per 1000 (from 55 fewer to 382 more)		

a Rees (1999): no report on sequence generation, allocation concealment and blinding; no log-transformation of data
b Confidence interval crossed both MID points
c No standard deviation; unknown if sample size was sufficient

Table 89 – Recombinant platelet-derived growth factor-BB (1.0µg/g) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RPDGF-BB (1.0ug/ml)	Placebo	Relative (95% CI)	Absolute		
Proportion of patients completely healed – denervated patients – stage III and IV – classification not reported												
Robson 1992b	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/4 (0%)	0/7 (0%)	not pooled	RD 0 more (from 310 fewer to 310 more)	⊕⊕OO LOW	CRITICAL OUTCOME
								0%		-		
Proportion of patients with infection – denervated patients – stage III and IV – classification not reported												
Robson 1992b	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/4 (0%)	0/7 (0%)	not pooled	RD 0 more (from 310 fewer to 310 more)	⊕⊕OO LOW	IMPORTANT OUTCOME
								0%		-		

a Robson (1992b): no report on sequence generation, unequal allocation and only blinding of outcome assessor

Table 90 – Recombinant platelet-derived growth factor-BB (1.0µg/g) versus recombinant platelet-derived growth factor-BB (10.0µg/g)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rPDGF-BB (1.0ug/ml)	rPDGF-BB (10.0ug/ml)	Relative (95% CI)	Absolute		
Proportion of patients completely healed – denervated patients – stage III and IV – classification not reported												
Robson 1992b	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/4 (0%)	0/4 (0%)	not pooled	RD 0 more (from 370 fewer to 370 more)	⊕⊕OO LOW	CRITICAL OUTCOME
								0%		-		
Proportion of patients with infection – denervated patients – stage III and IV – classification not reported												
Robson 1992b	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/4 (0%)	0/4 (0%)	not pooled	RD 0 more (from 370 fewer to 370	⊕⊕OO	IMPORTANT OUTCOME

										more)	LOW	
								0%		-		

a Robson (1992b): no report on sequence generation, unequal allocation and only blinding of outcome assessor

Table 91 – Recombinant platelet-derived growth factor-BB (1.0µg/g) versus recombinant platelet-derived growth factor-BB (100.0µg/g)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RPDGF-BB (1.0ug/ml)	rPDGF-BB (100ug/ml)	Relative (95% CI)	Absolute		
Proportion of patients completely healed – denervated patients – stage III and IV – classification not reported												
Robson 1992b	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	0/4 (0%)	2/5 (40%)	OR 0.13 (0.01 to 2.52)	320 fewer per 1000 (from 393 fewer to 227 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								40%		320 fewer per 1000 (from 393 fewer to 227 more)		
Proportion of patients with infection – denervated patients – stage III and IV – classification not reported												
Robson 1992b	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/4 (0%)	0/5 (0%)	not pooled	RD 0 more (from 340 fewer to 340 more)	⊕⊕OO LOW	IMPORTANT OUTCOME
								0%		-		

a Robson (1992b): no report on sequence generation, unequal allocation and only blinding of outcome assessor
b Confidence interval crossed both MID points

Table 92 – Recombinant platelet-derived growth factor-BB (10.0µg/g) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rPDGF-BB (10.0ug/ml)	Placebo	Relative (95% CI)	Absolute		
Proportion of patients completely healed – denervated patients – stage III and IV – classification not reported												
Robson 1992b	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/4 (0%)	0/7 (0%)	not pooled	RD 0 more (from 310 fewer to 310 more)	⊕⊕OO LOW	CRITICAL OUTCOME
								0%		-		
Proportion of patients with infection – denervated patients – stage III and IV – classification not reported												
Robson 1992b	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/4 (0%)	0/7 (0%)	not pooled	RD 0 more (from 310 fewer to 310 more)	⊕⊕OO LOW	IMPORTANT OUTCOME
								0%		-		

a Robson (1992b): no report on sequence generation, unequal allocation and only blinding of outcome assessor

Table 93 – Recombinant platelet-derived growth factor-BB (10.0µg/g) versus recombinant platelet-derived growth factor-BB (100.0µg/g)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rPDGF-BB (10.0ug/ml)	rPDGF-BB (100ug/ml)	Relative (95% CI)	Absolute		
Proportion of patients completely healed – denervated patients – stage III and IV – classification not reported												
Robson 1992b	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	0/4 (0%)	2/5 (40%)	OR 0.13 (0.01 to 2.52)	320 fewer per 1000 (from 393 fewer to 227 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								40%		320 fewer per 1000 (from 393 fewer to 227 more)		

Proportion of patients with infection – denervated patients – stage III and IV – classification not reported												
Robson 1992b	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/4 (0%)	0/5 (0%)	not pooled	RD 0 more (from 340 fewer to 340 more)	⊕⊕OO LOW	IMPORTANT OUTCOME
								0%		-		

a Robson (1992b): no report on sequence generation, unequal allocation and only blinding of outcome assessor
b Confidence interval crossed both MID points

Table 94 – Recombinant platelet-derived growth factor-BB (100.0µg/g) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rPDGF-BB (100ug/ml)	Placebo	Relative (95% CI)	Absolute		
Proportion of patients completely healed – denervated patients – stage III and IV – classification not reported												
Robson 1992b	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	2/5 (40%)	0/7 (0%)	OR 14.01 (0.73 to 267.29)	RD 400 more (from 30 fewer to 830 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								0%		-		
Proportion of patients with infection – denervated patients – stage III and IV – classification not reported												
Robson 1992b	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/5 (0%)	0/7 (0%)	not pooled	RD 0 more (from 280 fewer to 280 more)	⊕⊕OO LOW	IMPORTANT OUTCOME
								0%		not pooled		
Mean percentage reduction in ulcer depth – denervated patients – stage III and IV – classification not reported												
Robson 1992b	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	85.9 (SD 14.8)	65.1 (SD 13.4)	-	MD 20.8 higher (4.47 to 37.13 higher)	⊕⊕OO LOW	CRITICAL OUTCOME
Mean percentage reduction in ulcer volume – denervated patients – stage III and IV – classification not reported												
Robson 1992b	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	93.6 (SD 4)	78.2 (SD	-	MD 15.4 higher (4.54 to 26.26	⊕⊕OO LOW	CRITICAL OUTCOME

								5.6)		higher)		

a Robson (1992b): no report on sequence generation, unequal allocation and only blinding of outcome assessor; no log-transformation of data
b Confidence interval crossed both MID points

Table 95 – Basic fibroblast growth factor (different schedules and doses) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bFGF	Placebo	Relative (95% CI)	Absolute		
Proportion of patients healed > 70% – denervated patients – stage III and IV – classification not reported												
Robson 1992a	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	21/35 (60%)	4/14 (28.6%)	RR 2.1 (0.88 to 5.02)	314 more per 1000 (from 34 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL OUTCOME
								28.6%		315 more per 1000 (from 34 fewer to 1000 more)		
Mean percentage reduction in volume – denervated patients – stage III and IV – classification not reported												
Robson 1992a	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	69 (n=35)	59 (n=14)	-	not pooled	⊕OOO VERY LOW	CRITICAL OUTCOME

a Robson (1992a): no report on sequence generation, unequal allocation and only blinding of outcome assessor; no log-transformation of data
b Confidence interval crossed one MID point
c No standard deviation; small sample size

Table 96 – Interleukin 1-beta (0.01µg/cm²) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rIL-1beta (0.01ug/cm²)	Placebo	Relative (95% CI)	Absolute		
Proportion of patients completely healed – denervated patients – stage III and IV – classification not reported												
Robson 1994	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/6 (0%)	0/6 (0%)	not pooled	RD 0 more (from 270 fewer to 270 more)	⊕⊕OO LOW	CRITICAL OUTCOME
								0%		-		

a Robson (1994): no report on sequence generation, allocation concealment and report of double blinding, but no further information

Table 97 – Interleukin 1-beta (0.01µg/cm²) versus interleukin 1-beta (0.1µg/cm²)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rIL-1beta (0.01ug/cm²)	rIL-1beta (0.1ug/cm²)	Relative (95% CI)	Absolute		
Proportion of patients completely healed – denervated patients – stage III and IV – classification not reported												
Robson 1994	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/6 (0%)	0/6 (0%)	not pooled	RD 0 more (from 270 fewer to 270 more)	⊕⊕OO LOW	CRITICAL OUTCOME
								0%		-		

a Robson (1994): no report on sequence generation, allocation concealment and report of double blinding, but no further information

Table 98 – Interleukin 1-beta (0.01µg/cm²) versus interleukin 1-beta (1.0µg/cm²)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rIL-1beta (0.01ug/cm²)	rIL-1beta (1.0ug/cm²)	Relative (95% CI)	Absolute		
Proportion of patients completely healed – denervated patients – stage III and IV – classification not reported												
Robson 1994	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/6 (0%)	0/6 (0%)	not pooled	RD 0 more (from 270 fewer to 270 more)	⊕⊕OO LOW	CRITICAL OUTCOME
								0%		-		

a Robson (1994): no report on sequence generation, allocation concealment and report of double blinding, but no further information

Table 99 – Interleukin 1-beta (0.1µg/cm²) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rIL-1beta (0.1ug/cm²)	Placebo	Relative (95% CI)	Absolute		
Proportion of patients completely healed – denervated patients – stage III and IV – classification not reported												
Robson 1994	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/6 (0%)	0/6 (0%)	not pooled	RD 0 more (from 270 fewer to 270 more)	⊕⊕OO LOW	CRITICAL OUTCOME
								0%		-		

a Robson (1994): no report on sequence generation, allocation concealment and report of double blinding, but no further information

Table 100 – Interleukin 1-beta (0.1µg/cm²) versus interleukin 1-beta (1.0µg/cm²)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rIL-1beta (0.1ug/cm²)	rIL-1beta (1.0ug/cm²)	Relative (95% CI)	Absolute		
Proportion of patients completely healed – denervated patients – stage III and IV – classification not reported												
Robson 1994	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/6 (0%)	0/6 (0%)	not pooled	RD 0 more (from 270 fewer to 270 more)	⊕⊕OO LOW	CRITICAL OUTCOME
								0%		-		

a Robson (1994): no report on sequence generation, allocation concealment and report of double blinding, but no further information

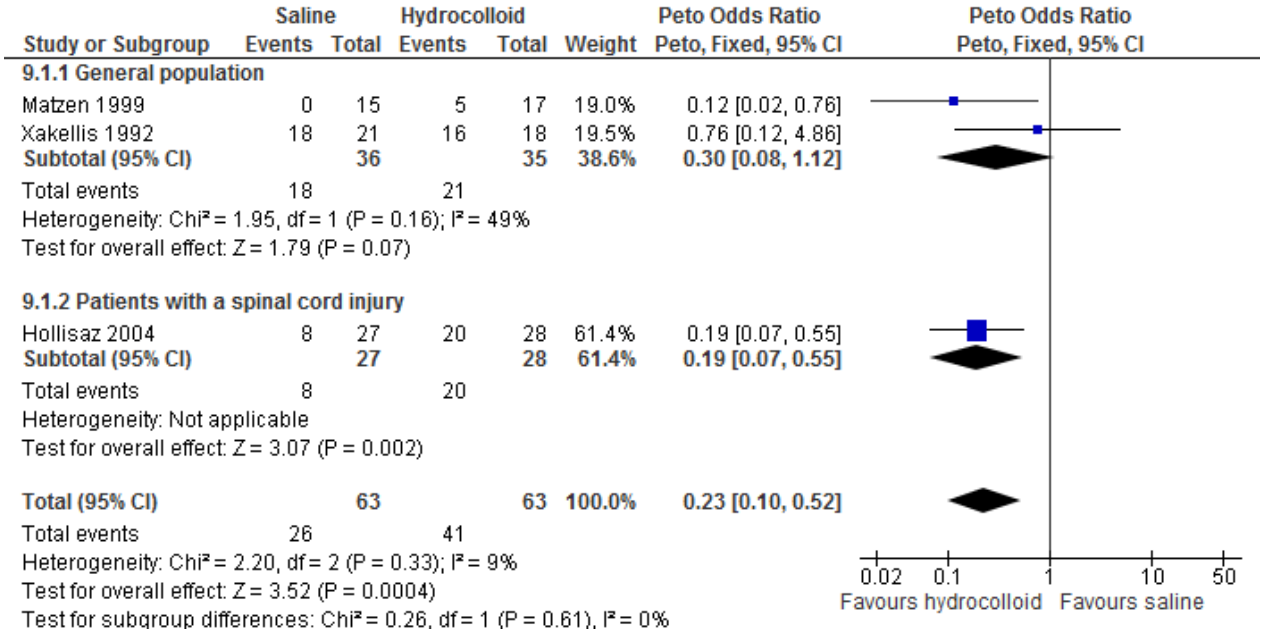
Table 101 – Interleukin 1-beta (1.0vg/cm²) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rIL-1beta (1.0ug/cm²)	Placebo	Relative (95% CI)	Absolute		
Proportion of patients completely healed – denervated patients – stage III and IV – classification not reported												
Robson 1994	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/6 (0%)	0/6 (0%)	not pooled	RD 0 more (from 270 fewer to 270 more)	⊕⊕OO LOW	CRITICAL OUTCOME
								0%		-		

a Robson (1994): no report on sequence generation, allocation concealment and report of double blinding, but no further information

6.1.2. Forrest plots

Figure 34 – Saline versus hydrocolloid dressing – proportion of patients completely healed



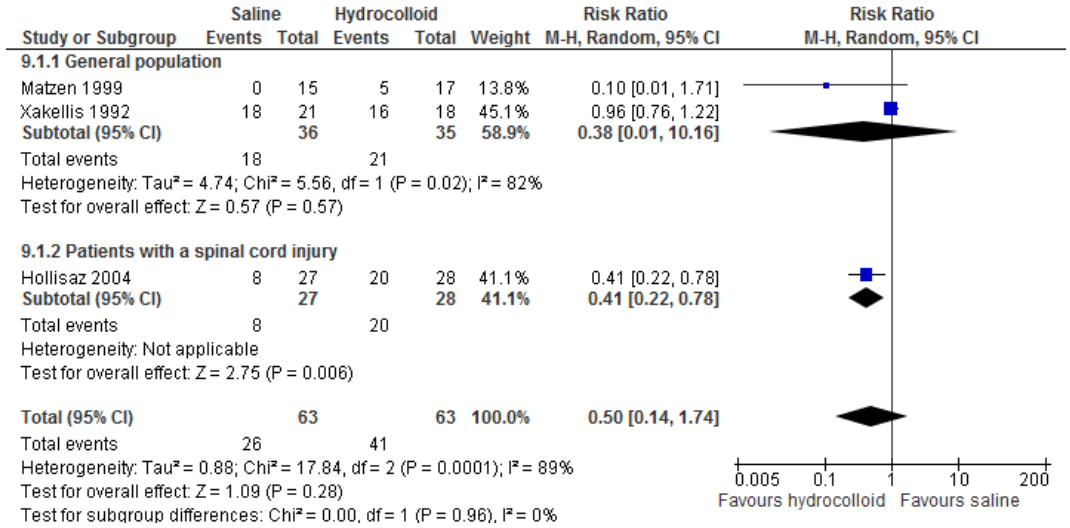


Figure 35 – Saline versus hydrocolloid dressing – proportion of ulcers completely healed (all stages – all sites)

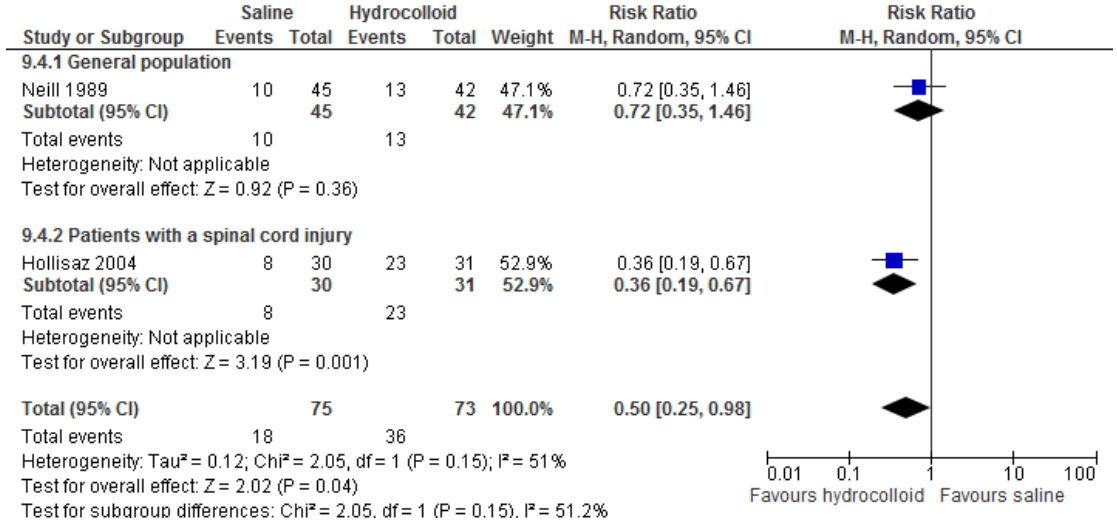


Figure 36 – Saline versus hydrocolloid dressing – proportion of ulcers completely healed (stage I – all sites)

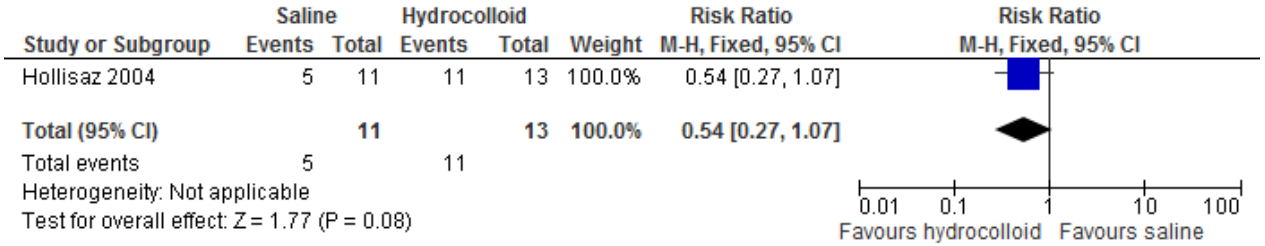


Figure 37 – Saline versus hydrocolloid dressing – proportion of ulcers completely healed (stage II – all sites)

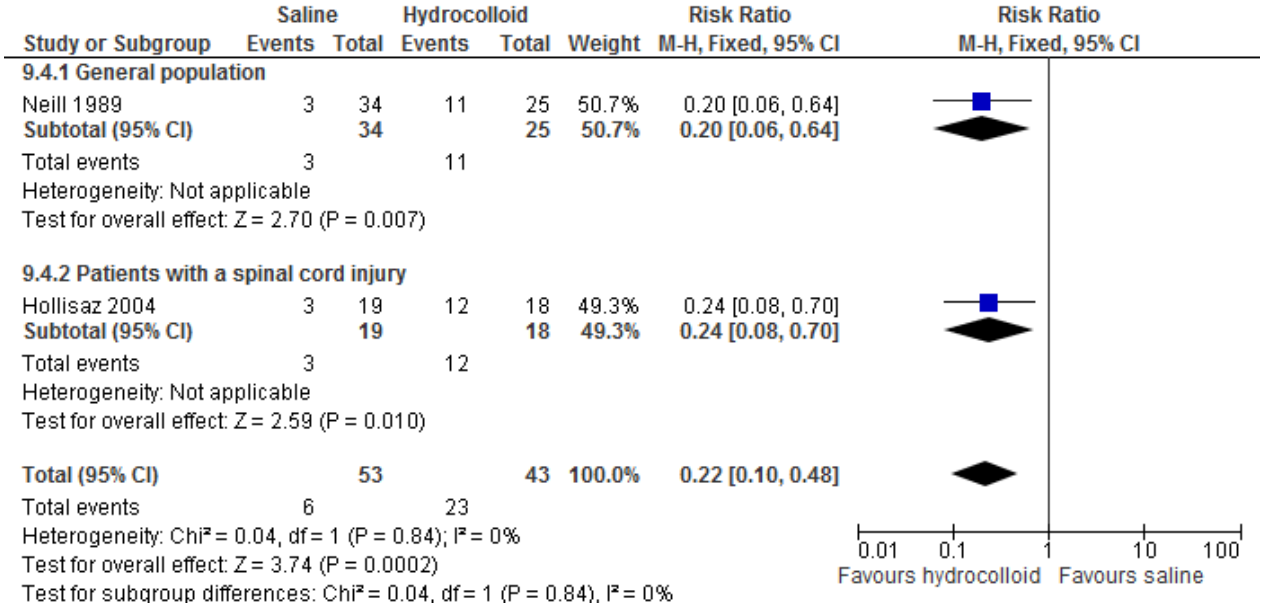


Figure 38 – Saline versus hydrocolloid dressing – proportion of ulcers completely healed (stage III – all sites)

Study or Subgroup	Saline Events	Saline Total	Hydrocolloid Events	Hydrocolloid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Neill 1989	1	11	2	17	100.0%	0.77 [0.08, 7.54]
Total (95% CI)		**11**		**17**	**100.0%**	**0.77 [0.08, 7.54]**
Total events	1		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.22 (P = 0.82)

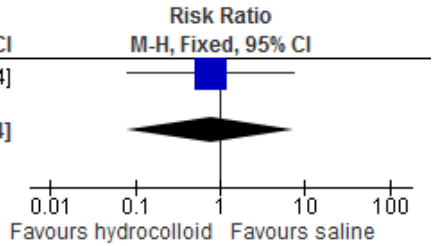


Figure 39 – Saline versus hydrocolloid dressing – proportion of ulcers completely healed (all stages – sacral area)

Study or Subgroup	Saline Events	Saline Total	Hydrocolloid Events	Hydrocolloid Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Hollisaz 2004	4	8	0	7	100.0%	10.87 [1.19, 99.73]
Total (95% CI)		**8**		**7**	**100.0%**	**10.87 [1.19, 99.73]**
Total events	4		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.11 (P = 0.03)

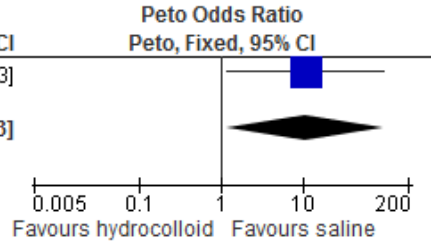


Figure 40 – Saline versus hydrocolloid dressing – proportion of ulcers improved

Study or Subgroup	Saline Events	Saline Total	Hydrocolloid Events	Hydrocolloid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hollisaz 2004	29	60	27	31	100.0%	0.55 [0.41, 0.75]
Total (95% CI)		**60**		**31**	**100.0%**	**0.55 [0.41, 0.75]**
Total events	29		27			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.92 (P < 0.0001)

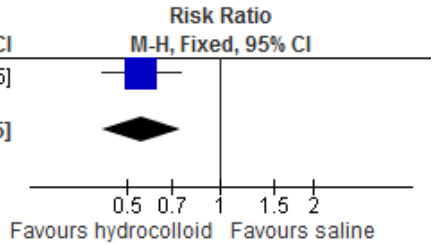


Figure 41 – Saline versus hydrocolloid dressing – proportion of ulcers worsened (all stages)

Study or Subgroup	Saline Events	Saline Total	Hydrocolloid Events	Hydrocolloid Total	Weight	Risk Ratio M-H, Random, 95% CI
9.10.1 General population						
Neill 1989	15	45	14	42	59.0%	1.00 [0.55, 1.81]
Subtotal (95% CI)		**45**		**42**	**59.0%**	**1.00 [0.55, 1.81]**
Total events	15		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
9.10.2 Patients with a spinal cord injury						
Hollisaz 2004	9	30	2	31	41.0%	4.65 [1.09, 19.78]
Subtotal (95% CI)		**30**		**31**	**41.0%**	**4.65 [1.09, 19.78]**
Total events	9		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.08 (P = 0.04)						
Total (95% CI)		**75**		**73**	**100.0%**	**1.88 [0.41, 8.68]**
Total events	24		16			
Heterogeneity: Tau² = 0.94; Chi² = 3.95, df = 1 (P = 0.05); I² = 75%						
Test for overall effect: Z = 0.81 (P = 0.42)						
Test for subgroup differences: Chi² = 3.70, df = 1 (P = 0.05), I² = 73.0%						

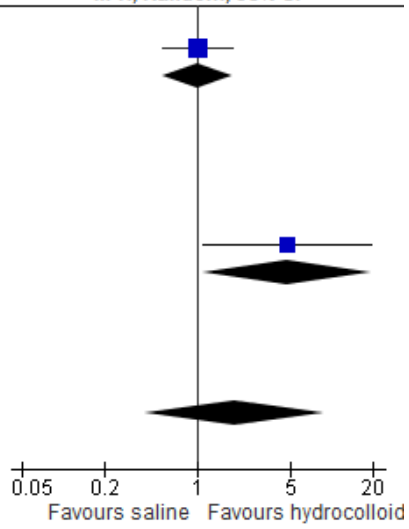


Figure 42 – Saline versus hydrocolloid dressing – proportion of ulcers worsened (stage II)

Study or Subgroup	Saline Events	Saline Total	Hydrocolloid Events	Hydrocolloid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Neill 1989	11	34	7	25	100.0%	1.16 [0.52, 2.56]
Total (95% CI)		**34**		**25**	**100.0%**	**1.16 [0.52, 2.56]**
Total events	11		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.36 (P = 0.72)						

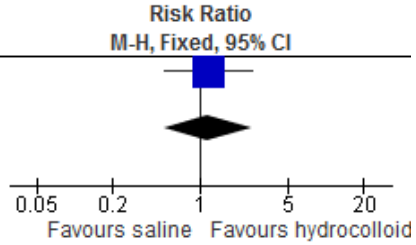


Figure 43 – Saline versus hydrocolloid dressing – proportion of ulcers worsened (stage III)

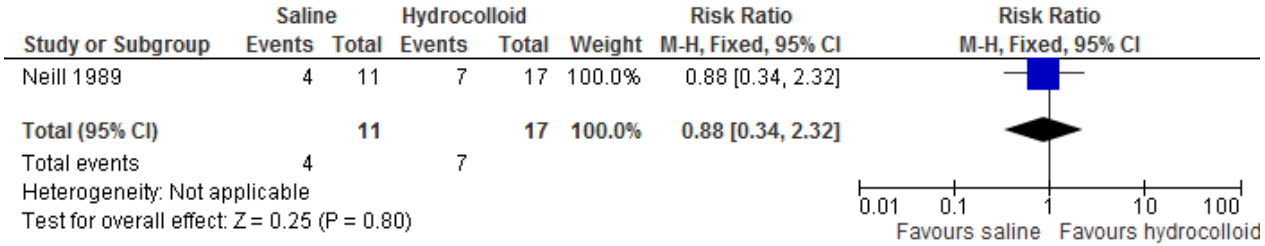


Figure 44 – Saline versus hydrocolloid dressing – mean percentage reduction in ulcer size

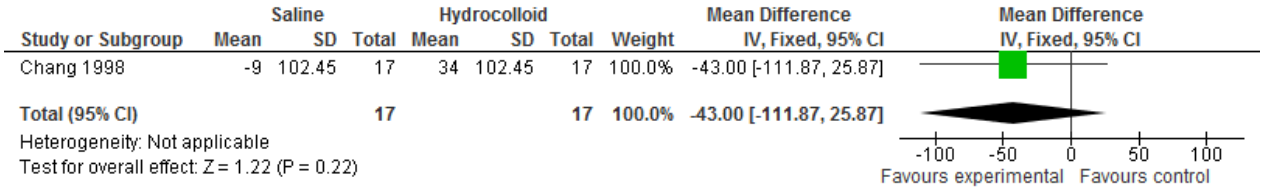


Figure 45 – Saline versus hydrocolloid dressing – mean percentage reduction in ulcer volume

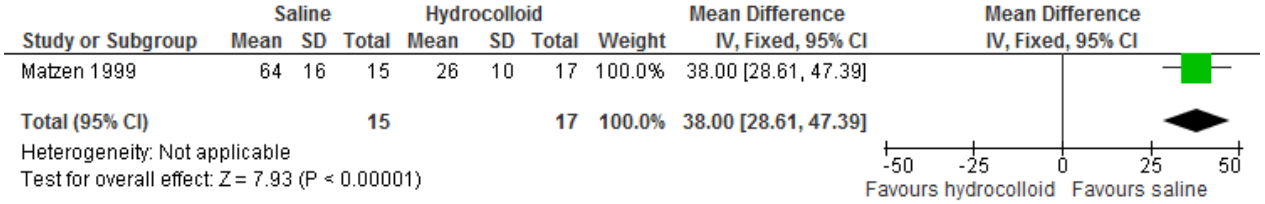


Figure 46 – Saline versus hydrocolloid dressing – median percentage reduction in ulcer size

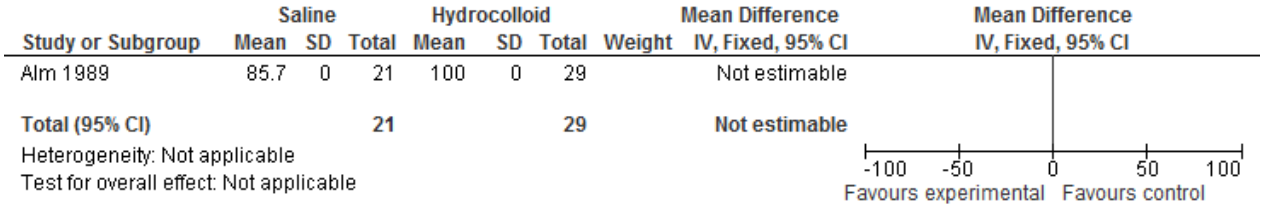


Figure 47 – Saline versus hydrocolloid dressing – median percentage reduction in ulcer size (stage II)

Study or Subgroup	Saline Mean	SD	Total	Hydrocolloid Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Neill 1989	48	0	34	91	0	25		Not estimable
Total (95% CI)			**34**			**25**		**Not estimable**

Heterogeneity: Not applicable
Test for overall effect: Not applicable

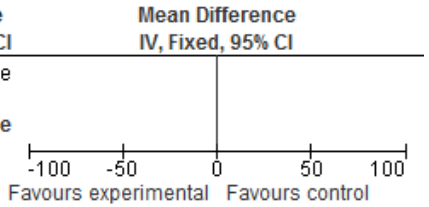


Figure 48 – Saline versus hydrocolloid dressing – median percentage reduction in ulcer size (stage III)

Study or Subgroup	Saline Mean	SD	Total	Hydrocolloid Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Neill 1989	30	0	11	0.3	0	17		Not estimable
Total (95% CI)			**11**			**17**		**Not estimable**

Heterogeneity: Not applicable
Test for overall effect: Not applicable

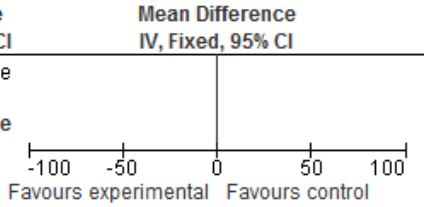


Figure 49 – Saline versus hydrocolloid dressing – median days to healing

Study or Subgroup	Saline Mean	SD	Total	Hydrocolloid Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Xakellis 1992	11	0	21	9	0	18		Not estimable
Total (95% CI)			**21**			**18**		**Not estimable**

Heterogeneity: Not applicable
Test for overall effect: Not applicable

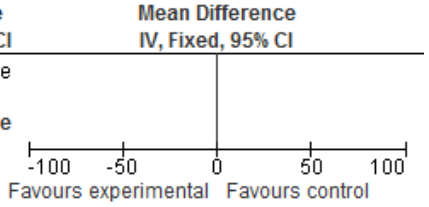


Figure 50 – Saline versus hydrocolloid dressing – proportion of patients with pain at dressing removal

Study or Subgroup	Saline Events	Total	Hydrocolloid Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Chang 1998	0	17	7	17	100.0%	0.09 [0.02, 0.45]
Total (95% CI)		**17**		**17**	**100.0%**	**0.09 [0.02, 0.45]**
Total events	0		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.92 (P = 0.003)

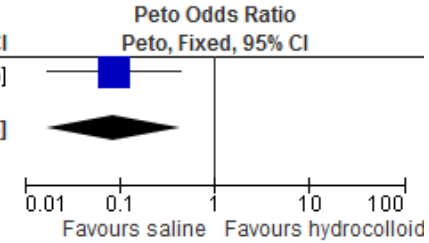


Figure 51 – Saline versus hydrocolloid dressing – median pain score

	Saline			Hydrocolloid				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Matzen 1999	2	0	15	2	0	17		Not estimable
Total (95% CI)			**15**			**17**		**Not estimable**

Heterogeneity: Not applicable
Test for overall effect: Not applicable

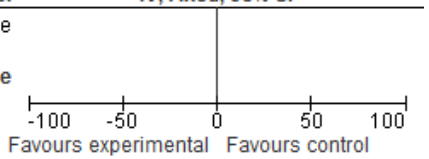


Figure 52 – Saline versus hydrocolloid dressing – proportion of patients with discomfort

	Saline		Hydrocolloid			Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI
Chang 1998	0	17	9	17	100.0%	0.07 [0.02, 0.32]
Total (95% CI)		**17**		**17**	**100.0%**	**0.07 [0.02, 0.32]**
Total events	0		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.45 (P = 0.0006)

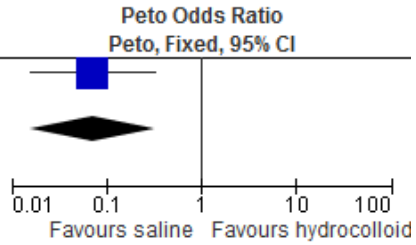


Figure 53 – Saline versus hydrocolloid dressing – median comfort score

	Saline			Hydrocolloid				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Matzen 1999	3	0	15	4	0	17		Not estimable
Total (95% CI)			**15**			**17**		**Not estimable**

Heterogeneity: Not applicable
Test for overall effect: Not applicable

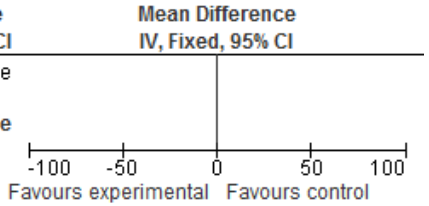


Figure 54 – Saline versus hydrocolloid dressing – proportion of patients with an infection

Study or Subgroup	Saline Events	Saline Total	Hydrocolloid Events	Hydrocolloid Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Chang 1998	0	17	0	17		Not estimable
Total (95% CI)		**17**		**17**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

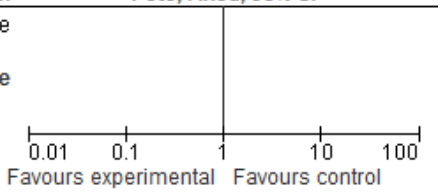


Figure 55 – Saline versus hydrocolloid dressing – median smell score

Study or Subgroup	Saline Mean	Saline SD	Saline Total	Hydrocolloid Mean	Hydrocolloid SD	Hydrocolloid Total	Weight	Mean Difference IV, Fixed, 95% CI
Matzen 1999	2	0	15	2	0	17		Not estimable
Total (95% CI)			**15**			**17**		**Not estimable**

Heterogeneity: Not applicable
Test for overall effect: Not applicable

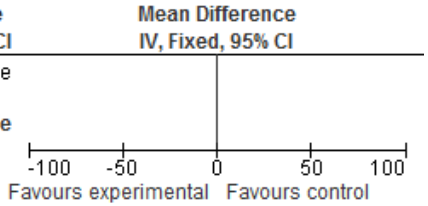


Figure 56 – Saline versus hydrocolloid dressing – proportion of patients with skin irritation

Study or Subgroup	Saline Events	Saline Total	Hydrocolloid Events	Hydrocolloid Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Neill 1989	0	50	9	50	100.0%	0.11 [0.03, 0.44]
Total (95% CI)		**50**		**50**	**100.0%**	**0.11 [0.03, 0.44]**
Total events	0		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.13 (P = 0.002)

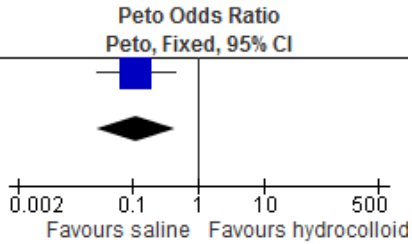


Figure 57 – Phenytoin versus saline – proportion of patients completely healed

Study or Subgroup	Phenytoin Events	Phenytoin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hollisaz 2004	11	28	8	27	100.0%	1.33 [0.63, 2.78]
Total (95% CI)		**28**		**27**	**100.0%**	**1.33 [0.63, 2.78]**
Total events	11		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.75 (P = 0.46)

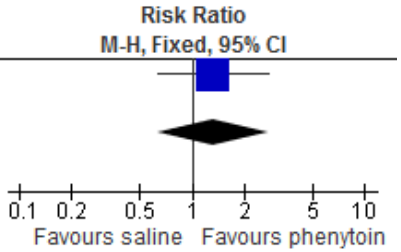


Figure 58 – Saline versus hydrogel dressing – proportion of patients completely healed

Study or Subgroup	Saline Events	Saline Total	Hydrogel Events	Hydrogel Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Thomas 1998	9	14	10	16	100.0%	1.03 [0.60, 1.77]
Total (95% CI)		**14**		**16**	**100.0%**	**1.03 [0.60, 1.77]**
Total events	9		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.10 (P = 0.92)

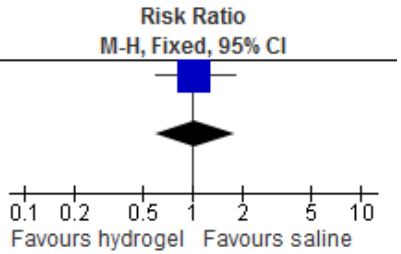


Figure 59 – Saline versus hydrogel dressing – proportion of patients worsened

Study or Subgroup	Saline Events	Saline Total	Hydrogel Events	Hydrogel Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Thomas 1998	1	19	1	22	100.0%	1.16 [0.08, 17.28]
Total (95% CI)		**19**		**22**	**100.0%**	**1.16 [0.08, 17.28]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.11 (P = 0.92)

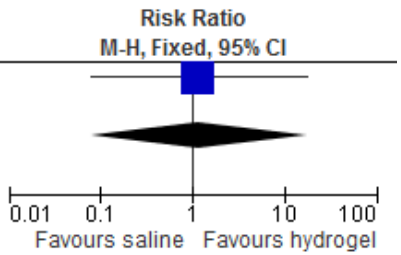


Figure 60 – Saline versus hydrogel dressing – mean weeks to healing

Study or Subgroup	Saline Mean	SD	Total	Hydrogel Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Thomas 1998	5.2	2.4	14	5.3	2.3	16	100.0%	-0.10 [-1.79, 1.59]
Total (95% CI)			**14**			**16**	**100.0%**	**-0.10 [-1.79, 1.59]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.12 (P = 0.91)

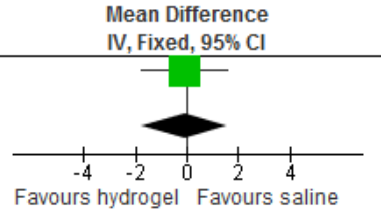


Figure 61 – Saline versus foam dressing – proportion of patients completely healed

Study or Subgroup	Saline Events	Total	Foam Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kraft 1993	3	14	10	24	45.3%	0.51 [0.17, 1.56]
Payne 2009	6	16	10	20	54.7%	0.75 [0.35, 1.62]
Total (95% CI)		**30**		**44**	**100.0%**	**0.64 [0.34, 1.22]**
Total events	9		20			

Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 1.35 (P = 0.18)

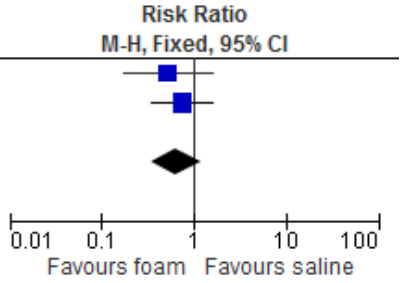


Figure 62 – Saline versus foam dressing – median days to 50% healing

Study or Subgroup	Saline Mean	SD	Total	Foam Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Payne 2009	28	0	16	28	0	20		Not estimable
Total (95% CI)			**16**			**20**		**Not estimable**

Heterogeneity: Not applicable
Test for overall effect: Not applicable

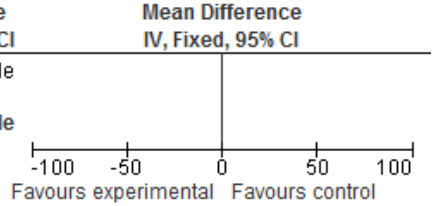


Figure 63 – Saline versus polyurethane dressing – proportion of ulcers completely healed

Study or Subgroup	Saline Events	Saline Total	Polyurethane Events	Polyurethane Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Oleske 1986	0	10	1	9	100.0%	0.12 [0.00, 6.14]
Total (95% CI)		**10**		**9**	**100.0%**	**0.12 [0.00, 6.14]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.29)

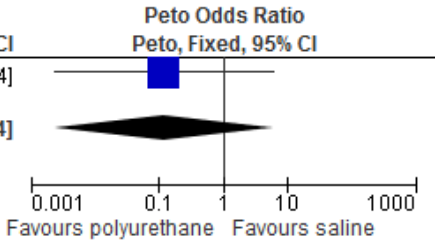


Figure 64 – Saline versus polyurethane dressing – proportion of ulcers worsened

Study or Subgroup	Saline Events	Saline Total	Polyurethane Events	Polyurethane Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Oleske 1986	2	10	1	9	100.0%	1.80 [0.19, 16.66]
Total (95% CI)		**10**		**9**	**100.0%**	**1.80 [0.19, 16.66]**
Total events	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.52 (P = 0.60)

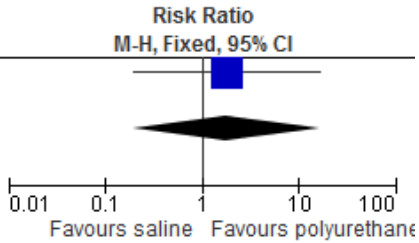


Figure 65 – Saline versus dextranomer – proportion of ulcers improved

Study or Subgroup	Gauze Events	Gauze Total	Dextranomer Events	Dextranomer Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ljungberg 2009	2	15	11	15	100.0%	0.18 [0.05, 0.68]
Total (95% CI)		**15**		**15**	**100.0%**	**0.18 [0.05, 0.68]**
Total events	2		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.52 (P = 0.01)

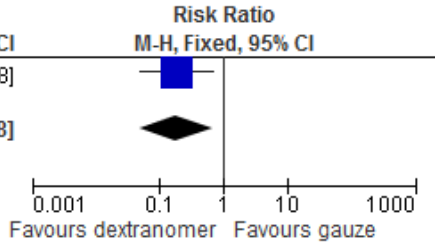


Figure 66 – Phenytoin versus saline – proportion of ulcers completely healed (all stages – all sites)

Study or Subgroup	Phenytoin Events	Phenytoin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hollisaz 2004	12	30	8	30	100.0%	1.50 [0.72, 3.14]
Total (95% CI)		**30**		**30**	**100.0%**	**1.50 [0.72, 3.14]**
Total events	12		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.08 (P = 0.28)

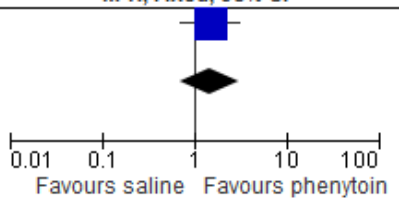


Figure 67 – Phenytoin versus saline – proportion of ulcers completely healed (stage I – all sites)

Study or Subgroup	Phenytoin Events	Phenytoin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hollisaz 2004	2	9	5	11	100.0%	0.49 [0.12, 1.95]
Total (95% CI)		**9**		**11**	**100.0%**	**0.49 [0.12, 1.95]**
Total events	2		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.01 (P = 0.31)

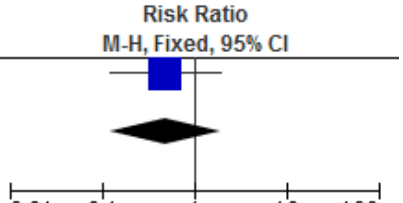


Figure 68 – Phenytoin versus saline – proportion of ulcers completely healed (stage II – all sites)

Study or Subgroup	Phenytoin Events	Phenytoin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hollisaz 2004	10	21	3	19	100.0%	3.02 [0.97, 9.35]
Total (95% CI)		**21**		**19**	**100.0%**	**3.02 [0.97, 9.35]**
Total events	10		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.91 (P = 0.06)

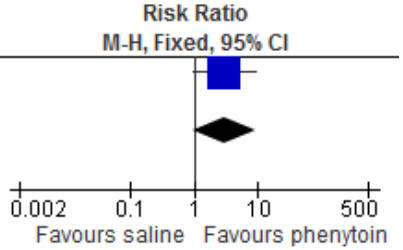


Figure 69 – Phenytoin versus saline – proportion of ulcers completely healed (all stages – sacral)

Study or Subgroup	Phenytoin Events	Total	Saline Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hollisaz 2004	2	5	4	8	100.0%	0.80 [0.22, 2.87]
Total (95% CI)		**5**		**8**	**100.0%**	**0.80 [0.22, 2.87]**
Total events	2		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.73)

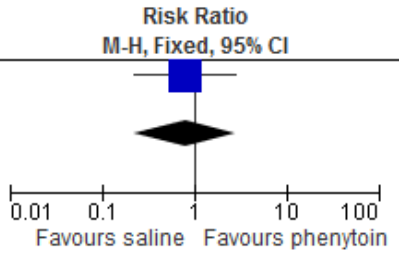


Figure 70 – Phenytoin versus saline – proportion of ulcers improved

Study or Subgroup	Phenytoin Events	Total	Saline Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hollisaz 2004	16	30	13	30	100.0%	1.23 [0.73, 2.09]
Total (95% CI)		**30**		**30**	**100.0%**	**1.23 [0.73, 2.09]**
Total events	16		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.77 (P = 0.44)

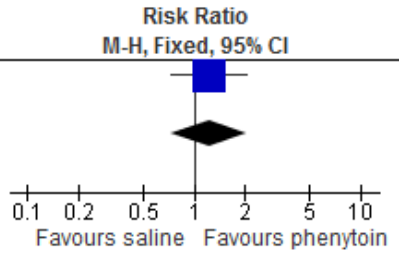


Figure 71 – Phenytoin versus saline – proportion of ulcers worsened

Study or Subgroup	Phenytoin Events	Total	Saline Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hollisaz 2004	2	30	9	30	100.0%	0.22 [0.05, 0.94]
Total (95% CI)		**30**		**30**	**100.0%**	**0.22 [0.05, 0.94]**
Total events	2		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.04 (P = 0.04)

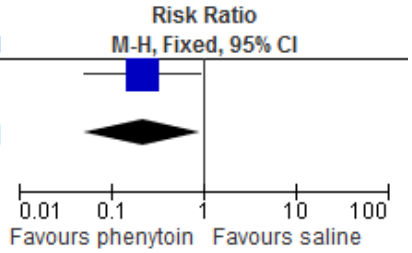


Figure 72 – Phenytoin versus saline – mean percentage reduction in ulcer size

Study or Subgroup	Phenytoin Mean	Phenytoin SD	Phenytoin Total	Saline Mean	Saline SD	Saline Total	Weight	Mean Difference IV, Fixed, 95% CI
Subbanna 2007	47.83	20.94	12	36.03	17.63	14	100.0%	11.80 [-3.22, 26.82]
Total (95% CI)			**12**			**14**	**100.0%**	**11.80 [-3.22, 26.82]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.54 (P = 0.12)

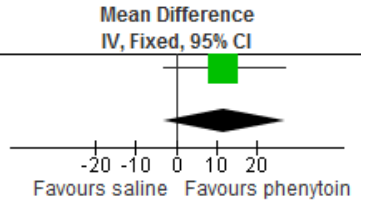


Figure 73 – Phenytoin versus saline – mean percentage reduction in ulcer volume

Study or Subgroup	Phenytoin Mean	Phenytoin SD	Phenytoin Total	Saline Mean	Saline SD	Saline Total	Weight	Mean Difference IV, Fixed, 95% CI
Subbanna 2007	53.94	31.2	12	55.76	27.75	14	100.0%	-1.82 [-24.69, 21.05]
Total (95% CI)			**12**			**14**	**100.0%**	**-1.82 [-24.69, 21.05]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.16 (P = 0.88)

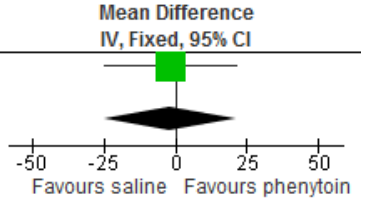


Figure 74 – Phenytoin versus saline – mean percentage reduction in PUSH score

Study or Subgroup	Phenytoin Mean	Phenytoin SD	Phenytoin Total	Saline Mean	Saline SD	Saline Total	Weight	Mean Difference IV, Fixed, 95% CI
Subbanna 2007	19.53	17.7	12	11.39	11.09	14	100.0%	8.14 [-3.44, 19.72]
Total (95% CI)			**12**			**14**	**100.0%**	**8.14 [-3.44, 19.72]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.38 (P = 0.17)

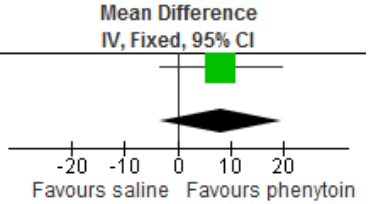


Figure 75 – Phenytoin versus hydrocolloid dressing – proportion of patients completely healed

Study or Subgroup	Phenytoin Events	Phenytoin Total	Hydrocolloid Events	Hydrocolloid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hollisaz 2004	11	28	20	28	100.0%	0.55 [0.33, 0.92]
Total (95% CI)		**28**		**28**	**100.0%**	**0.55 [0.33, 0.92]**
Total events	11		20			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.27 (P = 0.02)

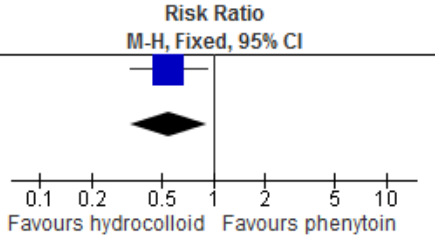


Figure 76 – Phenytoin versus hydrocolloid dressing – proportion of ulcers completely healed (all stages – all sites)

Figure 77 – Phenytoin versus hydrocolloid dressing – proportion of ulcers completely healed (stage I – all sites)

Figure 78 – Phenytoin versus hydrocolloid dressing – proportion of ulcers completely healed (stage II – all sites)

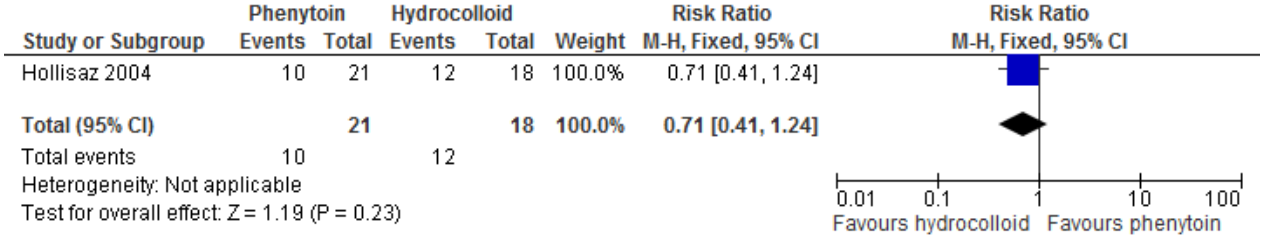


Figure 79 – Phenytoin versus hydrocolloid dressing – proportion of ulcers completely healed (all stages – sacral)

Study or Subgroup	Phenytoin Events	Phenytoin Total	Hydrocolloid Events	Hydrocolloid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hollisaz 2004	4	8	4	7	100.0%	0.88 [0.34, 2.25]
Total (95% CI)		**8**		**7**	**100.0%**	**0.88 [0.34, 2.25]**
Total events	4		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.28 (P = 0.78)

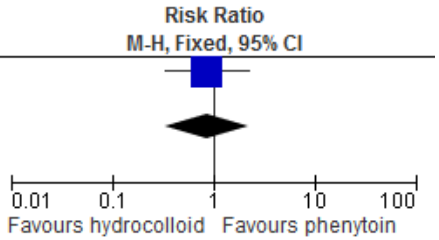


Figure 80 – Phenytoin versus hydrocolloid dressing – proportion of ulcers improved

Study or Subgroup	Phenytoin Events	Phenytoin Total	Hydrocolloid Events	Hydrocolloid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hollisaz 2004	16	30	27	31	100.0%	0.61 [0.43, 0.88]
Total (95% CI)		**30**		**31**	**100.0%**	**0.61 [0.43, 0.88]**
Total events	16		27			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.66 (P = 0.008)

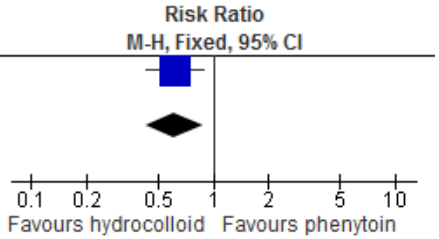


Figure 81 – Phenytoin versus hydrocolloid dressing – proportion of ulcers worsened

Study or Subgroup	Phenytoin Events	Phenytoin Total	Hydrocolloid Events	Hydrocolloid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hollisaz 2004	2	30	2	31	100.0%	1.03 [0.16, 6.87]
Total (95% CI)		**30**		**31**	**100.0%**	**1.03 [0.16, 6.87]**
Total events	2		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.97)

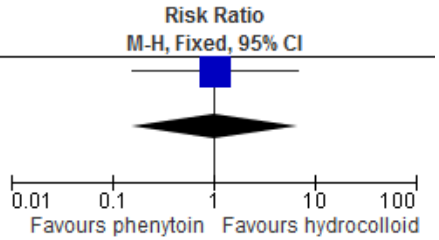


Figure 82 – Phenytoin versus hydrocolloid dressing – mean days of healing

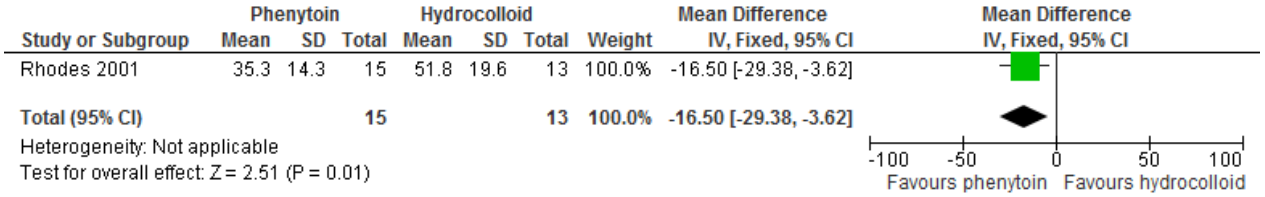


Figure 83 – Phenytoin versus triple antibiotics – mean days to healing

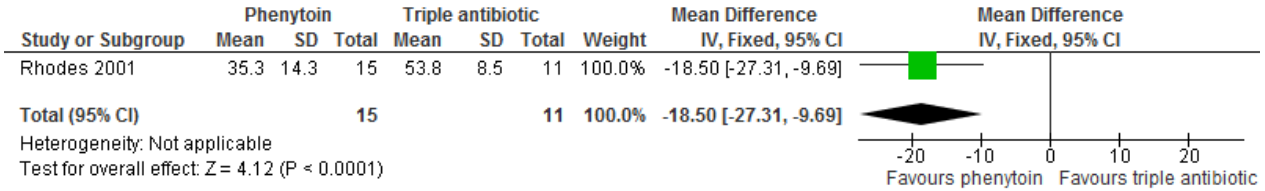


Figure 84 – Dialysate versus placebo – mean ml reduction in ulcer area

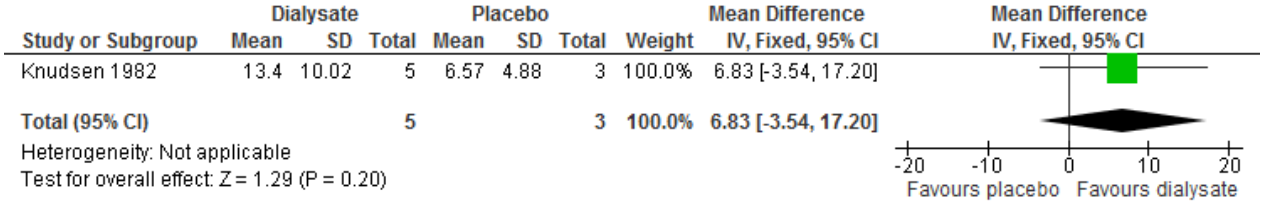


Figure 85 – Dialysate versus placebo – mean healing half-time (days)

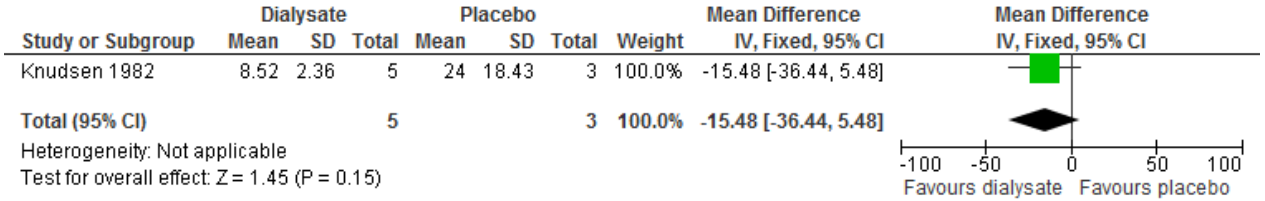


Figure 86 – Topical ointment with petrolatum versus petrolatum (base component) – proportion of patients completely healed

Study or Subgroup	Ointment Events	Ointment Total	Petrolatum Events	Petrolatum Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
23.1.1 Stage I						
Kuflik 2001	4	5	2	6	76.0%	5.54 [0.57, 53.72]
Subtotal (95% CI)		**5**		**6**	**76.0%**	**5.54 [0.57, 53.72]**
Total events	4		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.48 (P = 0.14)						
23.1.2 Stage II						
Kuflik 2001	1	5	0	3	24.0%	4.95 [0.09, 283.86]
Subtotal (95% CI)		**5**		**3**	**24.0%**	**4.95 [0.09, 283.86]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.77 (P = 0.44)						
Total (95% CI)		**10**		**9**	**100.0%**	**5.39 [0.74, 39.10]**
Total events	5		2			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.96); I² = 0%						
Test for overall effect: Z = 1.67 (P = 0.10)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.96), I² = 0%						

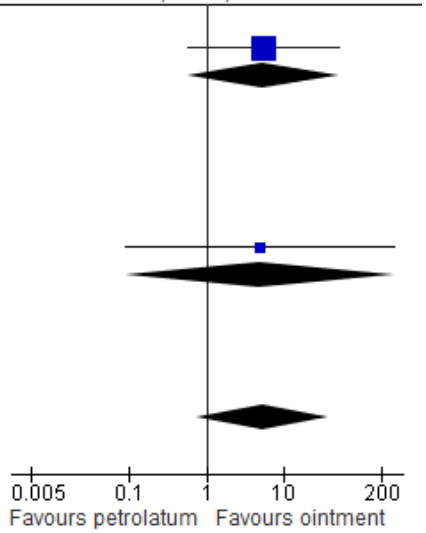
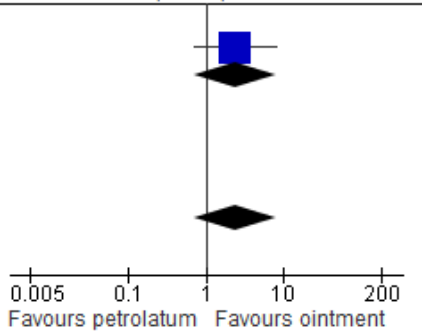
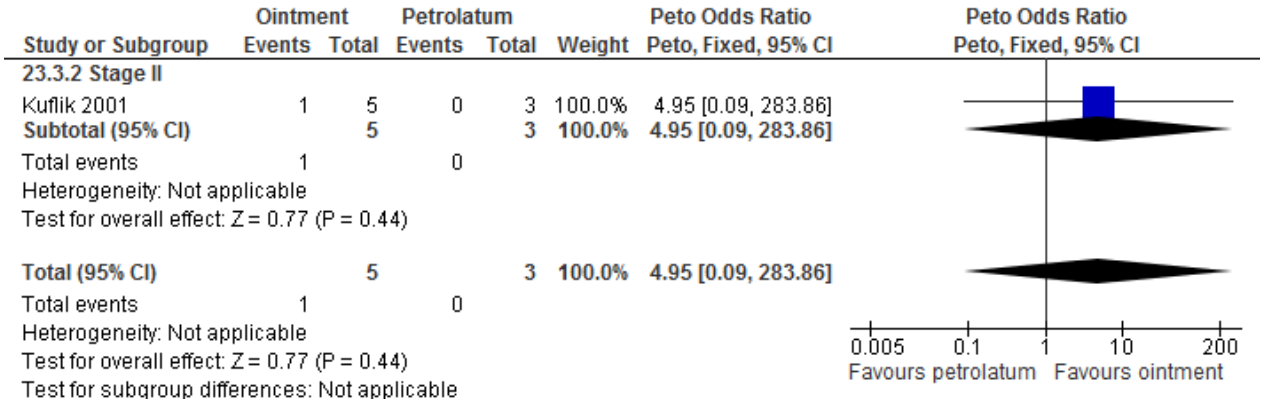


Figure 87 – Topical ointment with petrolatum versus petrolatum (base component) – proportion of patients improved

Study or Subgroup	Ointment Events	Ointment Total	Petrolatum Events	Petrolatum Total	Weight	Risk Ratio M-H, Fixed, 95% CI
23.2.1 Stage I						
Kuflik 2001	4	5	2	6	100.0%	2.40 [0.71, 8.08]
Subtotal (95% CI)		**5**		**6**	**100.0%**	**2.40 [0.71, 8.08]**
Total events	4		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.41 (P = 0.16)						
Total (95% CI)		**5**		**6**	**100.0%**	**2.40 [0.71, 8.08]**
Total events	4		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.41 (P = 0.16)						
Test for subgroup differences: Not applicable						




Ointment
Petrolatum
Peto Odds Ratio
Peto Odds Ratio
Study or Subgroup Events Total Events Total Weight Peto, Fixed, 95% CI
Peto, Fixed, 95% CI
23.3.2 Stage II
Kuflik 2001 1 5 0 3 100.0% 4.95 [0.09, 283.86]
Subtotal (95% CI) 5 3 100.0% 4.95 [0.09, 283.86]
Total events 1 0
Heterogeneity: Not applicable
Test for overall effect: Z = 0.77 (P = 0.44)
Total (95% CI) 5 3 100.0% 4.95 [0.09, 283.86]
Total events 1 0
Heterogeneity: Not applicable
Test for overall effect: Z = 0.77 (P = 0.44)
Test for subgroup differences: Not applicable
0.005 0.1 1 10 200
Favours petrolatum Favours ointment

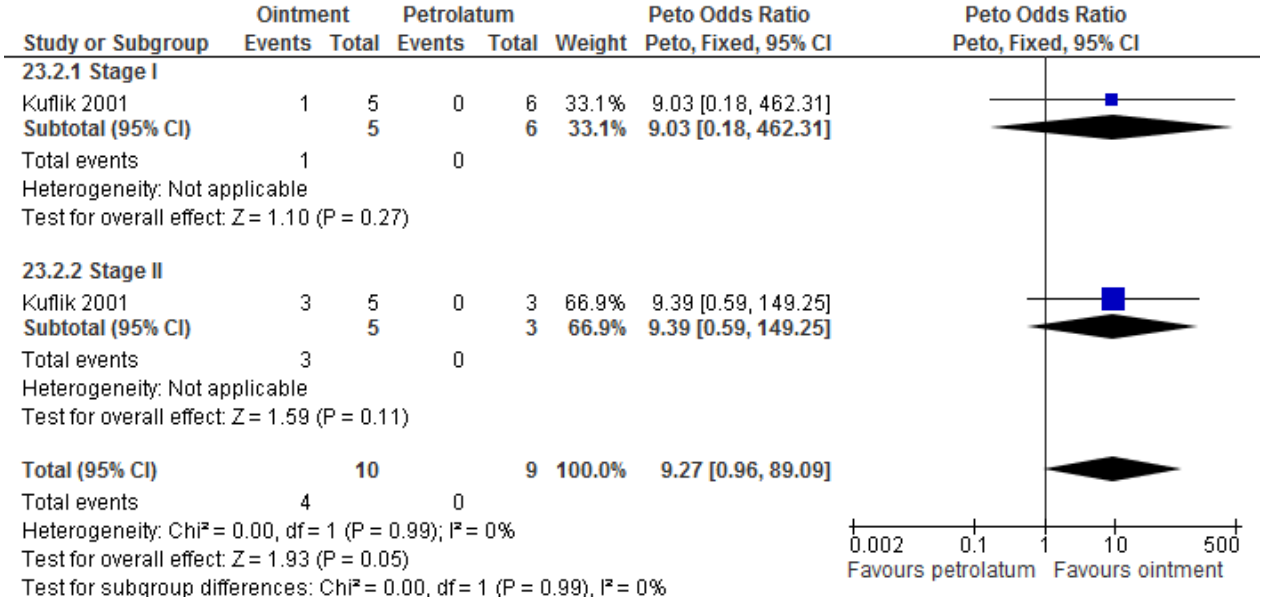

Ointment
Petrolatum
Peto Odds Ratio
Peto Odds Ratio
Study or Subgroup Events Total Events Total Weight Peto, Fixed, 95% CI
Peto, Fixed, 95% CI
23.2.1 Stage I
Kuflik 2001 1 5 0 6 33.1% 9.03 [0.18, 462.31]
Subtotal (95% CI) 5 6 33.1% 9.03 [0.18, 462.31]
Total events 1 0
Heterogeneity: Not applicable
Test for overall effect: Z = 1.10 (P = 0.27)
23.2.2 Stage II
Kuflik 2001 3 5 0 3 66.9% 9.39 [0.59, 149.25]
Subtotal (95% CI) 5 3 66.9% 9.39 [0.59, 149.25]
Total events 3 0
Heterogeneity: Not applicable
Test for overall effect: Z = 1.59 (P = 0.11)
Total (95% CI) 10 9 100.0% 9.27 [0.96, 89.09]
Total events 4 0
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.93 (P = 0.05)
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%
0.002 0.1 1 10 500
Favours petrolatum Favours ointment

Figure 88 – Topical ointment with petrolatum versus petrolatum (base component) – proportion of patients not changed

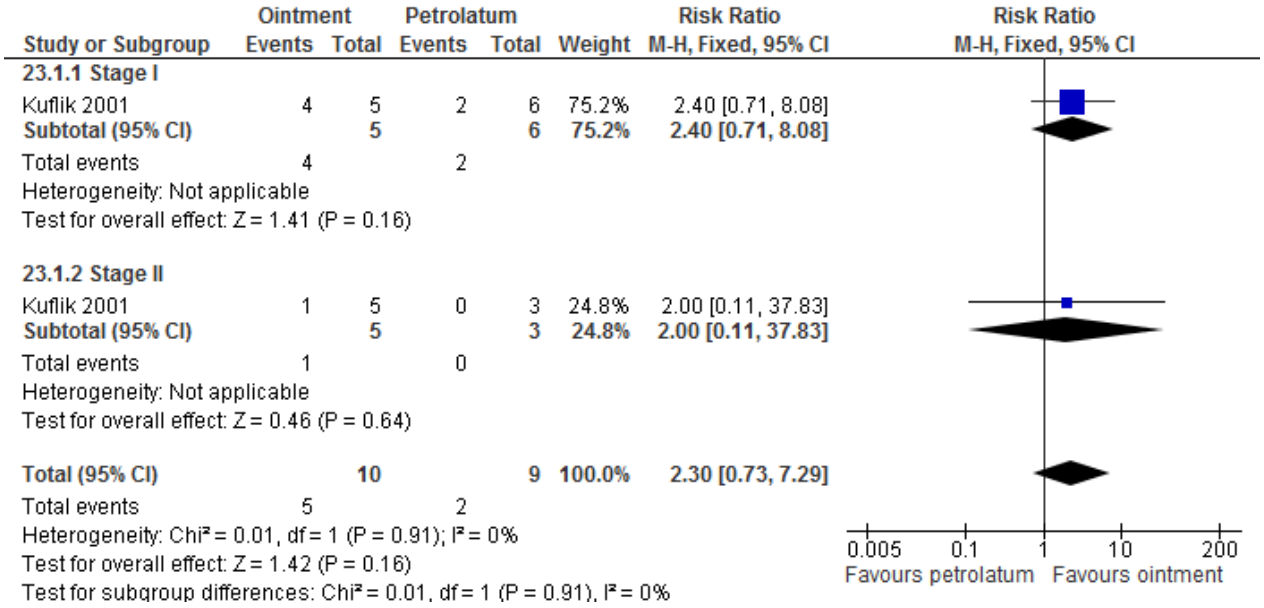
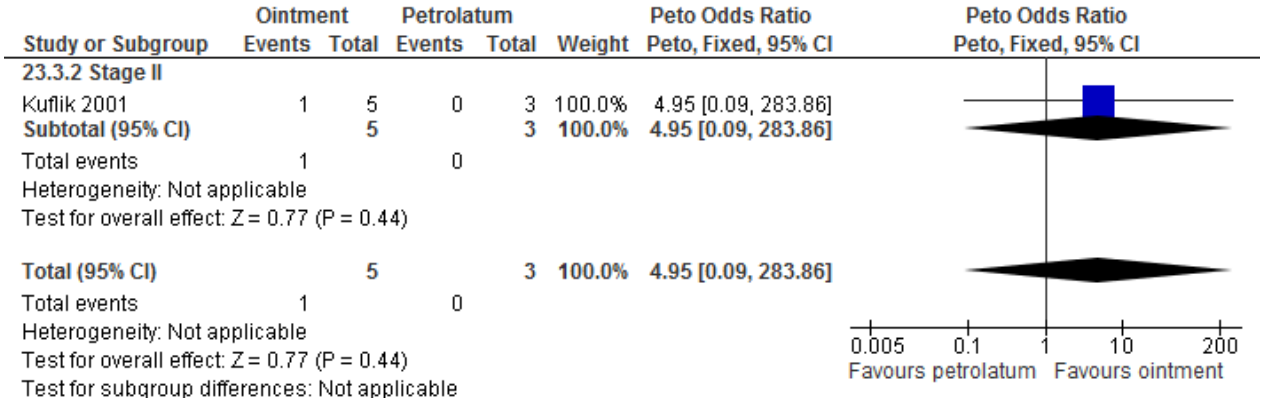


Figure 89 – Topical ointment with petrolatum versus petrolatum (base component) – proportion of patients worsened



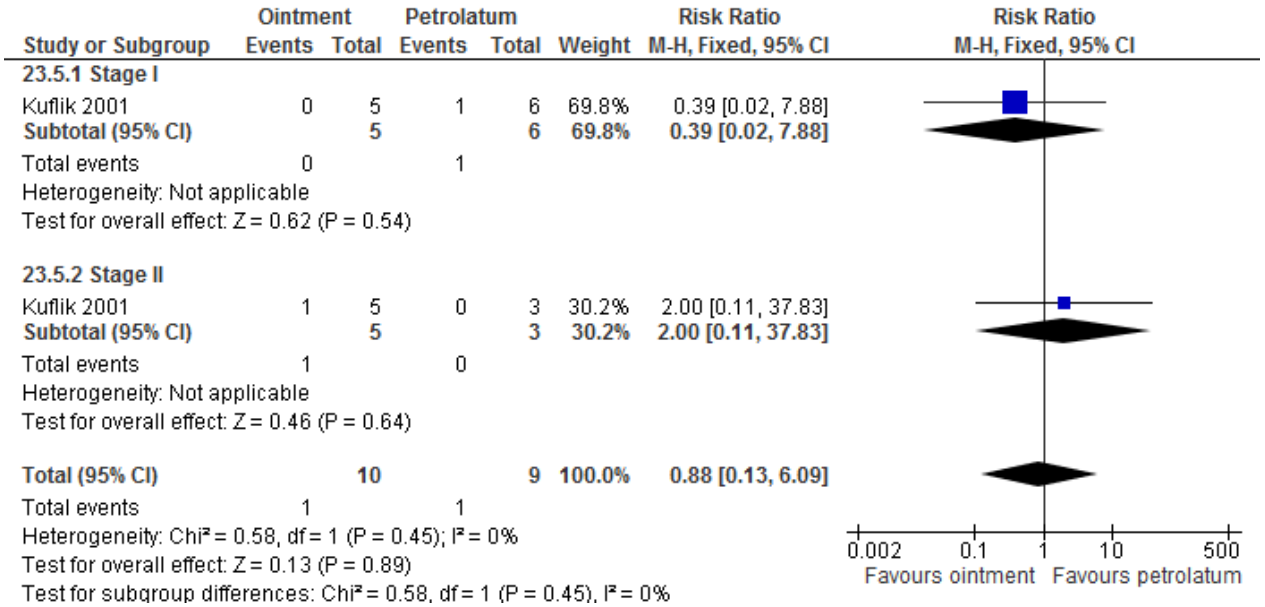

Ointment
Petrolatum
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
23.5.1 Stage I
Kuflik 2001 0 5 1 6 69.8% 0.39 [0.02, 7.88]
Subtotal (95% CI) 5 6 69.8% 0.39 [0.02, 7.88]
Total events 0 1
Heterogeneity: Not applicable
Test for overall effect: Z = 0.62 (P = 0.54)
23.5.2 Stage II
Kuflik 2001 1 5 0 3 30.2% 2.00 [0.11, 37.83]
Subtotal (95% CI) 5 3 30.2% 2.00 [0.11, 37.83]
Total events 1 0
Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.64)
Total (95% CI) 10 9 100.0% 0.88 [0.13, 6.09]
Total events 1 1
Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.89)
Test for subgroup differences: Chi² = 0.58, df = 1 (P = 0.45), I² = 0%
0.002
0.1
1
10
500
Favours ointment
Favours petrolatum

Figure 90 – Herbal extract versus standard treatment – proportion of patients healed > 80%

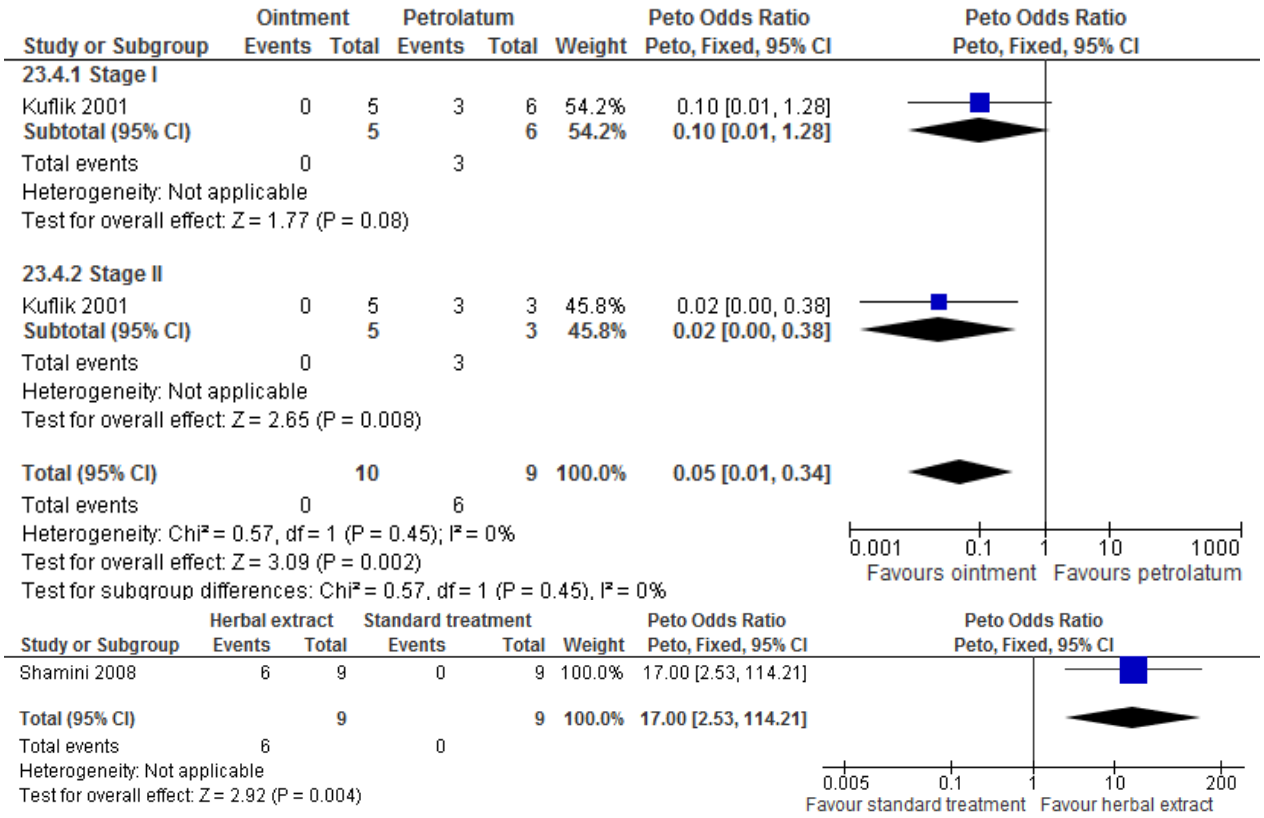


Figure 91 – Herbal extract versus standard treatment – proportion of patients healed 50-80%

Study or Subgroup	Herbal extract Events	Herbal extract Total	Standard treatment Events	Standard treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Shamini 2008	3	9	1	9	100.0%	3.00 [0.38, 23.68]
Total (95% CI)		**9**		**9**	**100.0%**	**3.00 [0.38, 23.68]**
Total events	3		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.04 (P = 0.30)

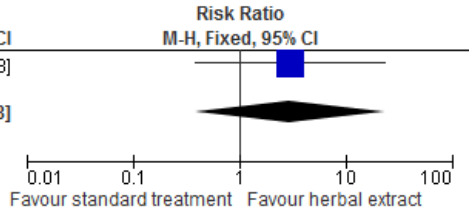


Figure 92 – Herbal extract versus standard treatment – proportion of patients healed < 20%

Study or Subgroup	Herbal extract Events	Herbal extract Total	Standard treatment Events	Standard treatment Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Shamini 2008	0	9	8	9	100.0%	0.03 [0.01, 0.20]
Total (95% CI)		**9**		**9**	**100.0%**	**0.03 [0.01, 0.20]**
Total events	0		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.69 (P = 0.0002)

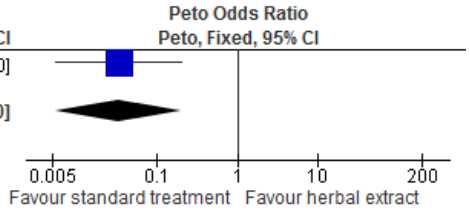


Figure 93 – Herbal extract versus standard treatment – mean cm² reduction in ulcer area

Study or Subgroup	Herbal extract Mean	Herbal extract SD	Herbal extract Total	Standard treatment Mean	Standard treatment SD	Standard treatment Total	Weight	Mean Difference IV, Fixed, 95% CI
Shamini 2008	48.2	85.3	9	2.8	6.2	9	100.0%	45.40 [-10.48, 101.28]
Total (95% CI)			**9**			**9**	**100.0%**	**45.40 [-10.48, 101.28]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.59 (P = 0.11)

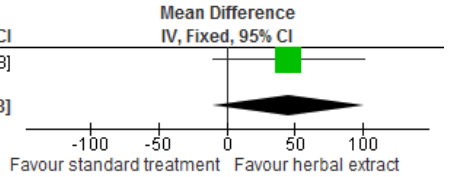


Figure 94 – Herbal extract versus standard treatment – mean percentage reduction in ulcer area

Study or Subgroup	Herbal extract Mean	Herbal extract SD	Herbal extract Total	Standard treatment Mean	Standard treatment SD	Standard treatment Total	Weight	Mean Difference IV, Fixed, 95% CI
Shamini 2008	78.3	12.5	9	6.3	22.7	9	100.0%	72.00 [55.07, 88.93]
Total (95% CI)			**9**			**9**	**100.0%**	**72.00 [55.07, 88.93]**

Heterogeneity: Not applicable
Test for overall effect: Z = 8.34 (P < 0.00001)

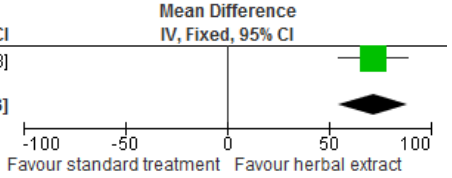


Figure 95 – Zinc oxide versus streptokinase-streptodornase – median percentage reduction in ulcer area

Study or Subgroup	Zinc oxide Mean	SD	Total	Streptokinase-streptodorn Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Agren 1985	2.4	0	14	-18.7	0	14		Not estimable
Total (95% CI)			**14**			**14**		**Not estimable**

Heterogeneity: Not applicable
Test for overall effect: Not applicable

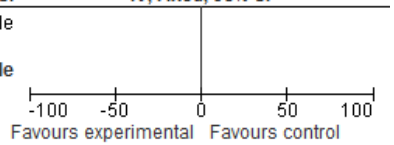


Figure 96 – Zinc oxide versus streptokinase-streptodornase – proportion of patients with an infection

Study or Subgroup	Zinc oxide Events	Total	Streptokinase-streptodorn Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Agren 1985	0	14	1	14	100.0%	0.14 [0.00, 6.82]
Total (95% CI)		**14**		**14**	**100.0%**	**0.14 [0.00, 6.82]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.00 (P = 0.32)

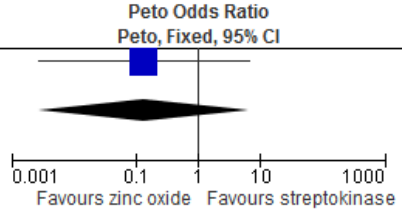


Figure 97 – Zinc oxide versus streptokinase-streptodornase – proportion of patients with skin reaction

Study or Subgroup	Zinc oxide Events	Total	Streptokinase-streptodorn Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Agren 1985	0	14	1	14	100.0%	0.14 [0.00, 6.82]
Total (95% CI)		**14**		**14**	**100.0%**	**0.14 [0.00, 6.82]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.00 (P = 0.32)

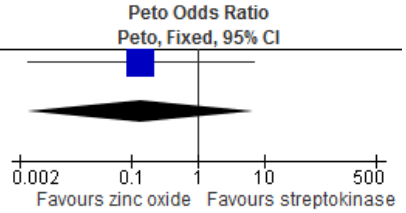


Figure 98 – Phenol versus A&D® -Petrolatum based ointment treatment – proportion of ulcers completely healed (all stages)

Study or Subgroup	Oxyquinoline Events	Total	A&D treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gerding 1993	43	86	21	51	100.0%	1.21 [0.82, 1.79]
Total (95% CI)		**86**		**51**	**100.0%**	**1.21 [0.82, 1.79]**
Total events	43		21			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)

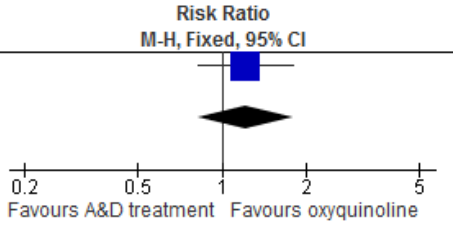


Figure 99 – Phenol versus A&D® -Petrolatum based ointment treatment – proportion of ulcers completely healed (stage I)

	Oxyquinoline		A&D treatment			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Gerding 1993	23	41	16	28	100.0%	0.98 [0.65, 1.49]
Total (95% CI)		**41**		**28**	**100.0%**	**0.98 [0.65, 1.49]**
Total events	23		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.09 (P = 0.93)						

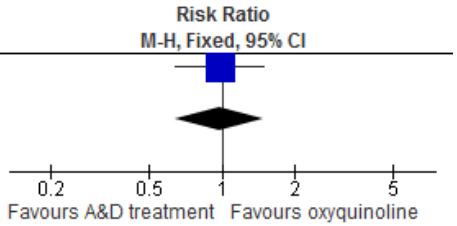


Figure 100 – Phenol versus A&D® -Petrolatum based ointment treatment – proportion of ulcers completely healed (stage II)

	Oxyquinoline		A&D treatment			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Gerding 1993	20	45	5	23	100.0%	2.04 [0.88, 4.74]
Total (95% CI)		**45**		**23**	**100.0%**	**2.04 [0.88, 4.74]**
Total events	20		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.67 (P = 0.10)						

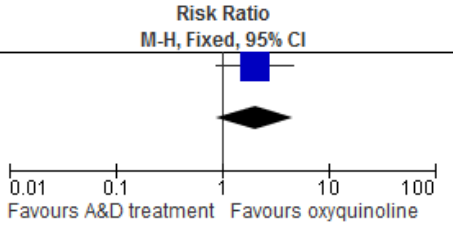


Figure 101 – Phenol versus A&D® -Petrolatum based ointment treatment – proportion of ulcers improved on day 15 (stage I)

	Oxyquinoline		A&D treatment			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Gerding 1993	15	41	6	28	100.0%	1.71 [0.76, 3.86]
Total (95% CI)		**41**		**28**	**100.0%**	**1.71 [0.76, 3.86]**
Total events	15		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.29 (P = 0.20)						

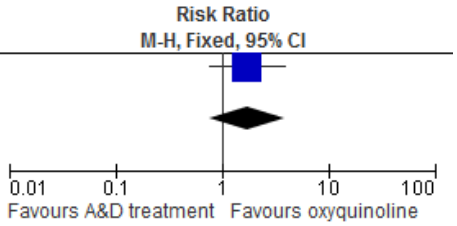


Figure 102 – Phenol versus A&D® -Petrolatum based ointment treatment – proportion of ulcers improved on day 22 (stage II)

Study or Subgroup	Oxyquinoline Events	Total	A&D treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gerding 1993	19	45	8	23	100.0%	1.21 [0.63, 2.34]
Total (95% CI)		**45**		**23**	**100.0%**	**1.21 [0.63, 2.34]**
Total events	19		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)

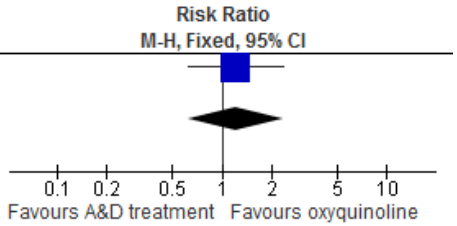


Figure 103 – Phenol versus A&D® -Petrolatum based ointment treatment – proportion of ulcers not changed on day 15 (stage I)

Study or Subgroup	Oxyquinoline Events	Total	A&D treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gerding 1993	4	41	4	28	100.0%	0.68 [0.19, 2.51]
Total (95% CI)		**41**		**28**	**100.0%**	**0.68 [0.19, 2.51]**
Total events	4		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.57)

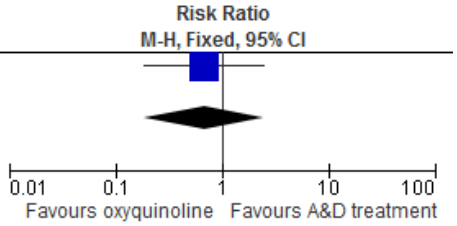


Figure 104 – Phenol versus A&D® -Petrolatum based ointment treatment – proportion of ulcers not changed on day 22 (stage II)

Study or Subgroup	Oxyquinoline Events	Total	A&D treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gerding 1993	5	45	7	23	100.0%	0.37 [0.13, 1.02]
Total (95% CI)		**45**		**23**	**100.0%**	**0.37 [0.13, 1.02]**
Total events	5		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.91 (P = 0.06)

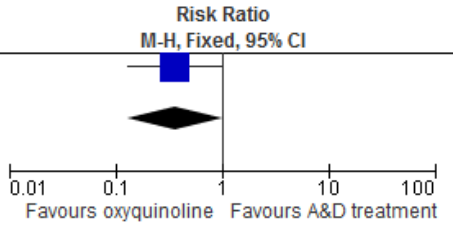


Figure 105 – Phenol versus A&D® -Petrolatum based ointment treatment – proportion of ulcers worsened on day 15 (stage I)

Study or Subgroup	Oxyquinoline Events	Oxyquinoline Total	A&D treatment Events	A&D treatment Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Gerding 1993	0	41	2	28	100.0%	0.08 [0.00, 1.41]
Total (95% CI)		**41**		**28**	**100.0%**	**0.08 [0.00, 1.41]**
Total events	0		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.72 (P = 0.08)

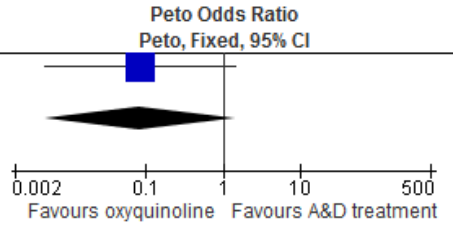


Figure 106 – Phenol versus A&D® -Petrolatum based ointment treatment – proportion of ulcers worsened on day 22 (stage II)

Study or Subgroup	Oxyquinoline Events	Oxyquinoline Total	A&D treatment Events	A&D treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gerding 1993	1	45	3	23	100.0%	0.17 [0.02, 1.55]
Total (95% CI)		**45**		**23**	**100.0%**	**0.17 [0.02, 1.55]**
Total events	1		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.57 (P = 0.12)

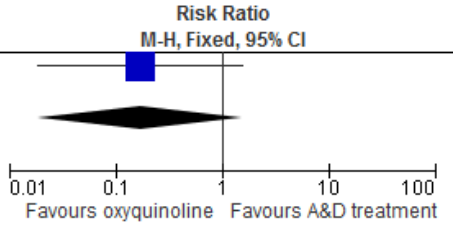


Figure 107 – Phenol versus A&D® -Petrolatum based ointment treatment – mean days to complete healing (all stages)

Study or Subgroup	Oxyquinoline Mean	Oxyquinoline SD	Oxyquinoline Total	A&D treatment Mean	A&D treatment SD	A&D treatment Total	Weight	Mean Difference IV, Fixed, 95% CI
Gerding 1993	7.23	4.15	86	8.62	5.16	51	100.0%	-1.39 [-3.06, 0.28]
Total (95% CI)			**86**			**51**	**100.0%**	**-1.39 [-3.06, 0.28]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.64 (P = 0.10)

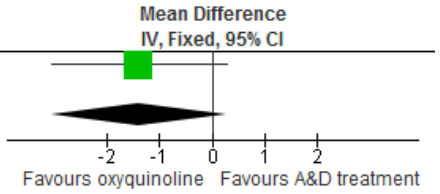


Figure 108 – Phenol versus A&D® -Petrolatum based ointment treatment – mean days to complete healing (stage I)

Study or Subgroup	Oxyquinoline Mean	Oxyquinoline SD	Oxyquinoline Total	A&D treatment Mean	A&D treatment SD	A&D treatment Total	Weight	Mean Difference IV, Fixed, 95% CI
Gerding 1993	6.75	3.9	41	7.25	4.8	28	100.0%	-0.50 [-2.64, 1.64]
Total (95% CI)			**41**			**28**	**100.0%**	**-0.50 [-2.64, 1.64]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.65)

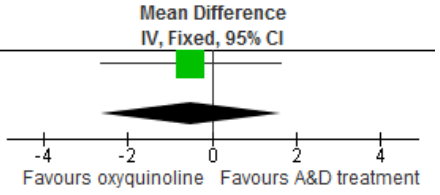


Figure 109 – Phenol versus A&D® -Petrolatum based ointment treatment – mean days to complete healing (stage II)

Study or Subgroup	Oxyquinoline Mean	SD	Total	A&D treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Gerding 1993	7.8	4.47	45	13	3.94	23	100.0%	-5.20 [-7.27, -3.13]
Total (95% CI)			45			23	100.0%	**-5.20 [-7.27, -3.13]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.92 (P < 0.00001)

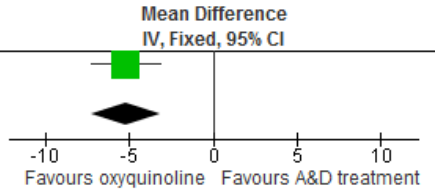


Figure 110 – Ethoxy-diaminoacridine plus nitrofuazone versus honey – proportion of ulcers completely healed

Study or Subgroup	Ethoxy-diaminoacridine Events	Total	Honey Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Günes 2007	0	25	5	25	100.0%	0.11 [0.02, 0.71]
Total (95% CI)		25		25	100.0%	**0.11 [0.02, 0.71]**
Total events	0		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.33 (P = 0.02)

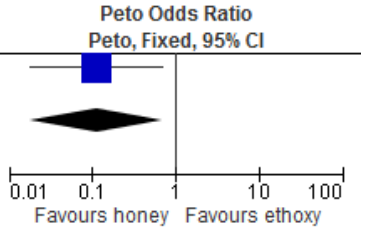


Figure 111 – Ethoxy-diaminoacridine plus nitrofuazone versus honey – mean percentage reduction in PUSH score

Study or Subgroup	Ethoxy-diaminoacridine Mean	SD	Total	Honey Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Günes 2007	12.9	28.92	25	56.3	28.92	25	100.0%	-43.40 [-59.43, -27.37]
Total (95% CI)			25			25	100.0%	**-43.40 [-59.43, -27.37]**

Heterogeneity: Not applicable
Test for overall effect: Z = 5.31 (P < 0.00001)

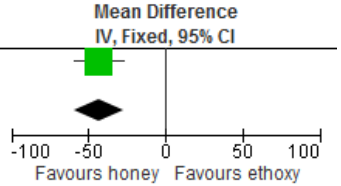


Figure 112 – Ethoxy-diaminoacridine plus nitrofuazone versus honey – mean percentage reduction in ulcer size

Study or Subgroup	Ethoxy-diaminoacridine Mean	SD	Total	Honey Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Günes 2007	13	29.39	25	56	29.39	25	100.0%	-43.00 [-59.29, -26.71]
Total (95% CI)			25			25	100.0%	**-43.00 [-59.29, -26.71]**

Heterogeneity: Not applicable
Test for overall effect: Z = 5.17 (P < 0.00001)

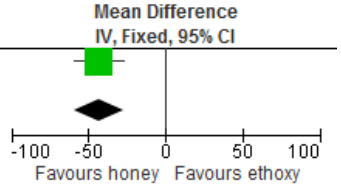


Figure 113 – Povidone-iodine versus hydrocolloid – proportion of patients completely healed

Figure 114 – Povidone-iodine versus hydrocolloid – mean speed of healing (mm²/day)

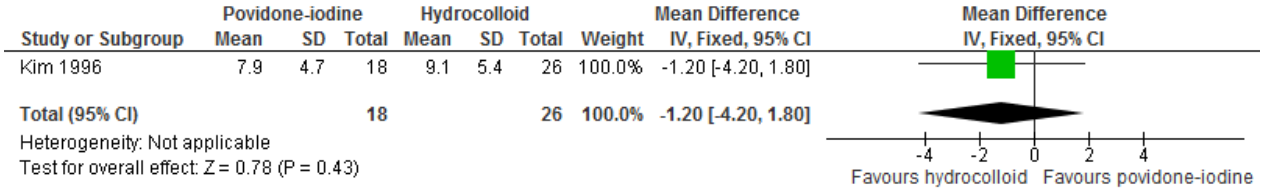


Figure 115 – Povidone-iodine versus hydrocolloid – proportion of patients with hypergranulation

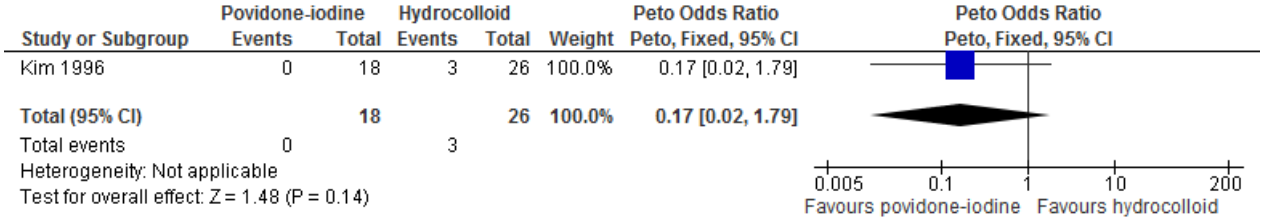


Figure 116 –Povidone-iodine versus hydrogel – mean cm²/day to healing

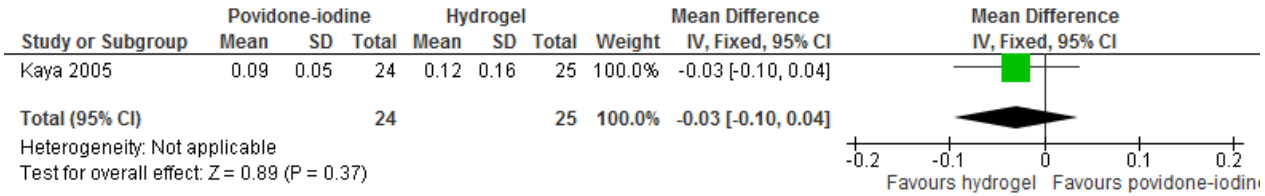


Figure 117 – Cadexomer iodine versus standard treatment – proportion of ulcers reduced > 50%

Study or Subgroup	Cadexomer iodine Events	Total	Standard treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Moberg 1983	8	16	1	18	100.0%	9.00 [1.26, 64.33]
Total (95% CI)		**16**		**18**	**100.0%**	**9.00 [1.26, 64.33]**
Total events	8		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.19 (P = 0.03)

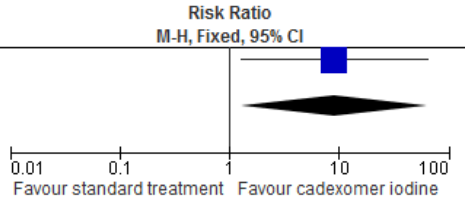


Figure 118 – Cadexomer iodine versus standard treatment – mean cm² reduction in ulcer area

Study or Subgroup	Cadexomer iodine Mean	SD	Total	Standard treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Moberg 1983	2.9	5.2	16	2.5	4.67	18	100.0%	0.40 [-2.94, 3.74]
Total (95% CI)			**16**			**18**	**100.0%**	**0.40 [-2.94, 3.74]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.81)

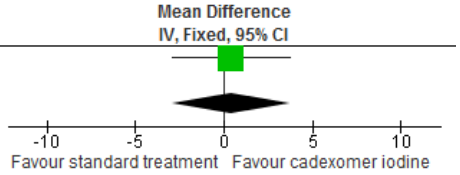


Figure 119 – Cadexomer iodine versus standard treatment – mean percentage reduction in ulcer area

Study or Subgroup	Cadexomer iodine Mean	SD	Total	Standard treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Moberg 1983	30.9	46	16	19.6	83.16	18	100.0%	11.30 [-33.24, 55.84]
Total (95% CI)			**16**			**18**	**100.0%**	**11.30 [-33.24, 55.84]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.50 (P = 0.62)

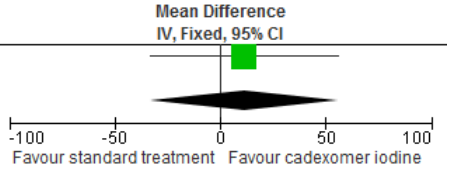


Figure 120 – Silver sulfazidine cream versus silver dressing – mean percentage reduction in ulcer area

Study or Subgroup	Cream Mean	SD	Total	Dressing Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Chuangsuwanich 2011	25.06	56.13	20	36.95	56.13	20	100.0%	-11.89 [-46.68, 22.90]
Total (95% CI)			**20**			**20**	**100.0%**	**-11.89 [-46.68, 22.90]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)

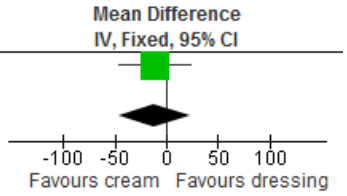


Figure 121 – Resin salve versus hydrofibre – proportion of patients completely healed

Study or Subgroup	Resin salve Events	Total	Hydrofibre Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sipponen 2008	12	13	4	9	100.0%	2.08 [0.98, 4.38]
Total (95% CI)		**13**		**9**	**100.0%**	**2.08 [0.98, 4.38]**
Total events	12		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.92 (P = 0.06)

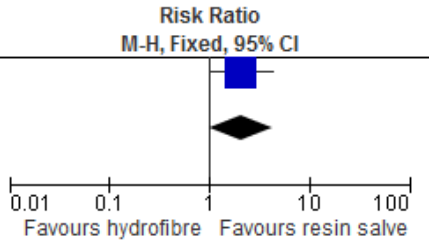


Figure 122 – Resin salve versus hydrofibre – proportion of ulcers completely healed

Study or Subgroup	Resin salve Events	Total	Hydrofibre Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sipponen 2008	17	18	4	11	100.0%	2.60 [1.18, 5.72]
Total (95% CI)		**18**		**11**	**100.0%**	**2.60 [1.18, 5.72]**
Total events	17		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.37 (P = 0.02)

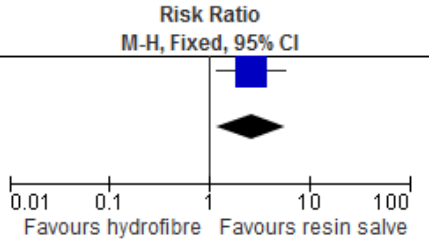


Figure 123 – Resin salve versus hydrofibre – proportion of ulcers improved

Study or Subgroup	Resin salve Events	Total	Hydrofibre Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sipponen 2008	18	18	10	11	100.0%	1.11 [0.89, 1.40]
Total (95% CI)		**18**		**11**	**100.0%**	**1.11 [0.89, 1.40]**
Total events	18		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.93 (P = 0.35)

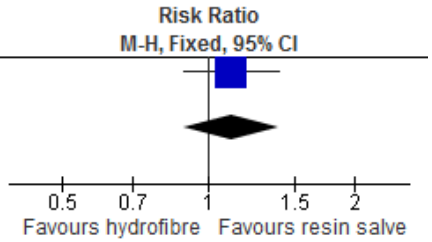


Figure 124 – Resin salve versus hydrofibre – proportion of ulcers worsened

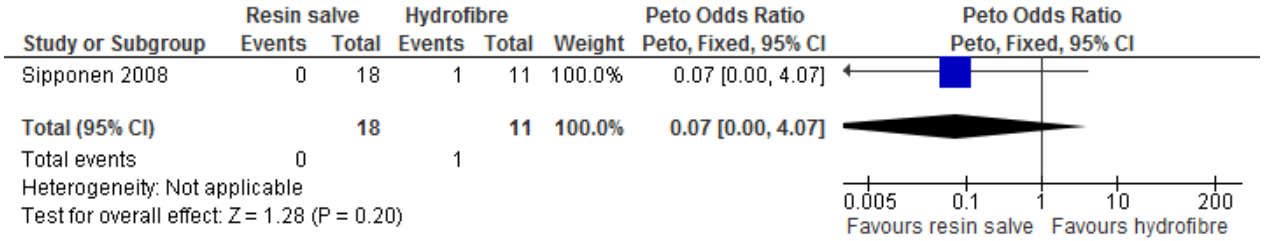


Figure 125 – Resin salve versus hydrofibre – proportion of patients with allergic skin reactions

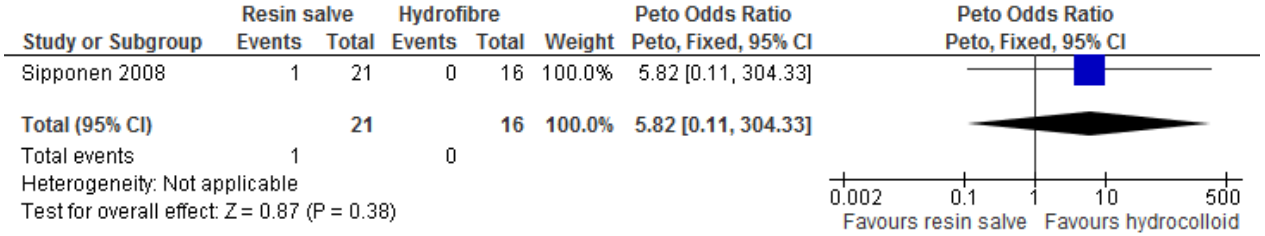


Figure 126 – Antibiotic ointment versus foam dressing – proportion of patients completely healed

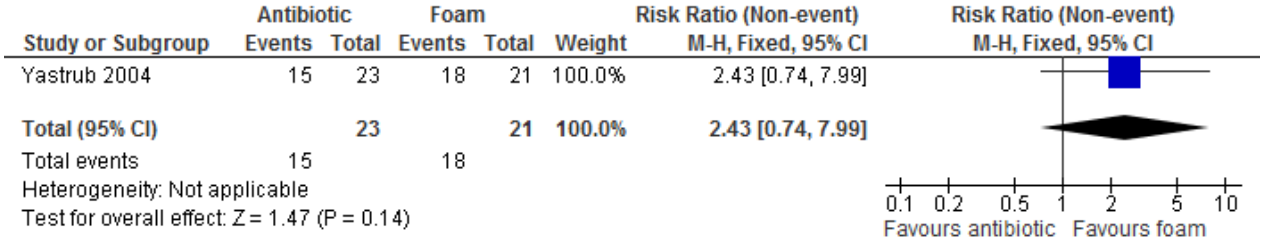


Figure 127 – FuChunSanYi Hao ointment versus iodophor – proportion of patients completely healed

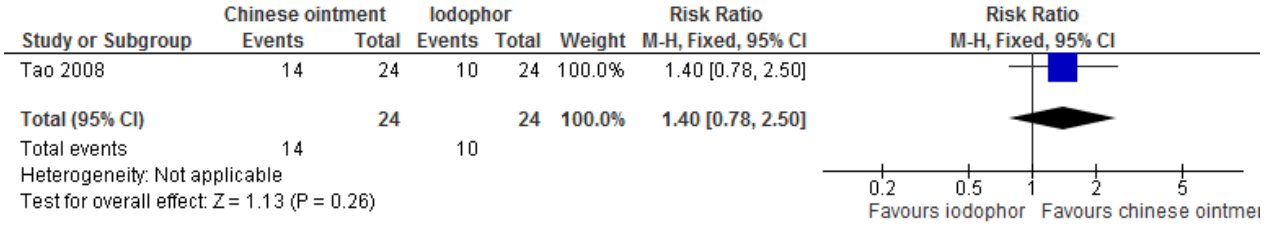


Figure 128 – FuChunSanYi Hao ointment versus iodophor – proportion of patients improved

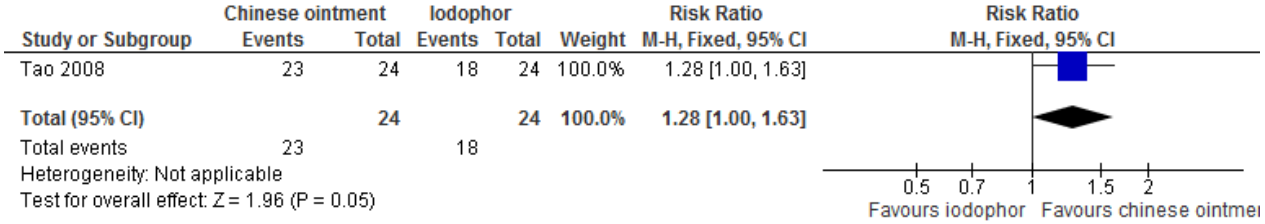


Figure 129 – FuChunSanYi Hao ointment versus iodophor – proportion of patients not changed or worsened

Figure 130 – RuYiZhuHuang ointment versus iodophor – proportion of patients completely healed

Study or Subgroup	Chinese ointment Events	Total	Iodophor Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Li 2007a	66	67	31	65	54.8%	2.07 [1.60, 2.67]
Li 2007b	18	20	7	20	12.2%	2.57 [1.39, 4.76]
Luo 1998	30	38	19	38	33.1%	1.58 [1.10, 2.26]
Total (95% CI)		**125**		**123**	**100.0%**	**1.97 [1.61, 2.40]**
Total events	114		57			

Heterogeneity: Chi² = 2.32, df = 2 (P = 0.31); I² = 14%
Test for overall effect: Z = 6.69 (P < 0.00001)

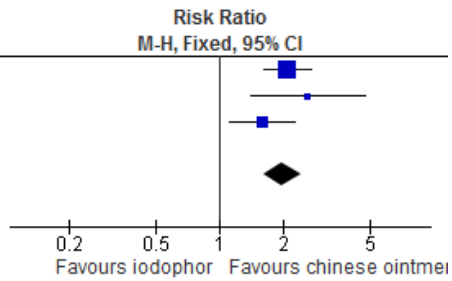


Figure 131 – RuYiZhuHuang ointment versus iodophor – proportion of patients improved

Study or Subgroup	Chinese ointment Events	Total	Iodophor Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Li 2007a	67	67	53	65	55.0%	1.22 [1.09, 1.38]
Li 2007b	20	20	15	20	15.7%	1.32 [1.02, 1.72]
Luo 1998	30	38	29	38	29.4%	1.03 [0.81, 1.32]
Total (95% CI)		**125**		**123**	**100.0%**	**1.18 [1.07, 1.31]**
Total events	117		97			

Heterogeneity: Chi² = 2.19, df = 2 (P = 0.33); I² = 9%
Test for overall effect: Z = 3.21 (P = 0.001)

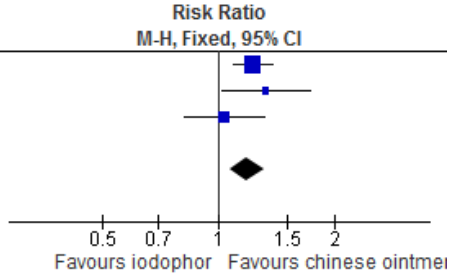


Figure 132 – RuYiZhuHuang ointment versus iodophor – proportion of patients not changed or worsened

Study or Subgroup	Chinese ointment Events	Total	Iodophor Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Li 2007a	0	67	12	65	45.3%	0.11 [0.03, 0.36]
Li 2007b	0	20	5	20	18.5%	0.11 [0.02, 0.69]
Luo 1998	1	38	9	38	36.2%	0.16 [0.04, 0.61]
Total (95% CI)		**125**		**123**	**100.0%**	**0.13 [0.06, 0.28]**
Total events	1		26			

Heterogeneity: Chi² = 0.23, df = 2 (P = 0.89); I² = 0%
Test for overall effect: Z = 5.11 (P < 0.00001)

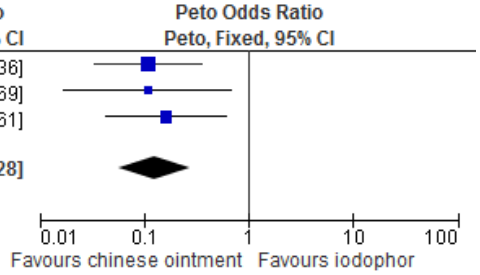


Figure 133 – ShenJi ointment versus iodophor – proportion of patients completely healed

Figure 134 – ShenJi ointment versus iodophor – proportion of patients improved

Figure 135 – ShenJi ointment versus iodophor – proportion of patients not changed or worsened

Figure 136 – JuFuYuan ointment versus gentamicin – proportion of patients completely healed

Study or Subgroup	Chinese ointment Events	Total	Gentamicin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bao 2006	18	23	4	23	100.0%	4.50 [1.80, 11.25]
Total (95% CI)		**23**		**23**	**100.0%**	**4.50 [1.80, 11.25]**
Total events	18		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.22 (P = 0.001)

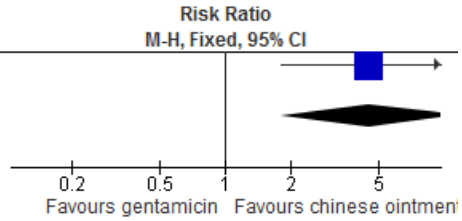


Figure 137 – JuFuYuan ointment versus gentamicin – proportion of patients improved

Study or Subgroup	Chinese ointment Events	Total	Gentamicin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bao 2006	22	23	15	23	100.0%	1.47 [1.07, 2.00]
Total (95% CI)		**23**		**23**	**100.0%**	**1.47 [1.07, 2.00]**
Total events	22		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.41 (P = 0.02)

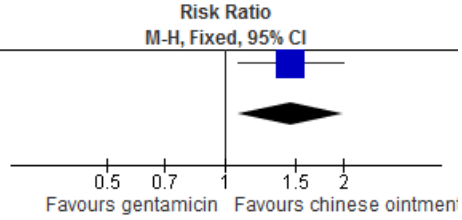


Figure 138 – JuFuYuan ointment versus gentamicin – proportion of patients not changed or worsened

Study or Subgroup	Chinese ointment Events	Total	Gentamicin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bao 2006	1	23	8	23	100.0%	0.13 [0.02, 0.92]
Total (95% CI)		**23**		**23**	**100.0%**	**0.13 [0.02, 0.92]**
Total events	1		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.04 (P = 0.04)

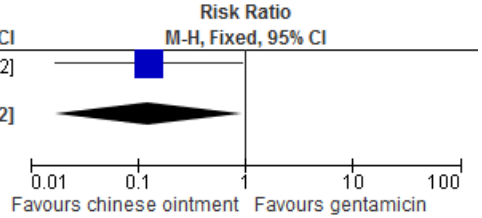


Figure 139 – FuFangDahuang Ding versus Chloramphenicol and sulfazidine silver powder – proportion of patients completely healed

Study or Subgroup	Chinese ointment Events	Total	Silver Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jing 2005	23	30	13	25	100.0%	1.47 [0.96, 2.26]
Total (95% CI)		**30**		**25**	**100.0%**	**1.47 [0.96, 2.26]**
Total events	23		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.79 (P = 0.07)

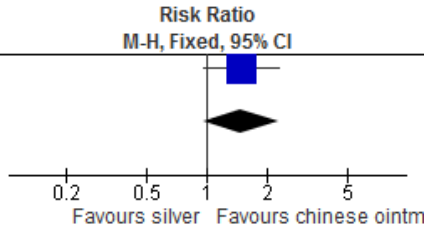


Figure 140 – FuFangDahuang Ding versus Chloramphenicol and sulfazidine silver powder – proportion of patients improved

Study or Subgroup	Chinese ointment Events	Total	Silver Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jing 2005	30	30	19	25	100.0%	1.31 [1.05, 1.65]
Total (95% CI)		**30**		**25**	**100.0%**	**1.31 [1.05, 1.65]**
Total events	30		19			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.35 (P = 0.02)

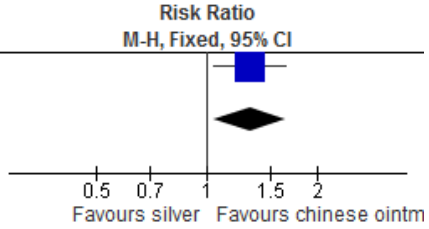


Figure 141 – FuFangDahuang Ding versus Chloramphenicol and sulfazidine silver powder – proportion of patients not changed or worsened

Study or Subgroup	Chinese ointment Events	Total	Silver Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Jing 2005	0	30	6	25	100.0%	0.09 [0.02, 0.48]
Total (95% CI)		**30**		**25**	**100.0%**	**0.09 [0.02, 0.48]**
Total events	0		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.82 (P = 0.005)

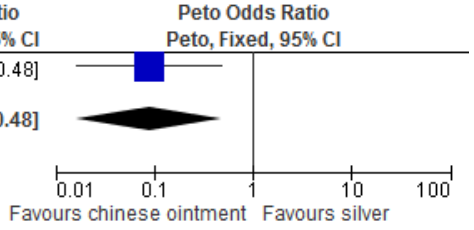


Figure 142 – ShenJiFuHong ointment versus saline – proportion of patients completely healed

Study or Subgroup	Chinese ointment Events	Total	Saline Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chen 2008	12	18	2	17	100.0%	5.67 [1.48, 21.69]
Total (95% CI)		**18**		**17**	**100.0%**	**5.67 [1.48, 21.69]**
Total events	12		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.53 (P = 0.01)

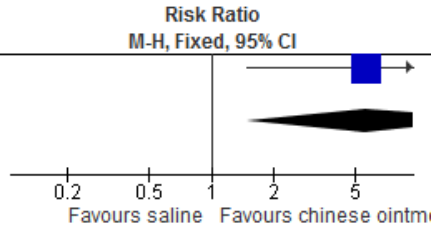


Figure 143 – ShenJiFuHong ointment versus saline – proportion of patients improved

Study or Subgroup	Chinese ointment Events	Total	Saline Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chen 2008	18	18	10	17	100.0%	1.67 [1.12, 2.48]
Total (95% CI)		**18**		**17**	**100.0%**	**1.67 [1.12, 2.48]**
Total events	18		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.53 (P = 0.01)

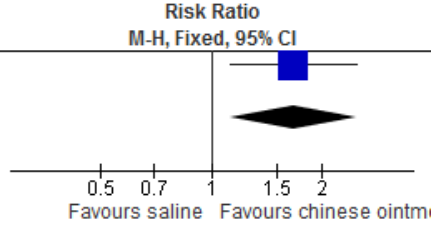


Figure 144 – ShenJiFuHong ointment versus saline – proportion of patients not changed or worsened

Study or Subgroup	Chinese ointment Events	Total	Saline Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Chen 2008	0	18	7	17	100.0%	0.08 [0.02, 0.42]
Total (95% CI)		**18**		**17**	**100.0%**	**0.08 [0.02, 0.42]**
Total events	0		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.00 (P = 0.003)

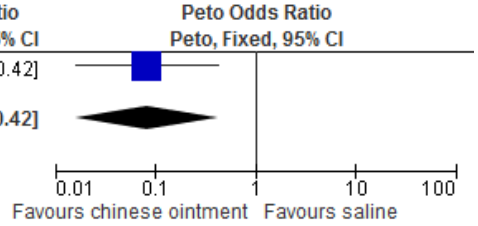


Figure 145 – ShenJi ointment versus antibacterial – proportion of patients completely healed

Study or Subgroup	Chinese ointment Events	Total	Antibacterial Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Zhang 2010	20	57	11	52	100.0%	1.66 [0.88, 3.12]
Total (95% CI)		**57**		**52**	**100.0%**	**1.66 [0.88, 3.12]**
Total events	20		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.57 (P = 0.12)

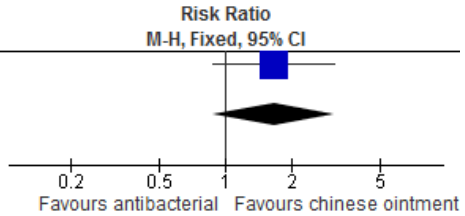


Figure 146 – ShenJi ointment versus antibacterial – proportion of patients improved

Study or Subgroup	Chinese ointment Events	Total	Antibacterial Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Zhang 2010	53	57	40	52	100.0%	1.21 [1.02, 1.43]
Total (95% CI)		**57**		**52**	**100.0%**	**1.21 [1.02, 1.43]**
Total events	53		40			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.25 (P = 0.02)

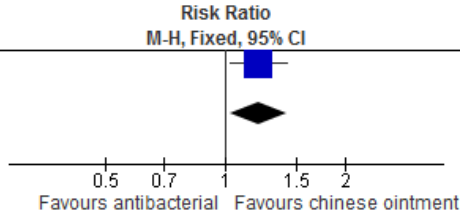


Figure 147 – ShenJi ointment versus antibacterial – proportion of patients not changed or worsened

Study or Subgroup	Chinese ointment Events	Total	Antibacterial Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Zhang 2010	4	57	12	52	100.0%	0.30 [0.10, 0.88]
Total (95% CI)		**57**		**52**	**100.0%**	**0.30 [0.10, 0.88]**
Total events	4		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.19 (P = 0.03)

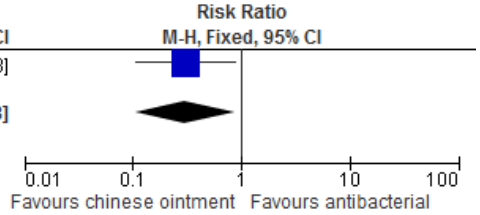


Figure 148 – SanHuangZhang Yu YouSha ointment versus nitrofurazone – proportion of patients completely healed

Study or Subgroup	Chinese ointment Events	Total	Nitrofurazone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Li 2008	84	200	22	108	100.0%	2.06 [1.37, 3.10]
Total (95% CI)		**200**		**108**	**100.0%**	**2.06 [1.37, 3.10]**
Total events	84		22			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.49 (P = 0.0005)

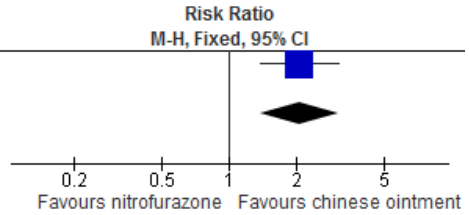


Figure 149 –SanHuangZhang Yu YouSha ointment versus nitrofurazone – proportion of patients improved

Study or Subgroup	Chinese ointment Events	Total	Nitrofurazone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Li 2008	188	200	80	108	100.0%	1.27 [1.13, 1.43]
Total (95% CI)		**200**		**108**	**100.0%**	**1.27 [1.13, 1.43]**
Total events	188		80			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.99 (P < 0.0001)

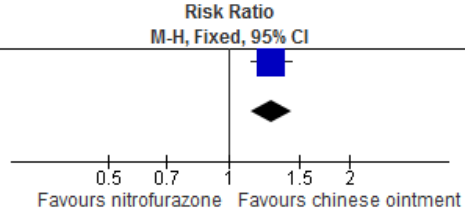


Figure 150 – SanHuangZhang Yu YouSha ointment versus nitrofurazone – proportion of patients not changed or worsened

Study or Subgroup	Chinese ointment Events	Total	Nitrofurazone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Li 2008	12	200	28	108	100.0%	0.23 [0.12, 0.44]
Total (95% CI)		**200**		**108**	**100.0%**	**0.23 [0.12, 0.44]**
Total events	12		28			

Heterogeneity: Not applicable
Test for overall effect: Z = 4.52 (P < 0.00001)

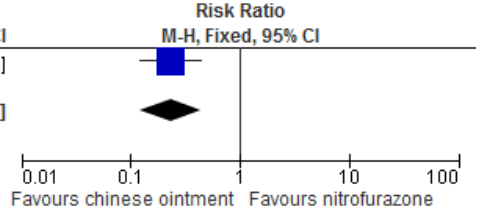


Figure 151 – Growth factors versus placebo – proportion of patients completely healed

Study or Subgroup	Growth factor Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
38.1.1 TGF-beta3 versus placebo						
Hirshberg 2003	1	9	0	5	3.0%	4.74 [0.08, 283.15]
Subtotal (95% CI)		**9**		**5**	**3.0%**	**4.74 [0.08, 283.15]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.75 (P = 0.46)

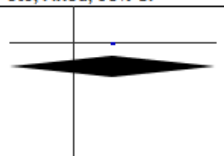
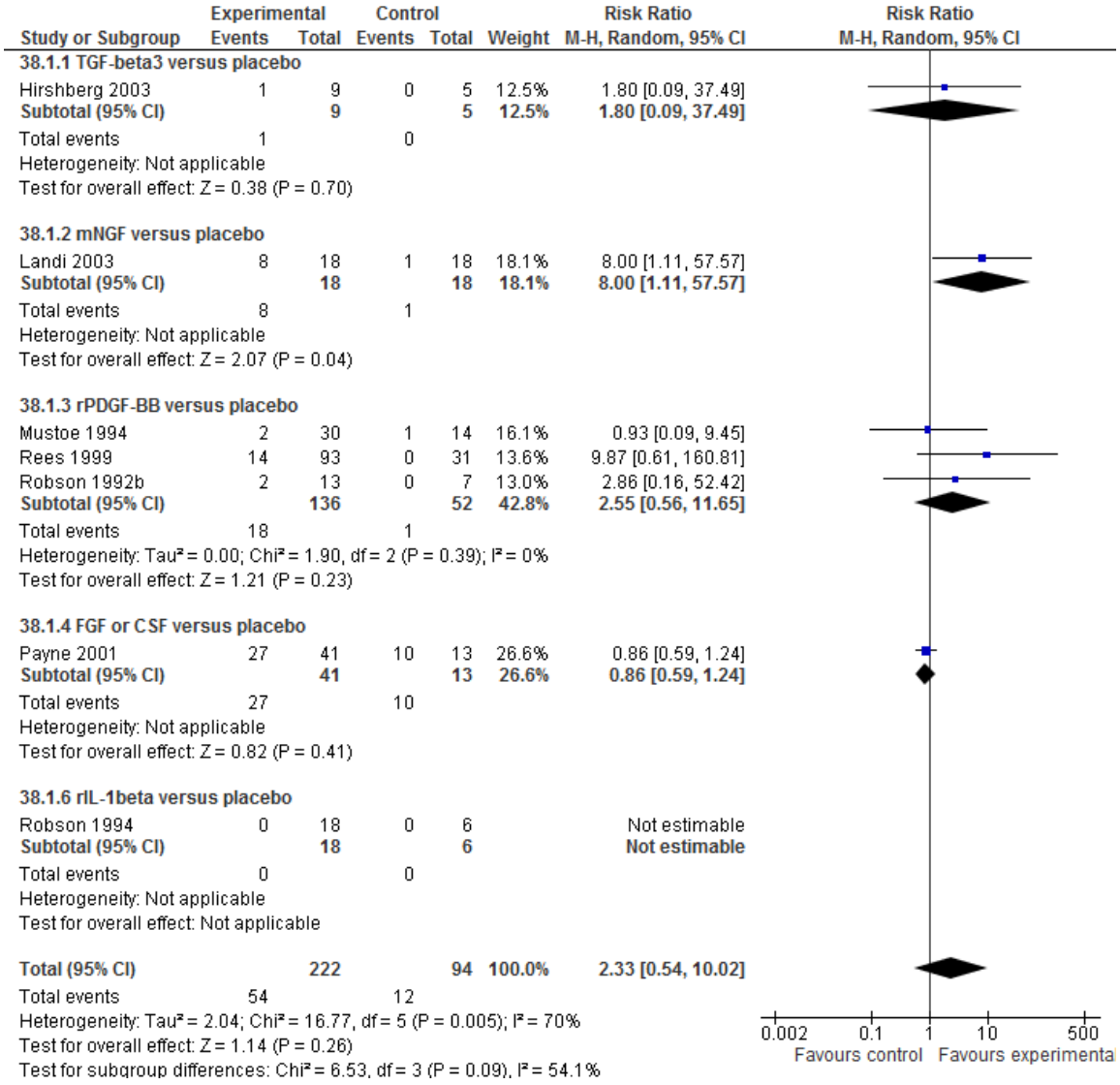


Figure 152 – Topical growth factor – beta 3: 1.0µg/cm² versus 2.5µg/cm² – proportion of patients completely healed



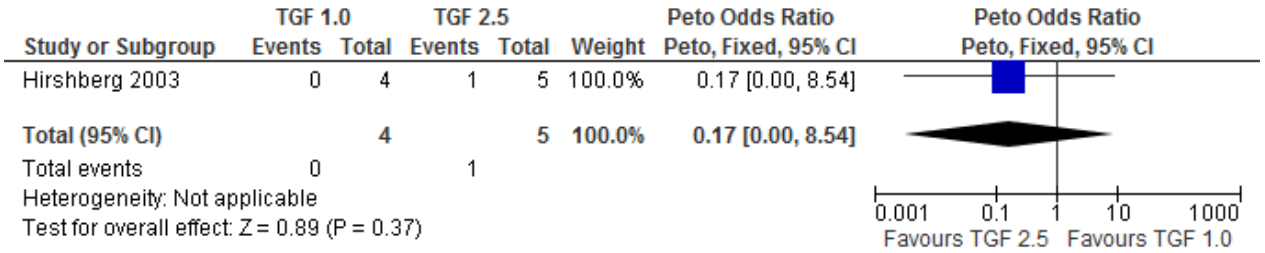


Figure 153 – Topical growth factor – beta 3 (2.5µg/cm²) versus placebo – proportion of patients completely healed

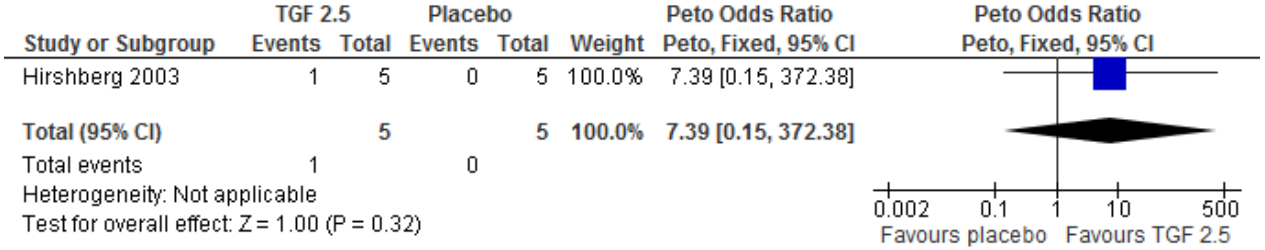


Figure 154 – Nerve growth factor (2.5 S murin) versus placebo – proportion of patients completely healed (foot ulcers)

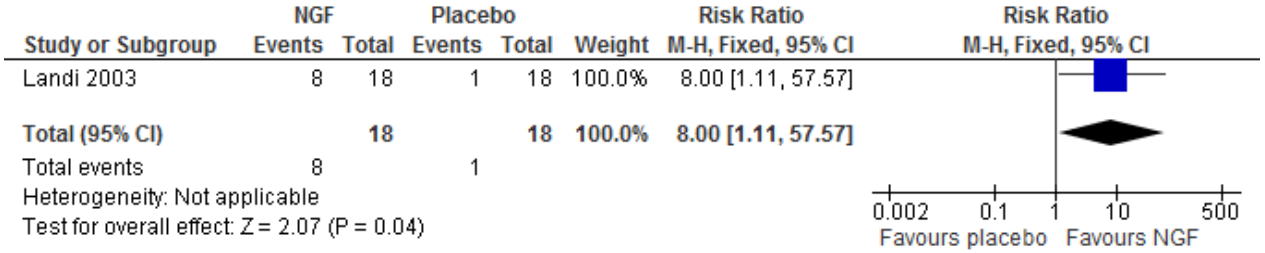


Figure 155 – Nerve growth factor (2.5 S murin) versus placebo – proportion of patients improved by 3 or more stages (foot ulcers)

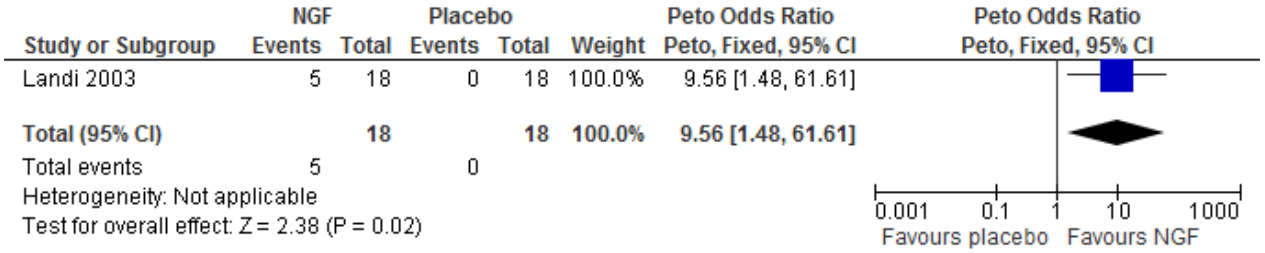


Figure 156 – Nerve growth factor (2.5 S murin) versus placebo – proportion of patients improved by 2 stages (foot ulcers)

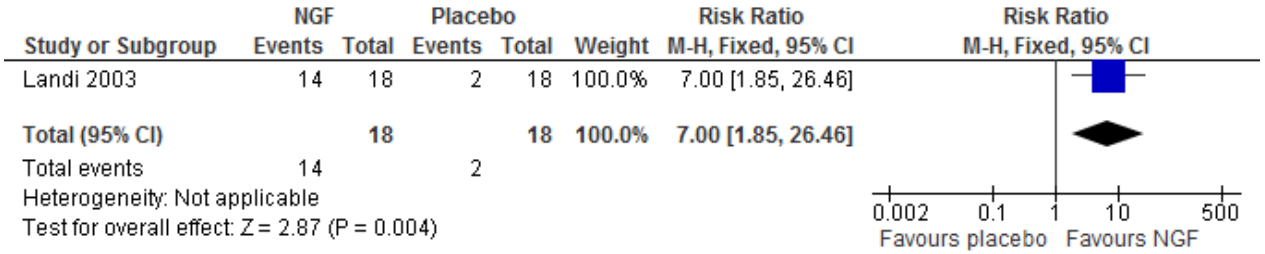


Figure 157 – Nerve growth factor (2.5 S murin) versus placebo – proportion of patients improved by 1 stage (foot ulcers)

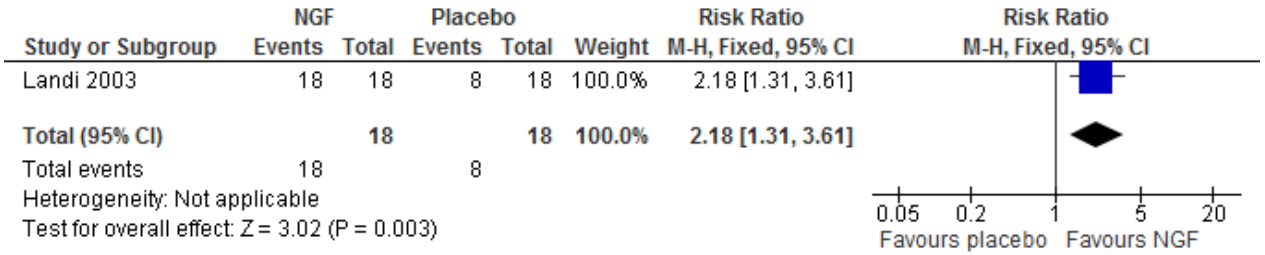


Figure 158 – Nerve growth factor (2.5 S murin) versus placebo – mean mm² reduction in ulcer area (foot ulcers)

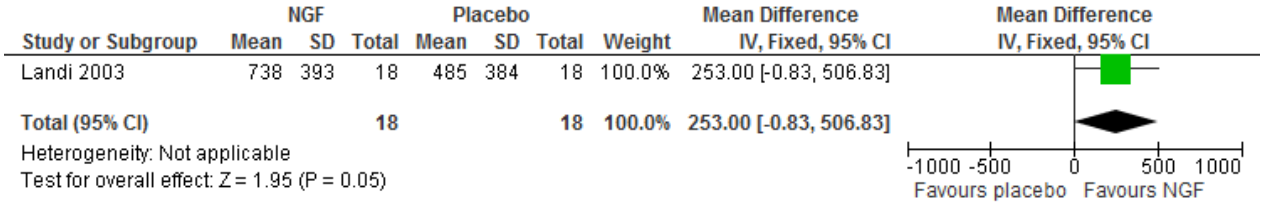


Figure 159 – Nerve growth factor (2.5 S murin) versus placebo – mean mm² reduction in ulcer area (foot ulcers) (adjusted for baseline ulcer area, location and duration)

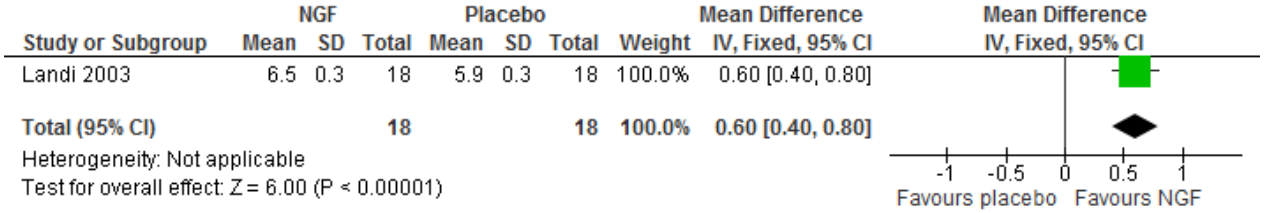


Figure 160 – Recombinant platelet-derived growth factor (100µg/ml) versus placebo – proportion of patients completely healed

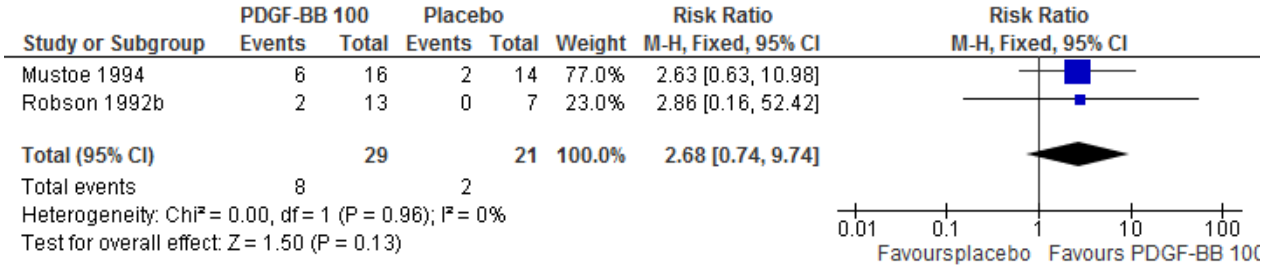


Figure 161 – Recombinant platelet-derived growth factor: 100µg/ml versus 300µg/ml – proportion of patients completely healed

Study or Subgroup	PDGF-BB 100 Events	Total	PDGF-BB 300 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mustoe 1994	6	16	3	12	100.0%	1.50 [0.47, 4.82]
Total (95% CI)		**16**		**12**	**100.0%**	**1.50 [0.47, 4.82]**
Total events	6		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)

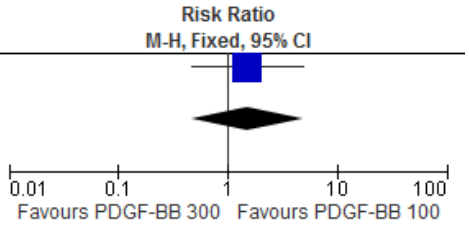


Figure 162 – Recombinant platelet-derived growth factor (300µg/ml) versus placebo – proportion of patients completely healed

Study or Subgroup	PDGF-BB 300 Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mustoe 1994	3	12	2	14	100.0%	1.75 [0.35, 8.79]
Total (95% CI)		**12**		**14**	**100.0%**	**1.75 [0.35, 8.79]**
Total events	3		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)

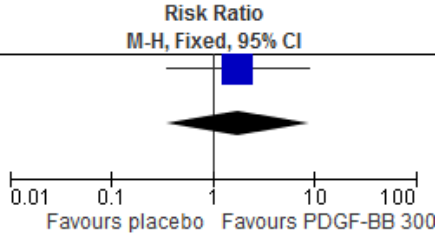


Figure 163 – Granulo-macrophage/colony-stimulating factor (2.0µg/cm²) versus placebo – proportion of patients completely healed (after 1 year)

Study or Subgroup	GM-CSF Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Payne 2001	8	14	10	13	100.0%	0.74 [0.43, 1.28]
Total (95% CI)		**14**		**13**	**100.0%**	**0.74 [0.43, 1.28]**
Total events	8		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.07 (P = 0.28)

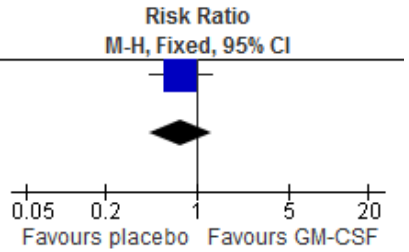


Figure 164 – Granulo-macrophage/colony-stimulating factor (2.0µg/cm²) versus placebo – proportion of patients worsened (after 1 year)

Study or Subgroup	GM-CSF Events	GM-CSF Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Payne 2001	2	14	0	13	100.0%	7.43 [0.44, 125.76]
Total (95% CI)		**14**		**13**	**100.0%**	**7.43 [0.44, 125.76]**
Total events	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.39 (P = 0.16)

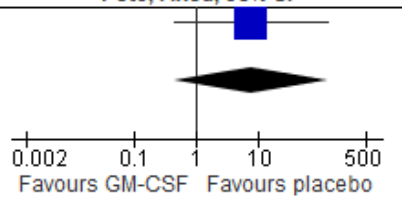


Figure 165 – Granulo-macrophage/colony-stimulating factor (2.0µg/cm²) versus placebo – mean percentage reduction in ulcer area

Study or Subgroup	GM-CSF Mean	GM-CSF SD	GM-CSF Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Robson 2000	67	24	15	71	11	15	100.0%	-4.00 [-17.36, 9.36]
Total (95% CI)			**15**			**15**	**100.0%**	**-4.00 [-17.36, 9.36]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.59 (P = 0.56)

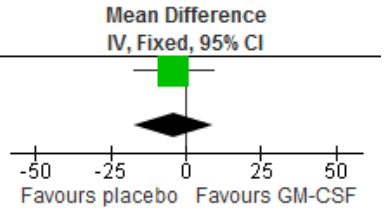


Figure 166 – Granulo-macrophage/colony-stimulating factor (2.0µg/cm²) versus basic fibroblast growth factor (5.0µg/cm²) – proportion of patients completely healed (after 1 year)

Study or Subgroup	GM-CSF Events	GM-CSF Total	BFGF Events	BFGF Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Payne 2001	8	14	10	14	100.0%	0.80 [0.46, 1.40]
Total (95% CI)		**14**		**14**	**100.0%**	**0.80 [0.46, 1.40]**
Total events	8		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.78 (P = 0.44)

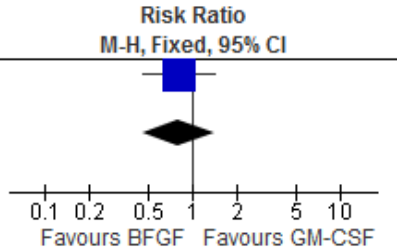


Figure 167 – Granulo-macrophage/colony-stimulating factor (2.0µg/cm²) versus basic fibroblast growth factor (5.0µg/cm²) – proportion of patients worsened (after 1 year)

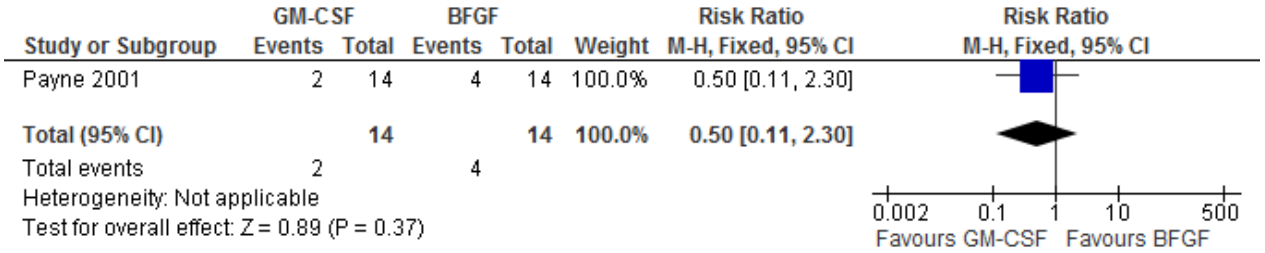


Figure 168 – Granulo-macrophage/colony-stimulating factor (2.0µg/cm²) versus basic fibroblast growth factor (5.0µg/cm²) – mean percentage reduction in ulcer area

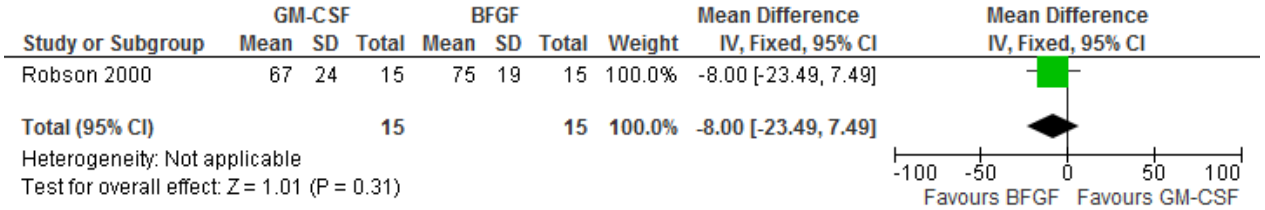


Figure 169 – Granulo-macrophage/colony-stimulating factor (2.0µg/cm²) versus granulo-macrophage/colony-stimulating factor (2.0µg/cm²) and basic fibroblast growth factor (5.0µg/cm²) – proportion of patients completely healed (after 1 year)

Figure 170 – Granulo-macrophage/colony-stimulating factor (2.0µg/cm²) versus granulo-macrophage/colony-stimulating factor (2.0µg/cm²) and basic fibroblast growth factor (5.0µg/cm²) – proportion of patients worsened (after 1 year)

Study or Subgroup	GM-CSF Events	GM-CSF Total	GM-CSF/BFGF Events	GM-CSF/BFGF Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Payne 2001	2	14	1	13	100.0%	1.86 [0.19, 18.13]
Total (95% CI)		**14**		**13**	**100.0%**	**1.86 [0.19, 18.13]**
Total events	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.59)

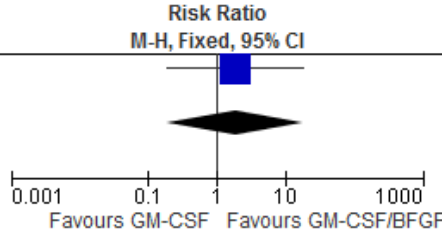


Figure 171 – Granulo-macrophage/colony-stimulating factor (2.0µg/cm²) versus granulo-macrophage/colony-stimulating factor (2.0µg/cm²) and basic fibroblast growth factor (5.0µg/cm²) – mean percentage reduction in ulcer area

Study or Subgroup	GM-CSF Mean	GM-CSF SD	GM-CSF Total	GM-CSF/BFGF Mean	GM-CSF/BFGF SD	GM-CSF/BFGF Total	Weight	Mean Difference IV, Fixed, 95% CI
Robson 2000	67	24	15	68	21	16	100.0%	-1.00 [-16.92, 14.92]
Total (95% CI)			**15**			**16**	**100.0%**	**-1.00 [-16.92, 14.92]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.12 (P = 0.90)

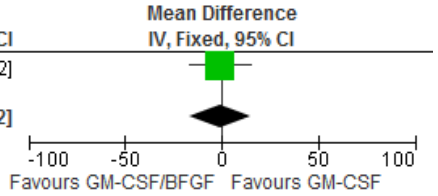


Figure 172 – Basic fibroblast growth factor (5.0µg/cm²) versus placebo – proportion of patients completely healed (after 1 year)

Study or Subgroup	BFGF Events	BFGF Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Payne 2001	10	14	10	13	100.0%	0.93 [0.59, 1.45]
Total (95% CI)		**14**		**13**	**100.0%**	**0.93 [0.59, 1.45]**
Total events	10		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)

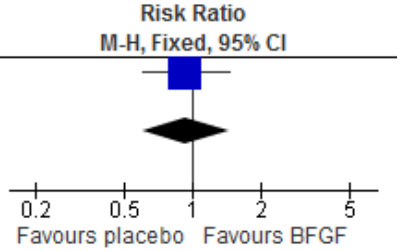


Figure 173 – Basic fibroblast growth factor (5.0µg/cm²) versus placebo – proportion of patients worsened (after 1 year)

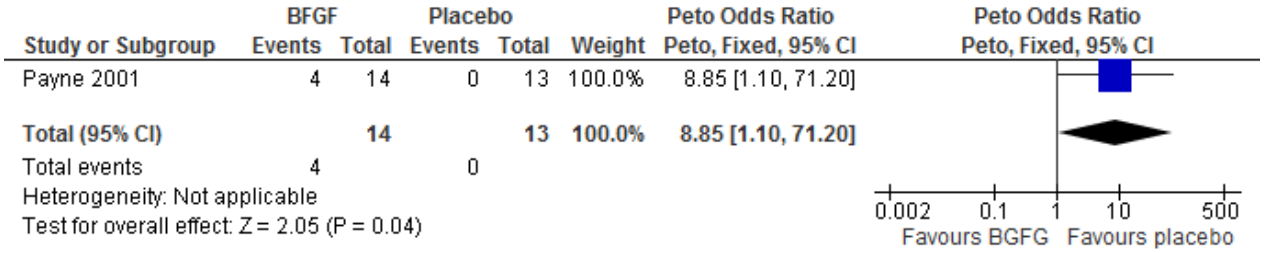


Figure 174 – Basic fibroblast growth factor (5.0µg/cm²) versus placebo – mean percentage reduction in ulcer area

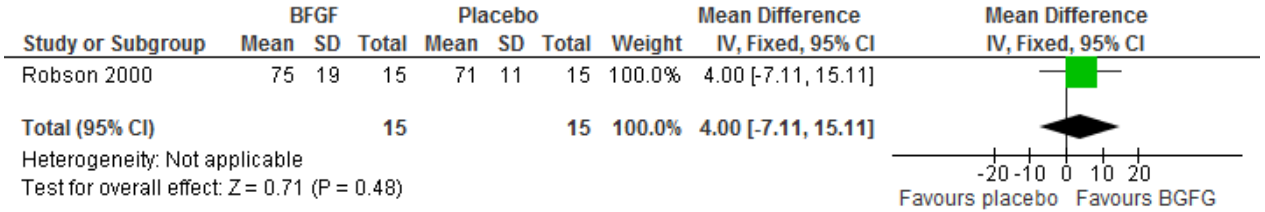


Figure 175 – Basic fibroblast growth factor (5.0µg/cm²) versus granulo-macrophage/colony-stimulating factor (2.0µg/cm²) and basic fibroblast growth factor (5.0µg/cm²) – proportion of patients completely healed (after 1 year)

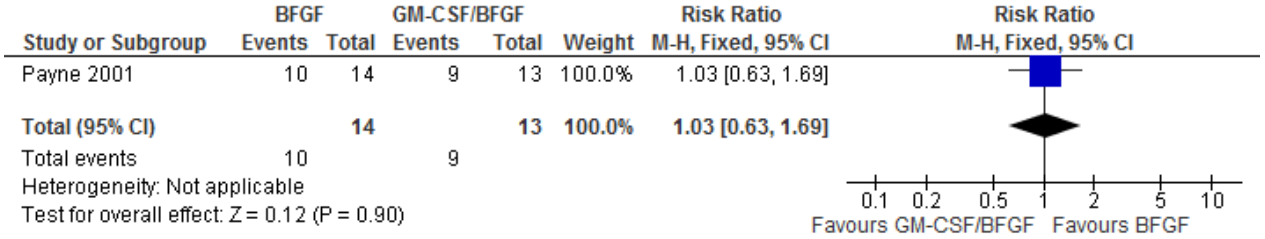


Figure 176 – Basic fibroblast growth factor (5.0µg/cm²) versus granulo-macrophage/colony-stimulating factor (2.0µg/cm²) and basic fibroblast growth factor (5.0µg/cm²) – proportion of patients worsened (after 1 year)

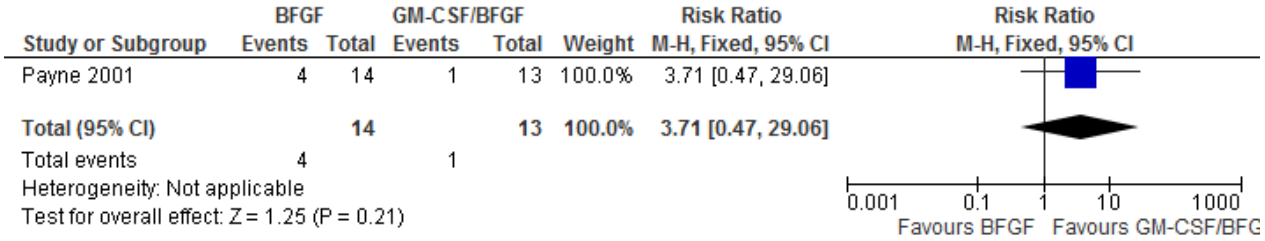


Figure 177 – Basic fibroblast growth factor (5.0µg/cm²) versus granulo-macrophage/colony-stimulating factor (2.0µg/cm²) and basic fibroblast growth factor (5.0µg/cm²) – mean percentage reduction in ulcer area

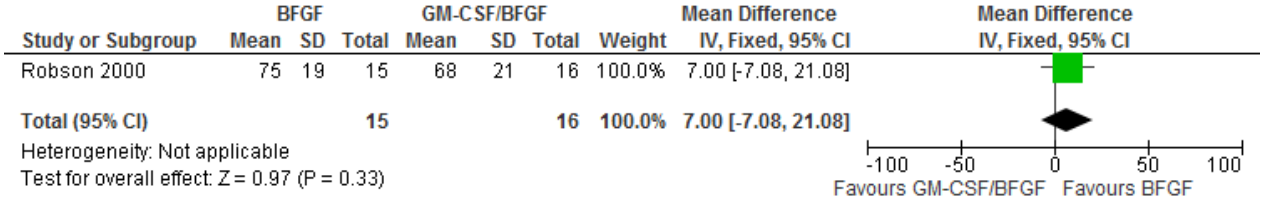


Figure 178 – Granulo-macrophage/colony-stimulating factor (2.0µg/cm²) and basic fibroblast growth factor (5.0µg/cm²) versus placebo – proportion of patients completely healed (after 1 year)

Figure 179 – Granulo-macrophage/colony-stimulating factor (2.0µg/cm²) and basic fibroblast growth factor (5.0µg/cm²) versus placebo – proportion of patients worsened (after 1 year)

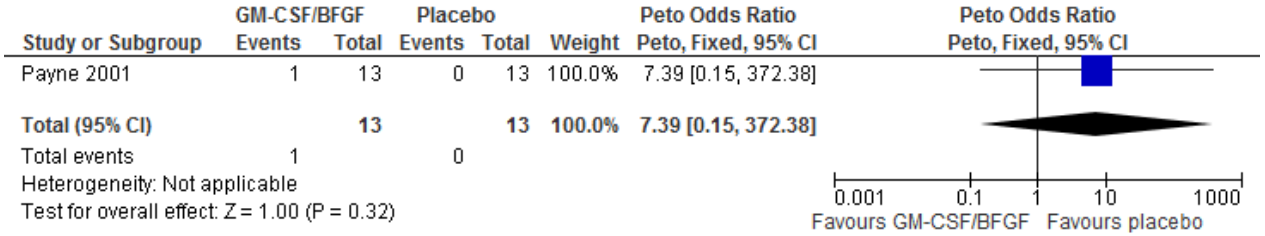


Figure 180 – Granulo-macrophage/colony-stimulating factor (2.0µg/cm²) and basic fibroblast growth factor (5.0µg/cm²) versus placebo – mean percentage reduction in ulcer area

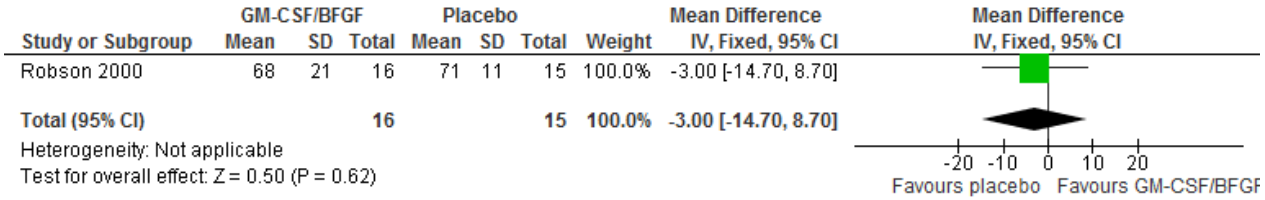


Figure 181 – Recombinant platelet-derived growth factor (100µg/g) versus placebo – proportion of patients completely healed

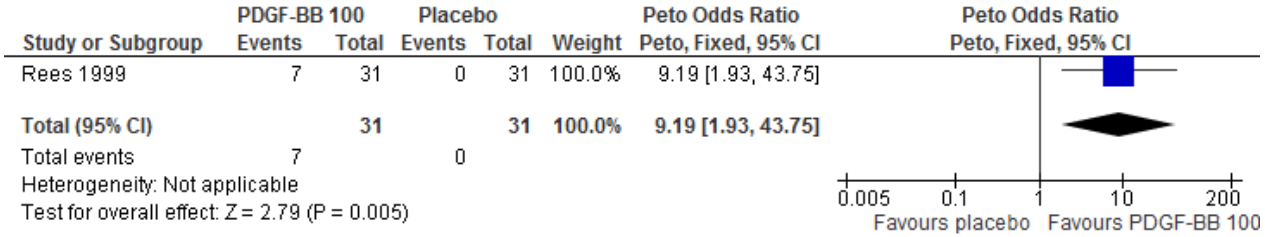


Figure 182 – Recombinant platelet-derived growth factor (100µg/g) versus placebo – proportion of patients ≥ 90% healed

Study or Subgroup	PDGF-BB 100 Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rees 1999	18	31	9	31	100.0%	2.00 [1.07, 3.74]
Total (95% CI)		**31**		**31**	**100.0%**	**2.00 [1.07, 3.74]**
Total events	18		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.17 (P = 0.03)

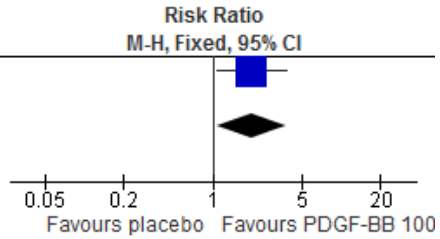


Figure 183 – Recombinant platelet-derived growth factor (100µg/g) versus placebo – proportion of patients with osteomyelitis

Study or Subgroup	PDGF-BB 100 Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rees 1999	2	31	1	31	100.0%	2.00 [0.19, 20.93]
Total (95% CI)		**31**		**31**	**100.0%**	**2.00 [0.19, 20.93]**
Total events	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)

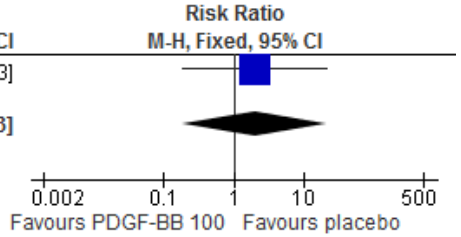


Figure 184 – Recombinant platelet-derived growth factor (100µg/g) versus placebo – proportion of patients with an infection

Study or Subgroup	PDGF-BB 100 Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Rees 1999	0	31	1	31	100.0%	0.14 [0.00, 6.82]
Total (95% CI)		**31**		**31**	**100.0%**	**0.14 [0.00, 6.82]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.00 (P = 0.32)

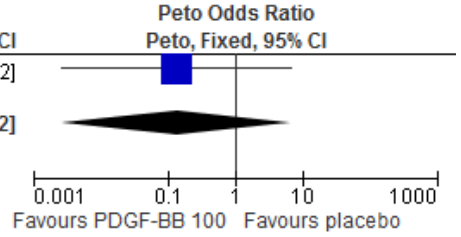


Figure 185 – Recombinant platelet-derived growth factor (100µg/g) versus placebo – proportion of patients with adverse events other than osteomyelitis, infection and sepsis

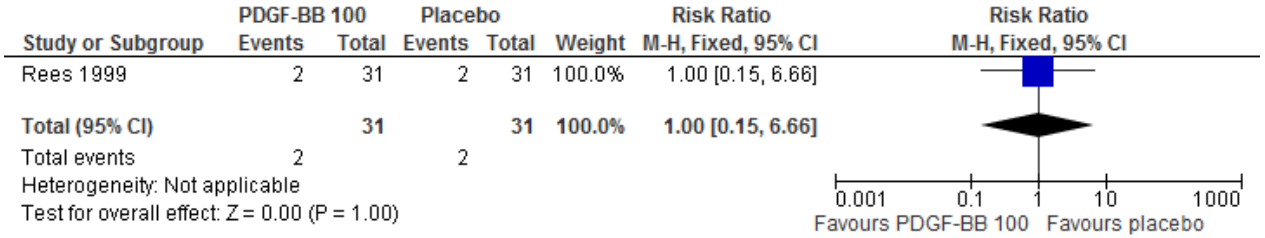


Figure 186 – Recombinant platelet-derived growth factor: 100µg/g versus 300µg/g alternated with placebo – proportion of patients completely healed

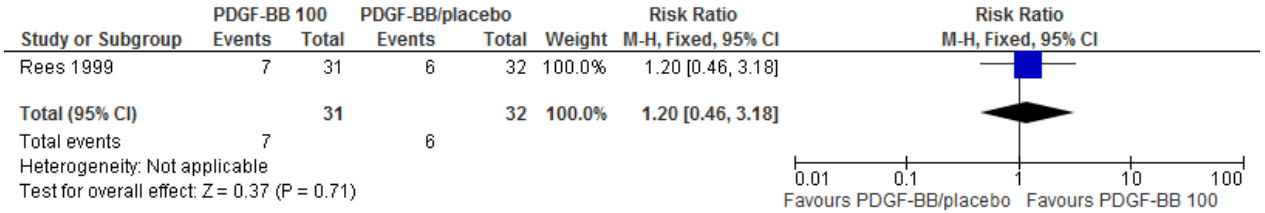


Figure 187 – Recombinant platelet-derived growth factor: 100µg/g versus 300µg/g alternated with placebo – proportion of patients ≥ 90% healed

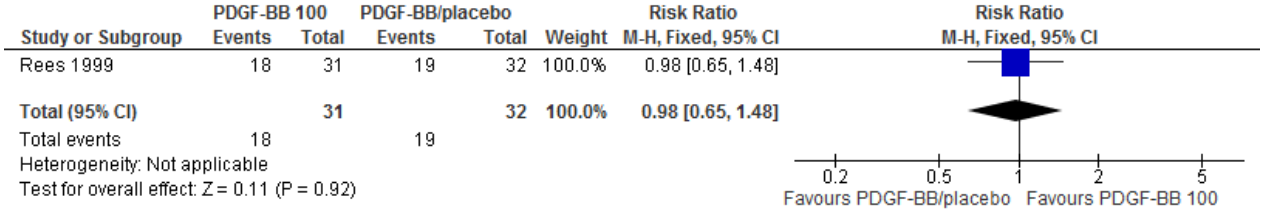


Figure 188 – Recombinant platelet-derived growth factor: 100µg/g versus 300µg/g alternated with placebo – proportion of patients with osteomyelitis

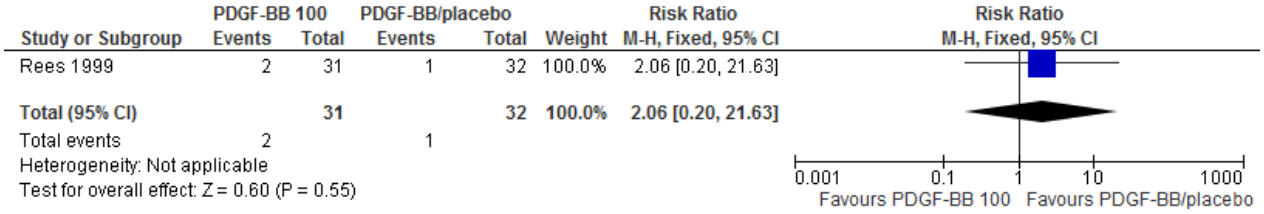


Figure 189 – Recombinant platelet-derived growth factor: 100µg/g versus 300µg/g alternated with placebo – proportion of patients with sepsis

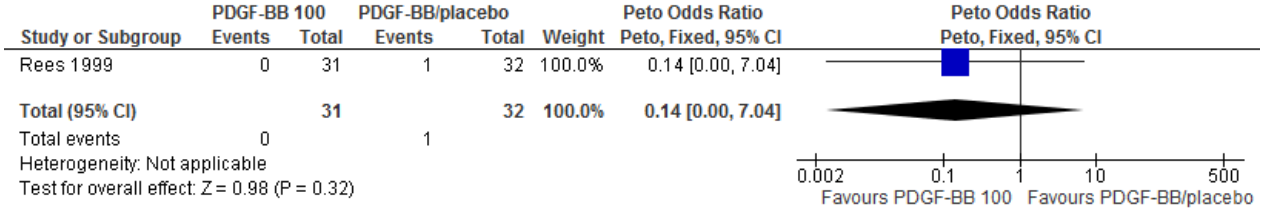


Figure 190 – Recombinant platelet-derived growth factor: 100µg/g versus 300µg/g alternated with placebo – proportion of patients with adverse events other than osteomyelitis, infection and sepsis

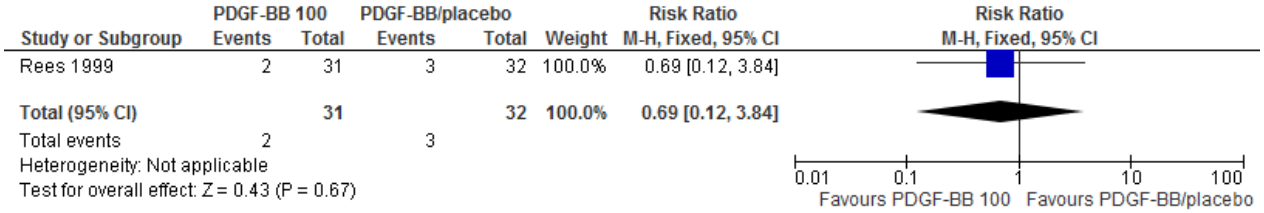


Figure 191 – Recombinant platelet-derived growth factor: 100µg/g versus 300µg/g – proportion of patients completely healed

Study or Subgroup	PDGF-BB 100 Events	Total	PDGF-BB 300 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rees 1999	7	31	1	30	100.0%	6.77 [0.89, 51.80]
Total (95% CI)		**31**		**30**	**100.0%**	**6.77 [0.89, 51.80]**
Total events	7		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.84 (P = 0.07)

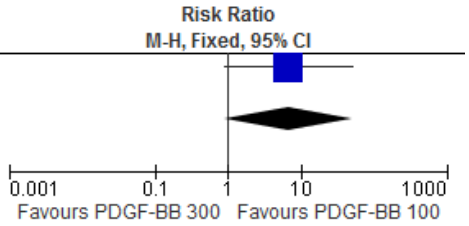


Figure 192 – Recombinant platelet-derived growth factor: 100µg/g versus 300µg/g – proportion of patients ≥ 90% healed

Study or Subgroup	PDGF-BB 100 Events	Total	PDGF-BB 300 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rees 1999	18	31	12	30	100.0%	1.45 [0.85, 2.47]
Total (95% CI)		**31**		**30**	**100.0%**	**1.45 [0.85, 2.47]**
Total events	18		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.38 (P = 0.17)

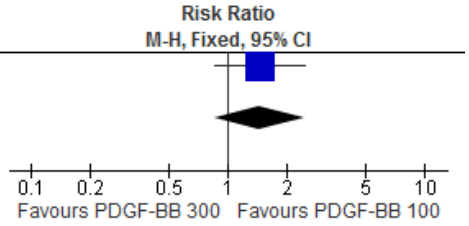


Figure 193 – Recombinant platelet-derived growth factor: 100µg/g versus 300µg/g – proportion of patients with osteomyelitis

Study or Subgroup	PDGF-BB 100 Events	Total	PDGF-BB 300 Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Rees 1999	2	31	0	30	100.0%	7.40 [0.45, 121.11]
Total (95% CI)		**31**		**30**	**100.0%**	**7.40 [0.45, 121.11]**
Total events	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.40 (P = 0.16)

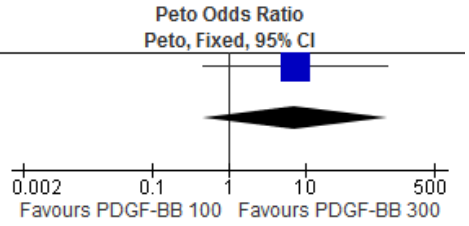


Figure 194 – Recombinant platelet-derived growth factor: 100µg/g versus 300µg/g – proportion of patients with an infection

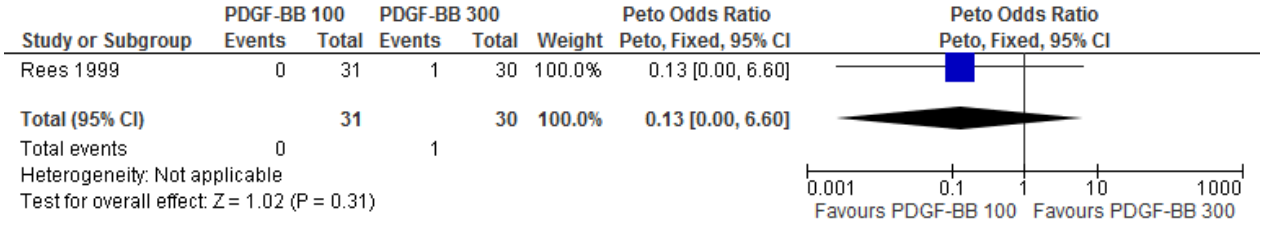


Figure 195 – Recombinant platelet-derived growth factor: 100µg/g versus 300µg/g – proportion of patients with adverse events other than osteomyelitis, infection and sepsis

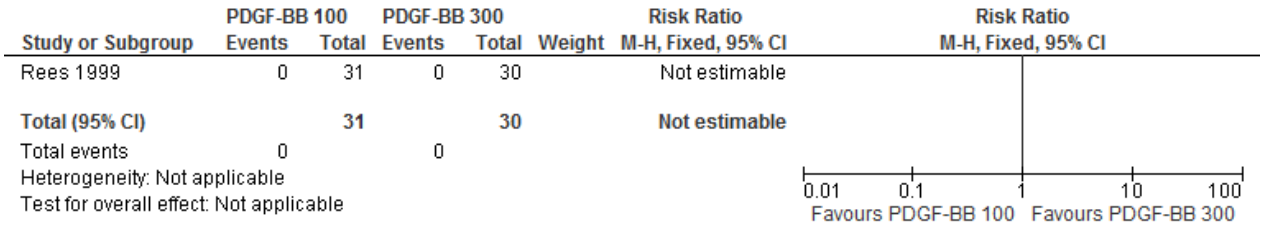


Figure 196 – Recombinant platelet-derived growth factor (300µg/g) alternated with placebo versus placebo – proportion of patients completely healed

Figure 197 – Recombinant platelet-derived growth factor (300µg/g) alternated with placebo versus placebo – proportion of patients ≥ 90% healed

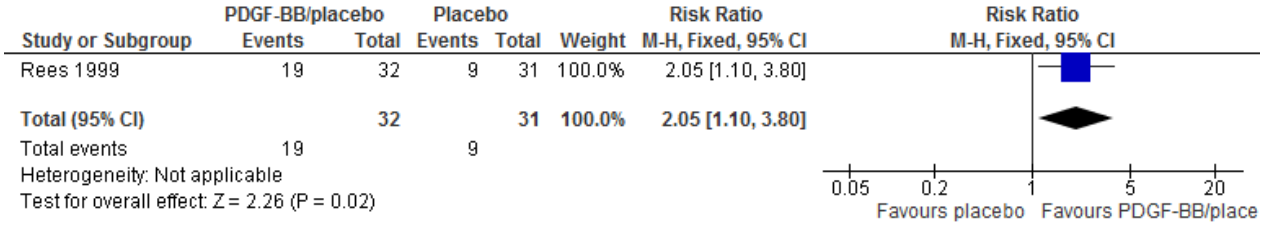


Figure 198 – Recombinant platelet-derived growth factor (300µg/g) alternated with placebo versus placebo – proportion of patients with osteomyelitis

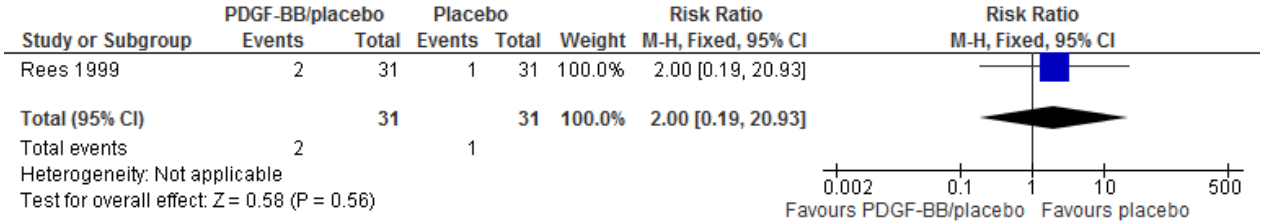


Figure 199 – Recombinant platelet-derived growth factor (300µg/g) alternated with placebo versus placebo – proportion of patients with an infection

Figure 200 – Recombinant platelet-derived growth factor (300µg/g) alternated with placebo versus placebo – proportion of patients with sepsis

Study or Subgroup	PDGF-BB/placebo Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Rees 1999	1	32	0	31	100.0%	7.16 [0.14, 361.11]
Total (95% CI)		**32**		**31**	**100.0%**	**7.16 [0.14, 361.11]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.32)

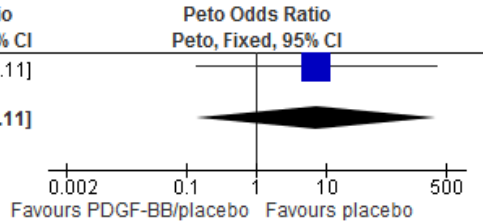


Figure 201 – Recombinant platelet-derived growth factor (300µg/g) alternated with placebo versus placebo – proportion of patients with adverse events other than osteomyelitis, infection and sepsis

Study or Subgroup	PDGF-BB/placebo Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rees 1999	3	32	2	31	100.0%	1.45 [0.26, 8.11]
Total (95% CI)		**32**		**31**	**100.0%**	**1.45 [0.26, 8.11]**
Total events	3		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.43 (P = 0.67)

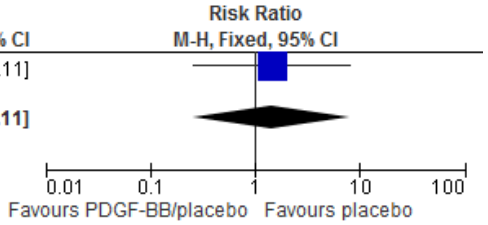


Figure 202 – Recombinant platelet-derived growth factor: 300µg/g alternated with placebo versus 300µg/g – proportion of patients completely healed

Study or Subgroup	PDGF-BB/placebo Events	Total	PDGF-BB 300 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rees 1999	6	32	1	30	100.0%	5.63 [0.72, 44.03]
Total (95% CI)		**32**		**30**	**100.0%**	**5.63 [0.72, 44.03]**
Total events	6		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.65 (P = 0.10)

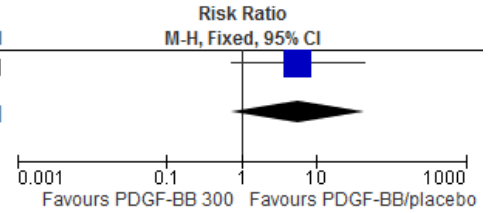


Figure 203 – Recombinant platelet-derived growth factor: 300µg/g alternated with placebo versus 300µg/g – proportion of patients ≥ 90% healed

Study or Subgroup	PDGF-BB/placebo Events	Total	PDGF-BB 300 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rees 1999	19	32	12	30	100.0%	1.48 [0.88, 2.51]
Total (95% CI)		**32**		**30**	**100.0%**	**1.48 [0.88, 2.51]**
Total events	19		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.48 (P = 0.14)

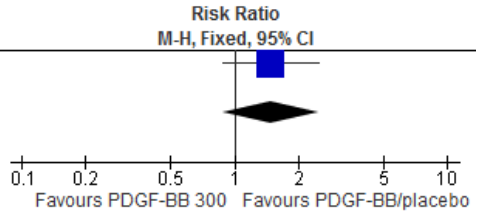


Figure 204 – Recombinant platelet-derived growth factor: 300µg/g alternated with placebo versus 300µg/g – proportion of patients with osteomyelitis

Study or Subgroup	PDGF-BB/placebo Events	Total	PDGF-BB 300 Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Rees 1999	1	32	0	30	100.0%	6.94 [0.14, 350.54]
Total (95% CI)		**32**		**30**	**100.0%**	**6.94 [0.14, 350.54]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.97 (P = 0.33)

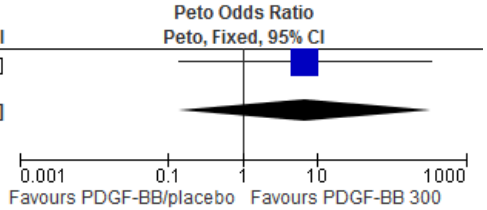


Figure 205 – Recombinant platelet-derived growth factor: 300µg/g alternated with placebo versus 300µg/g – proportion of patients with an infection

Study or Subgroup	PDGF-BB/placebo Events	Total	PDGF-BB 300 Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Rees 1999	0	32	1	30	100.0%	0.13 [0.00, 6.39]
Total (95% CI)		**32**		**30**	**100.0%**	**0.13 [0.00, 6.39]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.03 (P = 0.30)

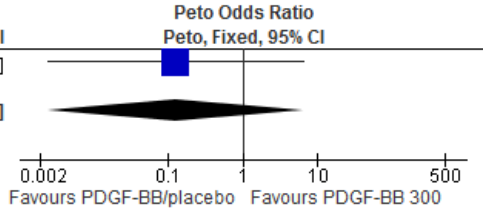


Figure 206 – Recombinant platelet-derived growth factor: 300µg/g alternated with placebo versus 300µg/g – proportion of patients with sepsis

Study or Subgroup	PDGF-BB/placebo Events	Total	PDGF-BB 300 Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Rees 1999	1	32	0	30	100.0%	6.94 [0.14, 350.54]
Total (95% CI)		**32**		**30**	**100.0%**	**6.94 [0.14, 350.54]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.97 (P = 0.33)

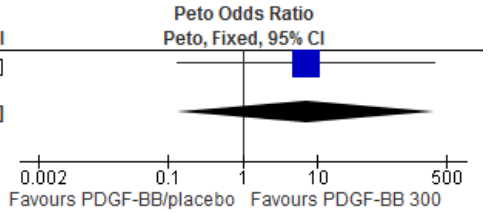


Figure 207 – Recombinant platelet-derived growth factor: 300µg/g alternated with placebo versus 300µg/g – proportion of patients with adverse events other than osteomyelitis, infection and sepsis

Study or Subgroup	PDGF-BB/placebo Events	Total	PDGF-BB 300 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rees 1999	3	32	2	30	100.0%	1.41 [0.25, 7.84]
Total (95% CI)		**32**		**30**	**100.0%**	**1.41 [0.25, 7.84]**
Total events	3		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.70)

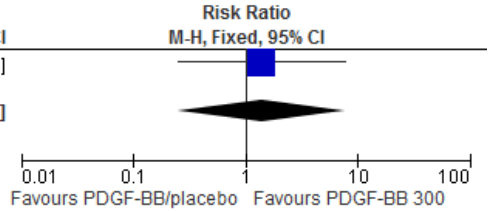


Figure 208 – Recombinant platelet-derived growth factor (300µg/g) versus placebo – proportion of patients completely healed

Study or Subgroup	PDGF-BB 300 Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Rees 1999	1	30	0	31	100.0%	7.64 [0.15, 385.21]
Total (95% CI)		**30**		**31**	**100.0%**	**7.64 [0.15, 385.21]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.02 (P = 0.31)

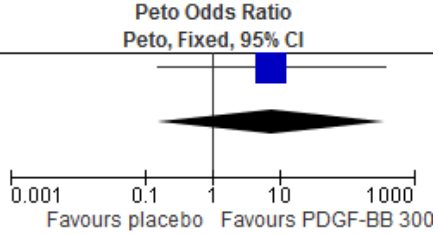


Figure 209 – Recombinant platelet-derived growth factor (300µg/g) versus placebo – proportion of patients ≥ 90% healed

Study or Subgroup	PDGF-BB 300 Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rees 1999	12	30	9	31	100.0%	1.38 [0.68, 2.78]
Total (95% CI)		**30**		**31**	**100.0%**	**1.38 [0.68, 2.78]**
Total events	12		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.89 (P = 0.37)

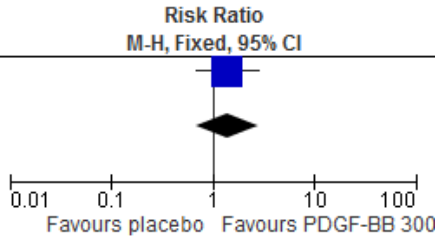


Figure 210 – Recombinant platelet-derived growth factor (300µg/g) versus placebo – proportion of patients with osteomyelitis

Study or Subgroup	PDGF-BB 300 Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Rees 1999	0	30	1	31	100.0%	0.14 [0.00, 7.05]
Total (95% CI)		**30**		**31**	**100.0%**	**0.14 [0.00, 7.05]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)

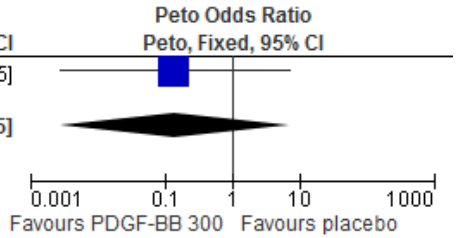


Figure 211 – Recombinant platelet-derived growth factor (300µg/g) versus placebo – proportion of patients with an infection

Study or Subgroup	PDGF-BB 300 Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rees 1999	1	30	1	31	100.0%	1.03 [0.07, 15.78]
Total (95% CI)		**30**		**31**	**100.0%**	**1.03 [0.07, 15.78]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.02 (P = 0.98)

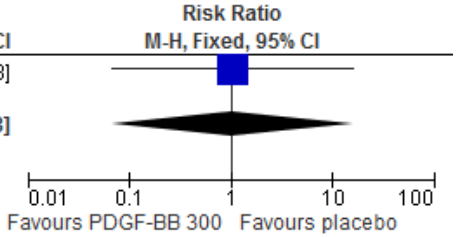


Figure 212 – Recombinant platelet-derived growth factor (300µg/g) versus placebo – proportion of patients with adverse events other than osteomyelitis, infection and sepsis

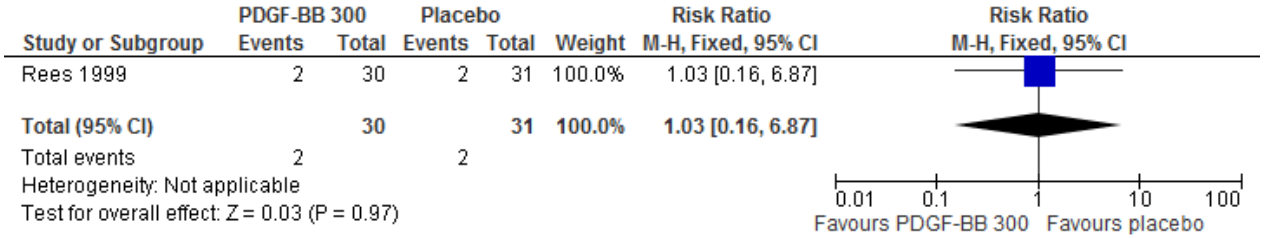


Figure 213 – Recombinant platelet-derived growth factor: 1.0µg/g versus 100.0µg/g – proportion of patients completely healed

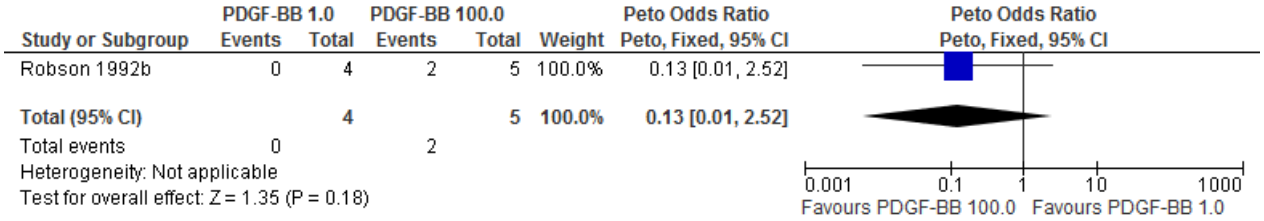


Figure 214 – Recombinant platelet-derived growth factor: 10.0µg/g versus 100.0µg/g – proportion of patients completely healed

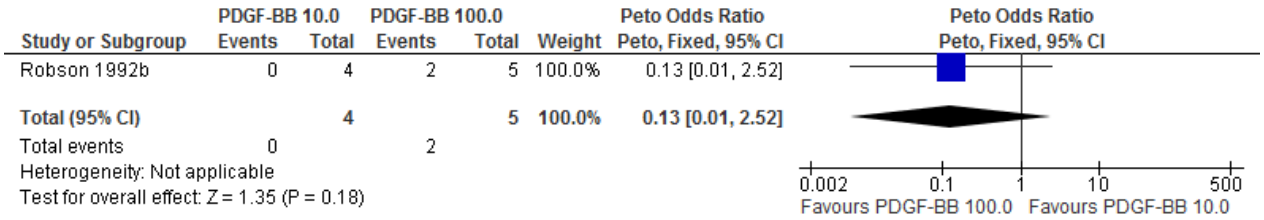


Figure 215 – Recombinant platelet-derived growth factor (100.0µg/g) versus placebo – proportion of patients completely healed

Study or Subgroup	PDGF-BB 100.0 Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Robson 1992b	2	5	0	7	100.0%	14.01 [0.73, 267.29]
Total (95% CI)		**5**		**7**	**100.0%**	**14.01 [0.73, 267.29]**
Total events	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.75 (P = 0.08)

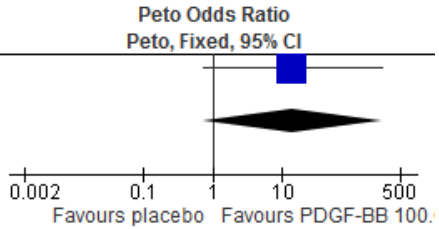


Figure 216 – Recombinant platelet-derived growth factor (100.0µg/g) versus placebo – mean percentage reduction in ulcer depth

Study or Subgroup	PDGF-BB 100.0 Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Robson 1992b	85.9	14.8	5	65.1	13.4	7	100.0%	20.80 [4.47, 37.13]
Total (95% CI)			**5**			**7**	**100.0%**	**20.80 [4.47, 37.13]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.50 (P = 0.01)

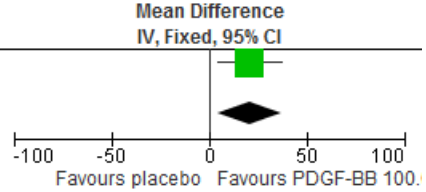


Figure 217 – Recombinant platelet-derived growth factor (100.0µg/g) versus placebo – mean percentage reduction in ulcer depth

Study or Subgroup	PDGF-BB 100.0 Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Robson 1992b	93.6	8	5	78.2	11.2	7	100.0%	15.40 [4.54, 26.26]
Total (95% CI)			**5**			**7**	**100.0%**	**15.40 [4.54, 26.26]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.78 (P = 0.005)

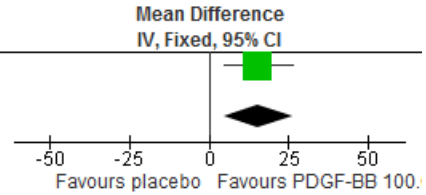
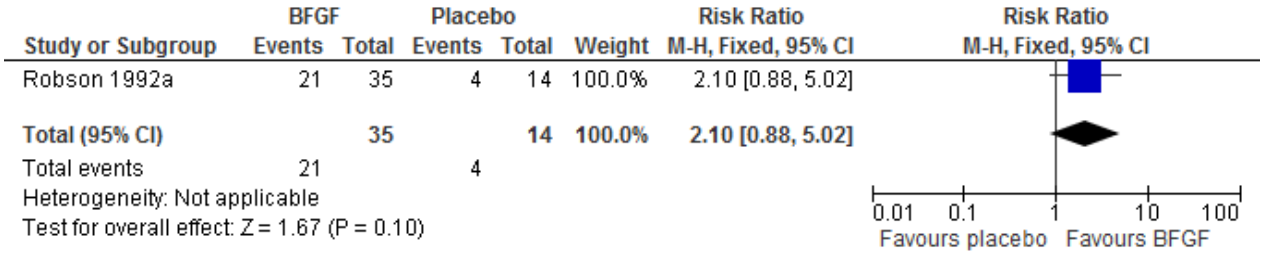


Figure 218 – Basic fibroblast growth factor (different schedules and doses) versus placebo – proportion of patients > 70% healed



6.1.3. Evidence tables

Table 102 – Moore 2011

Reference	Method	Patient characteristics	Intervention	Results	Critical appraisal of review quality
Author and year: **Moore (2011)** Title: **Wound cleansing for pressure ulcers (Review).** Journal: **Cochrane Database of Systematic Reviews, 2.**	**Design:** systematic review **Source of funding:** / **Search date**: 1966-2010 **Searched databases:** Ovid Medline; Ovid Embase; EBSCO CINAHL; CENTRAL; Cochrane wounds group specialist register; contact: drug companies as identified in the British National Formulary (2003), experts wound care, members EPUAP, NPUAP European Wound Management Association, and World Union of Wound Healing Societies **Included study**	**Eligibility criteria:** patients of any age, in any health care setting, with existing PUs **Patient characteristics** Elderly patients with a Grade II to IV PU (according to the NPUAP classification)	**Interventions (group 1):** Saline spray with aloe vera, silver chloride and decyl glucoside (Vulnopur). **Comparator (group 2):** Isotonic saline **Both groups:** Patients were treated for 14 days. The PSST was used to measure the outcome	**Outcome 1:** Percentage reduction in PSST from baseline **Group 1:** 27.8 (SD 31.3; min. 69.8, max. -123.5) **Group 1:** 20.5 (SD 24.1; min. 65.8, max. -22.7)	The validity of each study was initially appraised critically to check methodological rigour, using the quality assessment criteria suggested by Verhagen (1998) and Khan (2001). *Bellingeri 2004*: No adequate sequence generation, allocation concealment, and blinding. Incomplete data was addressed. The study was free of selective reporting and free of other bias. No ITT analysis. Small sample size. **Note:** The Bellingeri (2004) study was

	designs: randomized controlled trials **Inclusion criteria:** cleansing as intervention, cleansing was defined as the application of fluid to the pressure ulcer to aid removal of exudate, debris and contaminants, but not the use of dressings or mechanical debridement; comparators were no cleansing, another cleansing solution, another technique; primary outcomes were pressure ulcer healing, such as time to complete healing; absolute or percentage change in pressure ulcer area or volume over time; proportion of pressure ulcers healed at the completion of the trial period; or healing rate; secondary outcomes were procedural pain and ease of use of the method of cleansing. **Number of included studies:** three studies were included in the Cochrane review. However, only one study		published in Italian. **Excluded studies:** Burke (1998) and Griffiths (2001)

	met the inclusion criteria of our review.				

Table 103 – Zhang 2012

Reference	Method	Patient characteristics	Intervention	Results	Critical appraisal of review quality
Author and year: **Zhang (2012)** Title: **Traditional Chinese medicine for pressure ulcer: A meta-analysis** Journal: **International Wound Journal, doi: 10.1111/j.1742-481X.2012.00969.x**	**Design:** systematic review and meta-analysis **Source of funding:** Education Commission of Heilongjiang Province of China No.12511508 **Search date**: inception – April 2011 **Searched databases:** Medline, Embase, Central, CBM, CNKI, Wan Fang and VIP **Included study designs:** randomized controlled trials **Inclusion criteria:** Chinese herbal medicine ointment; acupuncture and moxibustion; pressure ulcers belonged to the I-IV phase; more than 30 subjects involved; more than one of the sham groups was placebo; at least one of the outcomes apllied **Number of included studies:** 10 studies were included	**Eligibility criteria:** pressure ulcers belonged to the I-IV phase; more than 30 subjects involved **Patient characteristics** Patients with a stage I to IV PU	**Interventions (group 1):** Chinese herbal medicine ointment **Comparator (group 2):** Iodophor; gentamicin; chloramphenicol and sulfadiazine silver powder; antibacterial; NaCl; Nitrofurazone	**Outcome 1:** Proportion of patients completely healed **Group 1:** Proportion of patients improved **Group 1:** Proportion of patients not changed or worsened	The validity of each study was assessed with Cochrane risk of bias. - Bao 2006: no report on sequence generation, allocation concealment, blinding. No selective reporting and attrition bias. - Chen 2008: no report on sequence generation, allocation concealment, blinding. No selective reporting and attrition bias. - Jing 2005: no report on sequence generation, blinding, selective reporting and incomplete data. Allocation concealment was reported - Li 2007A: no report on sequence generation, allocation concealment, blinding. No selective reporting and attrition bias. - Li 2007B: no report on blinding. No selective

						reporting and attrition bias. Report on allocation concealment and sequence generation - Li 2008: no report on sequence generation, allocation concealment, blinding. No selective reporting and attrition bias. - Luo 1998: no report on allocation concealment, blinding, selective reporting and incomplete data. Sequence generation was reported - Tao 2008: no report on sequence generation, allocation concealment, blinding, selective reporting and incomplete data. - Zhang 2010: no report on allocation concealment, blinding, selective reporting and incomplete data. Sequence generation was reported. No selective reporting and attrition bias. - Zhao 2010: no report on allocation concealment, blinding, selective reporting and incomplete data.

					Sequence generation was reported. No selective reporting and attrition bias. **Note:** All studies were published in Chinese

Table 104 – AGREN 1985

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Agren (1985)** **Title:** **Topical Treatment of Pressure Ulcers** **Journal: Scand J Plast Reconstr Surg, 19: 97-100** **Study type:** **randomized controlled trial** **Sequence generation: Patients were consecutively matched in pairs. Each member of the pair was randomly allocated.** **Allocation concealment: not reported**	**Patient group:** Geriatric patients with necrotic PUs. **All patients** **Randomised N:** 28 **Completed N:** 28 **Drop-outs:** 0 **Group 1** **Randomised N:** 14 **Completed N:** 14 **Dropouts:** 0 **Age (mean years; range):** 81 (46-92) **Gender (m/f):** (5/9) **Diabetes:** 5 **PU location:** Trochanter major: 1 Ichial tuberosity: 1	**Group 1:** Zinc oxide (400µg ZnO/cm²). Dry, sterile gauze compresses were premedicated with zinc oxide. Zinc dressings were changed once a day according to manufacturer's recommendations. **Group 2:** Streptokinase-streptodornase (Varidase®) Streptokinase works indirectly by transforming plasminogen into the active proteolytic enzyme plasmin via streptokinase-proactivator complex. Streptodornase dissolves deoxyribonucleoproteins commonly presented in pus (Hellgren). Varidase is believed to be beneficial in the treatment of necrotic and infected wounds. The varidase solution (100 000 IU	**Outcome 1:** Median percentage reduction in ulcer area **Outcome 2:** Proportion of patient with infection **Outcome 3:** Proportion of patient with skin reaction	**Group 1:** 2.4 **Group 2:** -18.7 **Group 1:** 0/14 **Group 2:** 1/14 **Group 1:** 0/14 **Group 2:** 1/14	**Funding:** / **Limitations:** sequence generation by matched pairs; no report on allocation concealment; no blinding of patients and nurses; small sample size; no information on PU classification or stages **Additional outcomes:** Disappearance of necrotic tissue occurred in 7 (50%) patient (4 women) treated with zinc and in 6

Blinding: an independent surgeon from another hospital assessed the result of therapy from photographs of the ulcers. **Addressing incomplete outcome data:** **Not drop-outs** **Statistical analysis:** **The statistical test was performed at 5% level. The authors tested whether the probability of the patient being assessed as successful was the same for zinc and the Varidase group. For the statistical test the result was measured as successful or unsuccessful. A sequential test procedure was used to minimize expected sample size.** **Baseline differences: The two groups were comparable with respect to age, sex, having diabetes mellitus, site of ulcer**	Knee: 1 Lower leg: 1 Malleolus: 2 Heel: 7 Base of big toe: 1 **Initial ulcer area (median cm²; range):** 5.8; 1.2-26.0 **Group 2** **Randomised N:** 14 **Completed N:**14 **Dropouts:** 0 **Age (mean years):** 86 **Gender (m/f):** (3/11) **Diabetes:** 4 **PU location:** Trochanter major: 1 Ischial tuberosity: 1 Lower leg: 2 Malleolus: 1 Heel: 7 Lateral edge foot: 1 Sole: 1 **Initial ulcer area (median cm²; range):** 4.2; 1.2-18.2 **Inclusion criteria:** Geriatric patients with one or more necrotic	streptokinase and 25 000 IU streptodornase dissolved in 20 ml sterile isotonic saline solution; Lederle Laboratories) was applied on a sterile gauze compress. Varidase was changed twice daily according to manufacturer's recommendations. **Both groups:** Dressings were secured with porous acrylic-based tapes. Before the study began, loosely attached necrotic material was removed, but ulcers were not surgically debrided subsequently. No patients were given antibiotics. Nursing care followed the standard routine of the department.	(43%) patients (5 women) treated with Varidase; The sequential analysis revealed a non-significant difference between the two treatments. The initial ulcer area was larger in the zinc group than in the Varidase group. The ulcers which were cleansed were on average half the size of the non-cleansed ulcers for both treatments. The median time to desloughing was 23 days (rage 7-56 days) for the zinc and 21 (range 7-42) days for the Varidase treated ulcers. **Notes:** /

and initial ulcer area (cm²). **Study power/sample size:** **The statistical test was designed to have the power of 0.95 to detect a 75% success rate in one group and a 25% success rate in the other. If a statistical non-significant difference was found it is reasonable to conclude that there is no large difference between the treatments. The number of patients needed with a conventional test (McNemar's Test) to achieve this power was too great to be practicable. A sequential test procedure was used to minimize expected sample size.** **Setting:** **Hospitalized and outpatients** **Length of study:** **8 weeks of treatment** **Assessment of PUs:**	PUs **Exclusion criteria:** /

PU classification not reported. The ulcers were photographed and the area was determined with a planimeter from in situ tracings made by one of the authors at weekly intervals. An independent surgeon from another hospital assessed the result of therapy from photographs of the ulcers. It was judged successful if the ulcer was free of necrotic tissue within 8 weeks – otherwise it was classified as unsuccessful. Multiple ulcers: In case of multiple necrotic ulcers, these were treated uniformly, but only the largest was monitored.					

Table 105 – ALM 1989

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Alm (1989)** Title: **Care of pressure sores: a controlled study of the use of a hydrocolloid dressing compared with wet saline gauze compresses.** Journal: **Acta Dermato-Venereologica, 149; 1-10** Study type: **randomized controlled trial** Sequence generation: **not reported** Allocation concealment: **stratified allocation based on Norton score** Blinding: **blinding of outcome assessor.** Addressing incomplete outcome data: **intention-to-treat analysis except the patients in which protocol was**	**Patient group:** Long stay patients PUs. **All patients** **Randomised N:** 50 patients and 56 PUs **Completed N:** 50 PUs for efficacy analysis and 51 PUs for safety analysis **Drop-outs:** 6 PUs for efficacy analysis (1 drop-out for unknown reason, 1 missing case report, 1 died during wash-out period, 2 in which protocol was violated, and 1 incomplete data)) and 5PUs for the safety analysis (1 drop-out for unknown reason, 1 missing case report, 1 died during wash-out period, and 2 in which protocol was violated) **Gender (m/f) (patients):** ±6/44 **Group 1** **Randomised N:** 31 PUs **Completed N:** 29 PUs for the safety analysis	**Group 1:** Hydrocolloid dressing: sheet, paste and powder (Comfeel®, Coloplast A/S, Espergaerde, Denmerk). The dressing was changed when necessary. Th sheet is used solely or on top of the filled ulcer. Six ulcers were filled with paste and one with both paste and powder during the treatment period. Comfeel® sheet: consists of sodium carboxymethylcellulose particles embedded in an adhesive, elastic mass. The side which faces away from the ulcer is covered with a 0.3mm polyurethane film. Comfeel® paste: consists of sodium carboxymethylcellulose particles and guar cellulose particles suspended in a paste basis from vaseline, liquid paraffin and cetanol. Comfeel® powder: a dry mixture of sodium carboxymethylcellulose, guar cellulose and xanthan cellulose. **Group 2:** wet saline gauze	**Outcome 1:** Relative median percentage decrease in ulcer area by 6 weeks **Outcome 2:** Median percentage decrease in ulcer area by 8 weeks **Outcome 3:** Median ulcer depth at week 4 **Outcome 4:** Healing distribution function **Outcome 5:** proportion of patient reporting pain at dressing change	**Group 1:** 100.0 **Group 2:** 69.0 **P value:** 0.016 **Group 1:** figure unclear; not reported **Group 2:** figure unclear; not reported **P value:** 0.047 **P value:** 0.15 Treatment with hydrocolloid needed to be stopped in one patient (n=1/49) due to great pain.	**Funding:** / **Limitations:** no report on sequence allocation; allocation concealment by stratification; drop-outs unclear; partial statistical measure of difference between groups; no blinding of patients and nurses; no information on classification of PU and unclear if grade I PUs were included; information on pain unclear; no report on preventive measures or debridement. **Additional outcomes:** Granulation tissue was larger in G1

violated, died in wash-out period, missing case-record and drop-out for unknown reason. Those were excluded. Statistical analysis: **Mean values, standard deviations and t-test were used when the values were apparently normally distributed. When values were normally distributed, median values and lower and upper hinges were calculated. The Mann-Whitney U-test was then used for probability evaluations. The statistical analysis was performed by means of the software package SYSTAT (Systat Inc., Illinois, USA).** **The healing outcome was analysed by means of the lifetest program SAS (SAS institute Inc., Cary, USA) The statistical analysis was**	and 28 or 29 PUs for the efficacy analysis (latter unclear). **Dropouts:** 2 for the safety analysis and 2 or 3 for the efficacy analysis (latter unclear). **Age (mean years (SD)):** 83.6 (9.2) **Norton score (mean (SD)):** 12 (2) **Duration PU (mean months (SD)):** 4.6 (10.9) **Ulcer location:** Heel: n=11 Sacrum: n=8 Malleolus: n=4 Gluteal region: n=3 Hip: n=4 Other: n=1 **Ulcer depth (median mm (IQR)):** 1.75 (0.30-3.00) **Ulcer area (median cm² (IQR)):** 2.02 (0.95-3.10) **Granulated area (median cm² (IQR)):** 0.32 (0.051-1.68) **Group 2** **Randomised N:** 25 PUs **Completed N:** 22 PUs for the safety analysis and 21 or 22 PUs for the efficacy analysis (latter unclear).	dressings which was changed twice daily. **Both groups:** after randomization all ulcers were dressed with wet saline gauze dressings for one week (wash-out period).		than G2 Nursing time: G1 versus G2, p<0.0001 **Notes:** /

performed by means of the software package SYSTAT (Systat Inc., Illinois, USA). **The probability outcomes was analysed by the log rank test. A two-tailed p-value of ≤ 0.05 was accepted as statistical significance.** Baseline differences: **Difference was not measured statistically except for ulcer depth, ulcer area and granulated area, which were not significantly different. Groups were comparable based on the average.** Study power/sample size: **No a priory sample size calculation.** Setting: **Long-term ward.** Length of study: **six weeks of treatment and follow-up for a further 3 to 6 weeks** Assessment of PUs: **PUs classification not reported.**	**Dropouts:** 3 for the safety analysis and 3 or 4 for the efficacy analysis (latter unclear). **Age (mean years (SD)):** 83.4 (9.4) **Norton score (mean (SD)):** 13 (3) **Duration PU (mean months (SD)):** 4.8 (6.4) **Ulcer location:** Heel: n=8 Sacrum: n=9 Malleolus: n=3 Gluteal region: n=2 Hip: n=1 Other: n=2 **Ulcer depth (median mm (IQR)):** 2.00 (1.00-5.00) **Ulcer area (median cm² (IQR)):** 2.44 (0.97-3.24) **Granulated area (median cm² (IQR)):** 0.25 (0.079-0.70) **Inclusion criteria:** having a PU. **Exclusion criteria:** Norton score <7	

Ulcers were photographed once a week. The area of the ulcer which was not covered with epithelium was determined after projection of the slide from below onto a horizontal glass plate which was covered with matt drawing foil. The relevant area was measured on the image which appeared on the matt foil, suing a Haff digital planimeter type 320 E (Haff, Pfronten, GFR) and the real area was then calculated, taking the degree of magnification into consideration. The depth and degree of cleanness en the extent and intensity of maceration were assessed and classified on rating scales. Multiple ulcers: **50 patients with 56 ulcers. Ulcers are unit of analysis and randomization.**		

Table 106 – CHANG 1998

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Chang (1998)** **Title: Pressure ulcers-randomised controlled trial comparing hydrocolloid and saline gauze dressings.** **Journal: The Medical journal of Malaysia, 53 (4); 428-431.** **Study type: randomized controlled trial** **Sequence generation: not reported** **Allocation concealment: not reported.** **Blinding: no blinding.** **Addressing incomplete outcome data: no drop-out.** **Statistical analysis: Overall performance, pain, adherence,**	**Patient group:** Patients aged 18 years and older with a stage II or III PU. **All patients** **Randomised N:** 34 **Completed N:** 34 **Drop-outs:** 0 **Age (mean years; range):** 57.6; 20-85 **Incontinence:** Urine: n=5 Faecal: n=16 Both: n=4 **Ulcer stage:** Stage II: n=21 Stage III: n=13 **Duration of PU (mean days; range):** 33; 4-274 **Ulcer location:** Sacrum: n=30 Ilium: n=3 Greater trochanter: n=1 **Group 1** **Randomised N:** 17 **Completed N:** 17	**Group 1:** Hydrocolloid dressing (DuoDermCGF®). Dressings were changed every seven days or when leakage occurred. Cavities were filled with hydrocolloid gel (DuoDerm Hydroactive Gel®). DuoDermCGF®: occlusive dressing, which is under the influence of wound exudate and provides a moist wound environment. The outer later is made of polyurethane foam which is impermeable. **Group 2:** Wet soaked saline gauze dressing. The saline dressing was covered with a Gamgee® pack. Dressings were changed once a day or when exudate is visible through the second dressing. **Both groups:** /	**Outcome 1:** Mean reduction (%) in ulcer area **Outcome 2:** percentage of patients reporting a dressing as uncomfortable **Outcome 3:** percentage of patients reporting moderate/severe pain during dressing removal **Outcome 4:** proportion of patients reporting with an infection	**Group 1:** 34 **Group 2:** -9 **P value:** 0.23 **Group 1:** 0 **Group 2:** 50 **P value:** <0.01 **Group 1:** 0 **Group 2:** 44 **P value:** <0.01 **Group 1:** 0/17 **Group 2:** 0/17	**Funding:** funded by a grant from 3M company **Limitations:** no report on sequence allocation; no report on allocation concealment; no blinding; no a priory sample size calculation; difference between groups concerning PU location at baseline; no report on drop-out and number of patient completing the study **Additional outcomes:** Ease of use (G1: 62% vs G2: 19; p<0.01) Cost per subject (mean dressing

comfort, ease of removal was analysed by Wilcoxon Rank Sum Test. **Rates of wound healing was analysed by Analysis of Variance Test. Baseline differences: No statistical difference between groups except ulcer location.** **Study power/sample size: No a priory sample size calculation.** **Setting: University hospital Kuala Lumpur.** **Length of study: 8 weeks of treatment or until complete healing.** **Assessment of PUs:** **PU classification not reported.** **Wound tracings of ulcer perimeter were made at each dressing change by moulding a piece of clear plastic food wrap over the ulcer and into the ulcer**	**Dropouts:** 0 **Ulcer stage:** Stage II: n=11 Stage III: n=6 **Group 2** **Randomised N:** 17 **Completed N:** 17 **Dropouts:** 0 **Ulcer stage:** (3 missing) Stage II: n=7 Stage III: n=7 **Inclusion criteria:** Stage II or III PU; at least 18 years of age; provide written informed consent **Exclusion criteria:** Immunocompromised; infected PU; known sensitivity to the study dressings	time and mean nursing cost): G1: RM 45.89 vs G2: RM105.30; p=0.025 Cost per subject (mean dressing time, mean nursing cost, and total cost material): G1: RM 271.45 vs G2: RM 173.05; p=0.12 **Notes:** /

cavity. The tracings were then transferred onto acetate transparencies using an Optomax Image Analyzer. Colour photographs were also taken. Assessments were done weekly. Multiple ulcers: only one PU per patient was eligible for study entry.					

Table 107 – CHUANGSUWANICH 2011

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Chuansuwanich (2011)** **Title: The efficacy of silver mesh dressing compared with silver sulfadiazine cream for the treatment of pressure ulcers.** **Journal: Journal of the Medical Association of Thailand, 94 (5); 559-565**	**Patient group:** In- and out-patients with a grade III or IV PU (according to the NPUAP 1989 classification). **All patients** **Randomised N:** 40 **Completed N:** 40 **Drop-outs:** 0 **Group 1** **Randomised N:** 20 **Completed N:** 20	**Group 1:** Silver mesh dressing (Tegaderm® Ag Mesh dressing) after wound bed cleansing. Cotton gauze was used as outer dressing. Dressings were changed every three days. **Group 2:** Silver sulfadiazine cream after wound bed cleansing. Cotton gauze was used as outer dressing. Dressings were changed twice a day. **Both groups:** Wounds were debrided as necessary.	**Outcome 1:** mean healing rate (%) at eight weeks **Outcome 2:** percentage reduction in PUSH score at eight weeks **Outcome 3:** complications	**Group 1:** 36.95 **Group 2:** 25.06 **P value:** 0.507 **Group 1:** 28.15 **Group 2:** 34.51 **P value:** 0.473 **Group 1:** 0/20 **Group 2:** 0/20	**Funding:** / **Limitations:** no report on allocation concealment; no blinding; no a priory sample size calculation and small sample size **Additional outcomes:** cost was calculated (drug cost + outer

Study type: randomized controlled trial **Sequence generation: randomly by computer** **Allocation concealment: not reported.** **Blinding: no blinding.** **Addressing incomplete outcome data: no missing reported** **Statistical analysis: All data analysis was performed using** **SPSS 13.0. Data were expressed as mean ± standard deviation (SD). Comparison of the mean between** **two groups of all parameters was evaluated for the** **significance by non-parametric Mann-Whitney U-test before treatment and at eight week of treatment. A p-value of less than 0.05 was considered significant.**	**Dropouts:** 0 **Age (mean years (SD)):** 62.60 (20.59) **Gender (m/f):** 8/12 **Duration of PU (mean days (SD)):** 232.00 (180.52) **Ulcer location:** Sacrum: n=16 Greater trochanter: n=1 Ischium: n=3 **Surface area (mean cm² (SD)):** 12.17 **Group 2** **Randomised N:** 20 **Completed N:** 20 **Dropouts:** 20 **Age (mean years (SD)):** 69.10 (16.02) **Gender (m/f):** 9/11 **Duration of PU (mean days (SD)):** 197.40 (131.65) **Ulcer location:** Sacrum: n=14 Greater trochanter: n=5 Ischium: n=1 **Surface area (mean cm² (SD)):** 22.82	dressing cost x time of dressing change/20). G1: 263 USD per patient; G2: 1812 USD per patient; p=0.00 **Notes:** /

Baseline differences: no statistical difference between groups. **Study power/sample size: No a priory sample size calculation.** **Setting: Siriraj Hospital** **Length of study: eight weeks** **Assessment of PUs:** **PU were classified according to the NPUAP classification (1989).** **Ulcer size was determined by using** **VISITRAK^{R} Wound measurement system and wound photography at the beginning en very two weeks.** **The PUSH score was assessed every two weeks.** **Multiple ulcers: not reported**	**Inclusion criteria:** Grade III or grade IV **Exclusion criteria:** /

Table 108 – GERDING 1993

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Gerding (1993)** **Title: Oxyquinoline-containing ointment vs standard therapy for stage I and stage II skin lesions.** **Journal: Dermatology Nursing, 4 (5): 389-398.** **Study type:** **Randomized controlled trial** **Sequence generation: a random allocation list maintained at each central nursing office was used.** **Allocation concealment: not reported** **Blinding: outcome assessors was blinded.** **Addressing incomplete outcome data: no drop outs**	**Patient group:** Palliative care patients with a stage II or III PU (according to the NPUAP classification). **All patients** **Randomised N:** 74 patients and 137 ulcers **Completed N:** 74 patients and 137 ulcers **Drop-outs:** 0 **Group 1** **Randomised N:** 86 **Completed N:** 86 **Dropouts:** 0 **Ulcers stage:** Stage I: 41 Stage II: 45 **Group 2** **Randomised N:** 51 **Completed N:** 51 **Dropouts:** 0 **Ulcers stage:** Stage I: 28	**Group 1:** Oxyquinoline-containing ointment (DermaMent™). Ulcers were cleansed with soap and water. Afterwards the ointment was applied at least three times a day or whenever cleansing the area. DermaMent™: is a bactericide, fungicide and trichomonicide. **Group 2:** A&D™ ointment. Ulcers were cleansed with soap and water. Afterwards the ointment was applied at least three times a day or whenever cleansing the area. **Both groups:** /	**Outcome 1:** Proportion of ulcers completely healed **Outcome 2:** Proportion of stage I ulcers completely healed **Outcome 3:** Proportion of stage II ulcers completely healed **Outcome 4:** Proportion of stage I ulcers improved on day 15 **Outcome 5:** Proportion of stage II ulcers improved on day 22 **Outcome 6:** Proportion of	**Group 1:** 43/86 **Group 2:** 21/51 **Group 1:** 23/41 **Group 2:** 16/28 **Group 1:** 20/45 **Group 2:** 5/23 **Group 1:** 15/41 **Group 2:** 6/28 **Group 1:** 19/45 **Group 2:** 8/23	**Funding:** Grant from InnoVisions, Inc. Dublin, OH **Limitations:** no report on allocation concealment; only blinding of outcome assessor; no report on baseline characteristics; no a priory sample size calculation; little information on ulcer assessment; no report on preventive measures **Additional outcomes:** preference of treatment rated by nursing staff not blinded to the treatment **Notes:** /

Statistical analysis: **Statistical analysis of the responses to the two different treatments included use of the 'fisher t-test' and chi-square analysis. No study controls were used for pressure relief, incontinence, or nutritional.** **Baseline differences: baseline characteristics were not reported.** **Study power/sample size: No a priory sample size calculation.** **Setting: three long-term care facilities** **Length of study:** **28 days of treatment or until complete healing** **Assessment of PUs:** **PU were classified according to the NPUAP classification (1989).** **Lesions were assessed on a daily basis. Progression of healing was**	Stage II: 23 **Inclusion criteria:** newly diagnosed stage I or II PU; treatment with an emollient ordered by the attending physician **Exclusion criteria:** /	stage I ulcers not changed on day 15 **Outcome 7:** Proportion of stage II ulcers not changed on day 22 **Outcome 8:** Proportion of stage I ulcers worsened on day 15 **Outcome 9:** Proportion of stage II ulcers worsened on day 22 **Outcome 10:** Mean days to complete healing **Outcome 11:** Mean days to complete healing of stage I ulcers **Outcome 12:** Mean days to	**Group 1:** 4/41 **Group 2:** 4/28 **Group 1:** 5/45 **Group 2:** 7/23 **Group 1:** 0/41 **Group 2:** 2/28 **Group 1:** 1/45 **Group 2:** 3/23 **Group 1:** 7.23 (4.15) **Group 2:** 8.62 (5.16) **Group 1:** 6.75 (3.90)

evaluated on the basis of change in lesion size intensity, and extent of surrounding erythema, presence /absence o drainage, and presence/absence of granulation tissue. **Multiple ulcers:** **74 patients with 137 ulcers. Ulcer was unit of analysis and randomization**			complete healing of stage II ulcers	**Group 2:** 7.25 (4.80) **Group 1:** 7.80 (4.47) **Group 2:** 13.0 (3.94) **P-value:** p<0.05	

Table 109 – GÜNES 2007

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Günes (2007)** **Title: Effectiveness of a honey dressing for healing pressure ulcers.** **Journal: Journal of Wound, Ostomy and Continence Nursing, 34 (2); 184-190.** **Study type: randomized controlled trial** **Sequence**	**Patient group:** Hospitalized patients aged 18 years and older with stage II or III PUs (according to the US Agency for Health Care Research and Quality's PU Guideline Panel classification). **All patients** **Randomised N:** 27 patients **Completed N:** 26 patients and 50 ulcers	**Group 1:** Honey dressing (3.8% concentration, and sterilized at 25kGy Gamma irradiation). Ulcers were irrigated with NaCl0.9% at each dressing change. A gauze dressing impregnated with honey (20ml) was used as a primary dressing. A semipermeable adhesive dressing was used as secondary dressing to prevent leakage of honey. Dressings were changed once daily or when contaminated with urine or	**Outcome 1:** Mean percentage decrease in PUSH score **Outcome 2:** Mean percentage reduction in ulcer size **Outcome 3:** Proportion of ulcers completely healed	**Group 1:** 56.3 **Group 2:** 12.9 **P value:** < 0.001 **Group 1:** 56 **Group 2:** 13 **P value:** < 0.001 **Group 1:** 5/25 **Group 2:** 0/25 **P value:** < 0.001	**Funding:** / **Limitations:** no report on sequence allocation; no report on allocation concealment; no blinding; no ITT analysis; no a priory sample size calculation **Additional**

generation: not reported **Allocation concealment: not reported** **Blinding: no blinding.** **Addressing incomplete outcome data: drop-outs were excluded.** **Statistical analysis: Data are analysed using the Statistical Package for the Social Sciences (Version 11.0 for Windows). PUSH scores were used to characterize PU healing. Chi-square analysis was conducted to compare wound and patient demographics by groups. Repeated anova were calculated to compare PU healing in both groups.** **Baseline differences: No statistical difference between groups..** **Study power/sample**	**Drop-outs:** 1 (died) **Ulcer stage:** Stage II: n=2 Stage III: n=48 **Group 1** **Randomised N:** 15 patients and 25 ulcers **Completed N:** 15 patients and 25 ulcers **Dropouts:** 0 **Age (mean years (SD)):** 65.80 (6.30) **Gender (m/f):** 9/6 **BMI (mean kg/m² (SD)):** 27.2 (1.38) **Mobility level (mean score (SD));** score 1 to 4, with 1 greater impairment**:** 1.20 (0.40) **Group 2** **Randomised N:** 12 patients **Completed N:** 11 patients and 25 ulcers **Dropouts:** 1 (died) **Age (mean years (SD)):** 66.56 (5.53) **Gender (m/f):** 8/3 **BMI (mean kg/m² (SD)):** 26.4 (1.40)	faeces. **Group 2:** Ethoxydiaminoacridine and nitrofurazone dressing. Ulcers were cleaned with ethoxydiaminoacridine solution (0.1%) and a nitrofurazone cream was spread to the surface of the wound. A gauze dressing soaked with ethoxydiaminoacridine covered the ulcer. A semipermeable adhesive dressing was used as secondary dressing. Dressings were changed once daily or when contaminated with urine or faeces. **Both groups:** all patients received preventive skin regimen (a turning and repositioning program and a pressure relieving mattress)	**Outcome 4:** Proportion of patients with adverse events attributed to the treatment	**Group 1:** 0/15 **Group 2:** 0/11	**outcomes:** / **Notes:** /

size: No a priory sample size calculation. **Setting: one university hospital in Izmir** **Length of study: maximum five weeks of treatment or until complete healing.** **Assessment of PUs:** **PU were classified according to the Agency Health Care Research and Quality's Pressure Ulcer Guideline Panel classification (1994)** **Ulcers were made by standard acetate hand tracing. Ulcer characteristics were documented via the PUSH instrument. Measurement was carried out at baseline and on each weekly visit. The total score ranged from 0 to 17, with 0 representing a healed wound.** **Multiple ulcers: 26 patients with 50 ulcers were included.**	**Mobility level (mean score (SD));** score 1 to 4, with 1 greater impairment**:** 1.32 (0.47) **Inclusion criteria:** Older than 18; life expectancy > 2 months **Exclusion criteria:** diabetes mellitus	

Table 110 HIRSHBERG 2003

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Hirshberg (2003)** **Title: TGF-beta3 in the treatment of pressure ulcers: a preliminary report.** **Journal: Advances IN Skin and Wound Care, 14 (2); 91-95** **Study type: randomized controlled trial (subset analysis)** **Sequence generation: not reported** **Allocation concealment: not reported** **Blinding: blinding, no further information.** **Addressing incomplete outcome data: intention to treat analysis.** **Statistical analysis: The Bonferroni adjustment (Dunn) t**	**Patient group:** Hospitalized patients aged 18 years and older with a stage III or IV PU (according to the NPUAP 1992 classification). **All patients** **Randomised N:** 14 **Completed N:** 8 **Drop-outs:** 6 (1 died, 2 developed osteomyelitis, 1 was non-compliant to pressure relief protocol, 1 had an unsatisfactory therapeutic effect, 1 had an aspiration pneumonia) **Group 1** **Randomised N:** 4 **Completed N:** 3 **Dropouts:** 1 (1 died) **Age (mean years (SD)):** 51.0 (7.9) **Gender (m/f):** 1/3 **Duration of PU (mean weeks (SD)):** 45 (28)	**Group 1:** Topical agent: 1.0µg/cm² transforming growth factor beta 3. After 15 minutes the wound was cleaned with saline and loosely packed with saline-moistened gauze. **Group 2:** Topical agent: 2.5µg/cm² transforming growth factor beta 3. After 15 minutes the wound was cleaned with saline and loosely packed with saline-moistened gauze. **Group 3:** placebo gel **Both groups:** All patients received standardized wound care: all target ulcers were debrided before randomization, gentle cleansing of the wound bed with saline, maintenance of a moist wound environment, recognition and treatment of infection, off-loading of pressure from the affected area using low-air-low surfaces, and nutritional support.	**Outcome 1:** proportion of patients completely healed **Outcome 2:** Mean relative reduction surface area (%) at termination **Outcome 3:** Mean relative reduction in volume (%) at termination	**Group 1:** 0/4 **Group 2:** 1/5 **Group 2:** 0/5 **Group 1:** 70 **Group 2:** 60 **Group 3:** 30 **Group 1:** 75 **Group 2:** 60 **Group 3:** 20	**Funding:** / **Limitations:** no report on sequence allocation; no report on allocation concealment; blinding, but no information; no a priory sample size calculation; no statistical measure of difference between groups; very small sample size and high drop-out **Additional outcomes:** /. **Notes:** /

test, a 1-way analysis of variance, was performed on the data at visits 4, 10, and 16 at the .05 level of significance. The relative PU volume and relative PU bed surface area were defined as the size at a particular visit divided by the baseline size. Thus, the reduction in size of the PU was evaluated relative to the original ulcer size. **Baseline differences: Difference not statistically measured. No clinically important differences were observed between groups** **Study power/sample size: No a priory sample size calculation.** **Setting: University wound care centre, Michigan** **Length of study: 16 weeks or until ulcer healed, whichever**	**Surface area (mean cm² (SD)):** 45.1 (25.2) **Ulcer volume (mean cm³ (SD)):** 32.6 (29.2) **Group 2** **Randomised N:** 5 **Completed N:** 2 **Dropouts:** 3 (2 developed osteomyelitis, and 1 was non-compliant to pressure relief protocol) **Age (mean years (SD)):** 34.0 (16.2) **Gender (m/f):** 4/1 **Duration of PU (mean weeks (SD)):** 43 (17) **Surface area (mean cm² (SD)):** 46.6 (13.1) **Ulcer volume (mean cm³ (SD)):** 31.5 (14.2) **Group 3** **Randomised N:** 5 **Completed N:** 3 **Dropouts:** 2 (1 had an unsatisfactory therapeutic effect, and 1 had an aspiration pneumonia) **Age (mean years (SD)):** 48.0 (21.0)	

occurred first. **Assessment of PUs:** **PU were classified according to the NPUAP (1992).** **Surface area site was measured by planimetry. A calcium alginate mold was made to measure the volume of the ulcer. The area of the PU bed was calculated using a dosage determination chart that converted area volume to ulcer bed area. If the volume was less than 10cm², the calculation was not done and the ulcer bed area was considered equal to ulcer surface area.** **Multiple ulcers: patients had between one and three ulcers. If more than 1 full-thickness PU was present, the PU closest to a volume of 40 cm^3 was designated as the target ulcer.**	**Gender (m/f):** 3/2 **Duration of PU (mean weeks (SD)):** 44 (23) **Surface area (mean cm² (SD)):** 43.2 (14.1) **Ulcer volume (mean cm^3 (SD)):** 28.1 (14.7) **Inclusion criteria:** Older than 18; PU surface area between 15 cm^2 and 120 cm^2 and the calcium alginate mold weight had to be 10 grams or more, following debridement at the baseline visit; ulcer present for at least 4 weeks; a serum albumin concentration of 2.5 grams/dL or more; bacterial counts of less than 10^5 per gram of tissue and no evidence of [beta]-hemolytic streptococci or malignancy. **Exclusion criteria:** osteomyelitis, determined by clinical evaluation, [chi]-ray, and/or bone biopsy; calcium alginate mold weight was 10 grams or less after debridement;	

	topical antibiotics or disinfectants were applied to the target ulcer during cleansing; autolytic or enzymatic debriding agents were used on the target ulcer; an experimental, nonapproved, or investigational drug was used within the past month or during the trial; malignancy at any PU site; administration of systemic corticosteroids of more than 20 mg per day, or administration of other immunosuppressive therapy; target ulcer failed to heal with previous cytokine therapy; patients received radiation therapy at the target ulcer site; women who were pregnant, nursing, or of childbearing age and not using an accepted method of birth control		

Table 111 – HOLLISAZ 2004

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Hollisaz (2004)** **Title: A randomized clinical trial comparing hydrocolloid, phenytoin and simple dressings for the treatment of pressure ulcers [ISRCTN33429693].** **Journal: BMC Dermatology, 4 (1); 18-26** **Study type: randomized controlled trial** **Sequence generation: random number table was used. The statistician in the team generated the random allocation sequence.** **Allocation concealment: stratified randomization (ulcers stage and**	**Patient group:** Patients with a spinal cord injury and a stage I or II PU (according to the NPUAP or Shea classification) **All patients** **Randomised N:** 83 patients with 91 ulcers **Completed N:** 83 patients with 91 ulcers **Drop-outs:** 0 **Group 1** **Randomised N:** 28 patients with 31 ulcers **Completed N:** 28 patients with 31 ulcers **Dropouts:** 0 **Age (mean years (SD)):** 36.81 (6.71) Gender (m/f): 28/0 **Duration of PU (mean weeks (SD)):** 7.63 (5.59) **Ulcer stage:** Stage I: n=13 Stage II: n=18	**Group 1:** Hydrocolloid adhesive dressing was used after cleaning and washing (3 times with normal saline) of the ulcer. The adhesive dressing was changed twice a week. **Group 2:** Phenytoin cream was used after cleaning and washing (3 times with normal saline) of the ulcer. A thin layer was applied to the ulcer before the dressing was performed. The dressing was changed daily. **Group 3:** Simple dressing was used after cleaning, washing (3 times with normal saline) and drying of the ulcer with a sterile gauze. The ulcer was covered with wet saline gauze dressing and was changed twice a day. **Both groups:** all ulcers were debrided before treatment. No concomitant topical or systematic antibiotic, glucocorticoid or immunosuppressive agent were allowed during the	**Outcome 1:** proportion of ulcers complete healed after eight weeks (all stages; all sites) **Outcome 2:** proportion of ulcers complete healed after eight weeks (stage I; all sites) **Outcome 3:** proportion of ulcers complete healed after eight weeks (stage II; all sites) **Outcome 4:** proportion of ulcers complete healed after eight weeks (all stages; gluteal) **Outcome 5:** proportion of ulcers complete	**Group 1:** 23/31 **Group 2:** 12/30 **Group 3:** 8/30 **P value G1 vs G2:** <0.01 **P value G1 vs G3:** <0.005 **Group 1:** 11/13 **Group 2:** 2/9 **Group 3:** 5/11 **P value G1 vs G2:** <0.005 **P value G1 vs G3:** <0.05 **Group 1:** 12/18 **Group 2:** 10/21 **Group 3:** 3/19 **P value G1 vs G2:** >0.05 **P value G1 vs G3:** <0.005 **Group 1:** 6/6 **Group 2:** 2/7 **Group 3:** 1/8 **P value G1 vs G2:** <0.005 **P value G1 vs G3:** <0.001	**Funding:** The study was supported by the Jaonbazan Medical and Engineering Research Center, the medical and research section of the official governmental body responsible for SCI war victims. **Limitations:** no blinding of patients and nurses; sample size lower than calculated sample size **Additional outcomes:** / **Notes:** /

location) was used. The statistician delivered the treatment category in an opaque sealed envelope bearing only the number of the patient. **Blinding: outcome assessor blinding.** **Addressing incomplete outcome data: no drop-out.** **Statistical analysis: All the data collected from the patients' preliminary and complementary questionnaires were analysed by SPSS software using ANOVA and Chi square tests, and P-values of <0.05 were assumed significant. The 95% confidence intervals were also calculated and reported. For rare events (more than 20 percent of cross tabulation cells had values less than 5), Fisher's exact test**	**Ulcer location:** Gluteal: n=6 Ischial: n=18 Sacral: n=7 **Surface area (mean cm² (SD)):** 7.26 (15.4) **Group 2** **Randomised N:** 28 patients with 30 ulcers **Completed N:** 28 patients with 30 ulcers **Dropouts:** 0 **Age (mean years (SD)):** 36.5 (4.99) Gender (m/f): 28/0 **Duration of PU (mean weeks (SD)):** 5.84 (8.04) **Ulcer stage:** Stage I: n=9 Stage II: n=21 **Ulcer location:** Gluteal: n=7 Ischial: n=18 Sacral: n=5 **Surface area (mean cm² (SD)):** 5.12 (3.63) **Group 3** **Randomised N:** 27	treatment.	healed after eight weeks (all stages; ischial) **Outcome 6:** proportion of ulcers complete healed after eight weeks (all stages; sacral) **Outcome 7:** proportion of ulcers partially healed after eight weeks **Outcome 8:** proportion of ulcers worsened after eight weeks **Outcome 9:** proportion of patients completely healed after eight weeks (one ulcer per patient randomly drawn)	**Group 1:** 13/18 **Group 2:** 8/18 **Group 3:** 3/14 **P value G1 vs G2:** <0.1 **P value G1 vs G3:** <0.005 **Group 1:** 4/7 **Group 2:** 2/5 **Group 3:** 4/8 **P value G1 vs G2:** >0.35 **P value G1 vs G3:** >0.20 **Group 1:** 4/31 **Group 2:** 4/30 **Group 3:** 5/30 **Group 1:** 2/31 **Group 2:** 2/30 **Group 3:** 9/30 **Group 1:** 20/28 **Group 2:** 11/28 **Group 3:** 8/27

was used. Based on stage and location of ulcers, subgroup analyses were performed using the same statistical tests. **Baseline differences: no statistical difference between groups.** **Study power/sample size: A response rate of 30%, 40% and 80%w was assumed for SD, PC and HD, respectively. Based on** **a 40% difference, power of 0.85, 95% confidence level and estimated follow-up loss of 10%, 29 patients were required for each study group. Final sample size lower than calculated.** **Setting: home care and long-term care centres** **Length of study: 8 weeks of treatment** **Assessment of PUs:** **PUs were classified according to the**	patients with 30 ulcers **Completed N:** 27 patients with 30 ulcers **Dropouts:** 0 **Age (mean years (SD)):** 36.6 (6.17) Gender (m/f): 27/0 **Duration of PU (mean weeks (SD)):** 5.25 (5.39) **Ulcer stage:** Stage I: n=11 Stage II: n=19 **Ulcer location:** Gluteal: n=8 Ischial: n=14 Sacral: n=8 **Surface area (mean cm² (SD)):** 10.27 (15.32) **Inclusion criteria:** Paraplegia caused by spinal cord injury; PU stage I or II according to Shea or NPUAP classification; informed consent; smoothness of ulcer area to establish whether adhesive could be used at the site **Exclusion criteria:** Addiction; heavy		**P value G1 vs G2:** <0.01 **P value G1 vs G3:** <0.005

NPUAP (1989) and Shea (1975) classification. **The general practitioner filled in a questionnaire on ulcer status every two weeks. Completely healed ulcer patients were followed up by monthly visits from GP for further 4 months after end of trial.** **One of the authors assesses complete/partial/without/worsening healing at the end of the study.** **Ulcer surface area was measured by tracing on an paper overly, which was scanned, redrawn and measured by AutoCAD 2000** **Multiple ulcers: if a patient had more than one ulcer, all ulcers were treated by the same method. Ulcers was unit of analysis.**	smoking (more than 20 cigarettes a day or more than 10 packs per year; concomitant chronic disease (e.g. diabetes mellitus or frank vascular disease such as Buerger's disease).	

Table 112 – KAYA 2005

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: Kaya (2005) **Title:** The effectiveness of a hydrogel dressing compared with standard management of pressure ulcers. **Journal:** Journal of Wound Care, 14 (1); 42-44 **Study type:** randomized controlled trial **Sequence generation:** not reported **Allocation concealment:** not reported **Blinding:** not reported **Addressing incomplete outcome data:** not reported. **Statistical analysis:** The Mann-Whitney U test was used to	**Patient group:** Hospitalized patients with a spinal cord injury and with PUs (according to the NPUAP classification) **All patients** **Randomised N:** 27 patients and 49 ulcers **Completed N:** not reported **Drop-outs:** not reported Gender (m/f): 24/3 **Group 1** **Randomised N:** 15 patients and 25 ulcers **Completed N:** not reported **Dropouts:** not reported **Age (mean years (SD); range):** 35.27 (14.57; 16-56) **Ulcer grade:** Grade I: 6 Grade II: 17 Grade III: 2	**Group 1:** Hydrogel dressing (Elasto-Gel™, South-West Technologies, North Kansas City, Missouri, USA). Dressings were changed every four days, or more if membrane became contaminated or non-occlusive. **Group 2:** Povidone-iodine soaked gauze dressings which were changed every daily. **Both groups:** necrotic areas were mechanically debrided	**Outcome 1:** Mean healing rate (cm²/day; range)	**Group 1:** 0.12 (0.16); 0.02-0.36 **Group 2:** 0.09 (0.05); 0.03-0.23 **P value:** 0.97	**Funding:** / **Limitations:** no report on sequence allocation; no report on allocation concealment; no report on drop-outs; no report on blinding; little information on ulcer assessment and statistical analysis; no information on preventive measures. **Additional outcomes:** Treatment time (mean days (SD); range): G1: 51.56 (20.07); 15-91; G2: 51.54 (23.69); 16-106 **Notes:** /

compare arithmetic means and differences between groups. All statistical analyses were performed using SPSS **Baseline differences: No statistical difference between groups.** **Study power/sample size: No a priory sample size calculation.** **Setting: Hospital.** **Length of study: Not reported** **Assessment of PUs:** **PUs were classified according to the NPUAP classification.** **Ulcers were measured in cm². The surface area was evaluated every four days until epithelisation was complete.** **Multiple ulcers: 27 patients with 49 ulcers.**	**Ulcer location:** Sacral: n=7 Ischia: n=6 Heel: n=6 Greater trochanter: n=3 Knee: n=1 Lateral malleolus: n=2 **Ulcer area (mean cm² (SD); range):** 4.13 (2.73) **Group 2** **Randomised N:** 12 patients and 24 ulcers **Completed N:** not reported **Dropouts:** not reported **Age (mean years (SD); range):** 29.67 (6.41); 17-39 **Ulcer grade:** Grade I: 6 Grade II: 17 Grade III: 1 **Ulcer location:** Sacral: n=6 Ischia: n=3 Heel: n=2 Greater trochanter: n=4 Iliac cest: n=4 Knee: n=2

	Fibula: n=2 Foot: n=1 **Ulcer area (mean cm² (SD); range):** 6.45 (6.88); 2-35 **Inclusion criteria:** SCI patient; PU **Exclusion criteria:** /				

Table 113 – KIM 1996

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Kim (1996)** **Title: Efficacy of hydrocolloid occlusive dressing technique in decubitus ulcer treatment: a comparative study.** **Journal: Yonsei Medical Journal, 37 (3); 181-185** **Study type: randomized controlled trial** **Sequence generation: not reported**	Patient group: Patients with a stage I or II PU (according to the NPUAP classification). All patients Randomised N: 44 Completed N: 44 Drop-outs: 0 Group 1 Randomised N: 26 Completed N: 26 Dropouts: 0 Age (mean years (SD)): 50.5 (18.3) Gender (m/f): 23/3	Group 1: Hydrocolloid occlusive dressing (DuoDerm®, Squib, Princeton, NJ). Ulcers were cleaned with saline irrigation and boric solution prior to application of the dressing. Dressings were changed every 4-5 days. Group 2: Wet-to-dry dressing. Ulcers were cleaned with saline irrigation and boric solution prior to application of the povidone soaked wet gauze. Dressings were changed three times a day. Both groups: All ulcers were debrided prior to application	Outcome 1: Healing rate (%) Outcome 2: Mean healing speed (mm²/day) Outcome 3: Proportion of patients with complete healing Outcome 4: Proportion of patients with hypergranulation	Group 1: 80.8 Group 2: 77.8 P value: > 0.05 Group 1: 9.1 (5.4) Group 2: 7.9 (4.7) P value: > 0.05 Group 1: 21/26 Group 2: 14/18 Group 1: 3/26 Group 2: 0/18	Funding: / Limitations: no report on sequence allocation; no report on allocation concealment; no report on blinding; no a priory sample size calculation; no report on multiple ulcers Additional outcomes: cost (won): G1: 8204 (2664) versus G2:

Allocation concealment: not reported **Blinding: not reported.** **Addressing incomplete outcome data: no missings reported** **Statistical analysis: The chi-square and t-test were used for the statistical analysis.** **Baseline differences: No statistical difference between groups** **Study power/sample size: No a priory sample size calculation.** **Setting: department of rehabilitation medicine** **Length of study: mean treatment duration was 18.9 (8.2) days in G1 and 24.3 (11.2) days in G2** **Assessment of PUs:** **PU were classified according to the NPUAP classification (1989).**	Incontinence: Urine: n=19 Faecal: n=10 Ulcer stage: Stage I: n=6 Stage II: n=20 Ulcer location: Sacrum: n=7 Pelvic girdle: n=7 Other: n=12 Surface area (mean cm²): unclear Group 2 Randomised N: 18 Completed N: 18 Dropouts: 0 Age (mean years (SD)): 46.9 (16.8) Gender (m/f): 13/5 Incontinence: Urine: n=12 Faecal: n=7 Ulcer stage: Stage I: n=6 Stage II: n=12 Ulcer location: Sacrum: n=4 Pelvic girdle: n=7 Other: n=7	of the dressing. All patients received position change to relieve the pressure to the ulcer site.	14571 (6700) Notes: /

Ulcer size was estimated by measuring the longest diameters and the longest diameter perpendicular to it. Other measured variables were ulcer site, size and degree, presence of necrotic tissue, exudate, serum albumin level, hemoglobin level and urinary and faecal incontinence. **Multiple ulcers: not reported.**	Surface area (mean cm^2): unclear Inclusion criteria: PUs stage I or II Exclusion criteria: PU stage III or IV; systemic infection, endocrinological disorder, difficulty keeping pressure relieving positions; aggravated general condition due to other factors				

Table 114 – KNUDSEN 1982

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Knudsen (1982)** **Title: The use of a haemodialysate in the treatment of decubital ulcer: A double-blind randomized clinical study.** **Journal: Current Therapeutic Research, 32 (3);**	**Patient group:** Patients with a spinal cord injury and a PU. **All patients** **Randomised N:** 16 **Completed N:** 8 **Drop-outs:** 8 (3 underwent plastic surgery, 3 fistels and sinuses broke through, 2 transferred)	**Group 1:** Dialysate (Solcoseryl®, Solco Basle Ltd., Basle, Switzerland). Jelly was used for the ulcer crater and ointment was used for the ulcer edges and zones where epithelialization occurred. The edges were covered with Melolin bandage. The bandages were changed and fresh jelly and ointment was applied three times a day during the	**Outcome 1:** Mean ml decrease in ulcer size **Outcome 2:** Mean percentage decrease in ulcer size at day 10 **Outcome 3:** Mean percentage	**Group 1:** 13.4 (10.02) **Group 2:** 6.57 (4.88) **Group 1:** 39 **Group 2:** 28 **Group 1: 80**	**Funding:** Solco Bazle Ltd. provided the test drug **Limitations:** no report on sequence generation; concealment no report on allocation concealment;

498-504 **Study type: randomized controlled trial** **Sequence generation: a not reported** **Allocation concealment: not reported** **Blinding: double blind, no further information** **Addressing incomplete outcome data: drop-outs were excluded** **Statistical analysis: The student t-test was used for analysis of the differences between the regression coefficients for the active and the placebo treatments.** **Baseline differences: Difference was not measured statistically.** **Study power/sample size: No a priory sample size calculation.**	**Group 1** **Randomised N:** not reported **Completed N:** 5 **Dropouts:** not reported **Characteristics of completed N** **Age (mean years (SD); range):** 33.6 (8.17); 22-40 **Gender (m/f):** 3/2 **Ulcer size (mean ml (SD); range):** 17.44 (13.88); 7.6-40.9 **Ulcer location:** sacral area **Group 2** **Randomised N:** not reported **Completed N:** 3 **Dropouts:** not reported **Characteristics of completed N** **Age (mean years (SD); range):** 42 (19.47); 20-57 **Gender (m/f):** 2/1 **Ulcer size (mean ml (SD); range):** 14.1 (8.16); 5.7-22.0	first week and twice a day during the following two weeks. Solcoseryl®: a protein-free dialysate of calf blood **Group 2:** Placebo. Jelly was used for the ulcer crater and ointment was used for the ulcer edges and zones where epithelialization occurred. The edges were covered with Melolin bandage. The bandages were changed and fresh jelly and ointment was applied three times a day during the first week and twice a day during the following two weeks. **Both groups:** all patients were placed on water mattresses. Patients were turned 10 times at regular intervals over 24 hours. Systemic and local antibiotics were stopped at least one week prior to the start of the study.	decrease in ulcer size at day 20 **Outcome 4:** Mean healing half-time (days) **Outcome 5:** Side effects	**Group 2: 59** **Group 1:** 8.52 (2.36) **Group 2:** 24.0 (18.43) **P-value:** p<0.05 (favour G1) **Group 1:** 0/5 **Group 2:** 0/3	double-blind no further information; no ITT analysis; no a priory sample size calculation; small sample size and high dropout; no classification of PU; no information on number of randomized patients per group; no characteristics on patients who dropped out; no statistical measurement of differences between groups **Additional outcomes:** / **Notes:** /

Setting: hospital **Length of study: three weeks of treatment.** **Assessment of PUs:** **PU classification not reported.** **Ulcers were measured 9 times and loss of substance 5 times. The logarithm of the product length, width and depth of the ulcer was used as one parameter for the ulcer size. In addition, the exact volume of lost substance was measured by filling the ulcer crater with placebo gel to skin level using a syringe. Ulcers were photographed in color 4 times under standardized conditions during the course of treatment.** **Multiple ulcers: not reported**	**Ulcer location:** sacral area **Inclusion criteria:** Para-tetraplegic patients; decubital ulcer with a size which could be measured in three dimensions and with a measurable loss of substance of at least 1 ml **Exclusion criteria:** > 60 years; diabetes mellitus; cardiac and/or peripheral vascular disease	

Table 115 – KRAFT 1993

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Kraft (1993)** **Title: A comparison of Epi-Lock and saline dressings in the treatment of pressure ulcers.** **Journal: Decubitus, 6 (6); 42-48** **Study type: randomized controlled trial** **Sequence generation: not reported** **Allocation concealment: not reported** **Blinding: not reported.** **Addressing incomplete outcome data: intention-to-treat analysis** **Statistical analysis: Not reported except for correlation between determined variables and ulcer**	**Patient group:** Male veterans with a stage II or III PU (according to the Enterstomal Therapy definition). **All patients** **Randomised N:** 34 **Completed N:** 17 **Drop-outs:** 17 (2 died, 2 withdrew, staff requested withdrawal for 6 patients, 1 had surgery, 1 had special bed treatment, 5 had a reaction to RX) **Age (mean years; range):** 56; 28-78 **Gender (m/f):** 38/0 **Spinal cord injury:** 33 **Ulcer stage:** Stage II: n=22 Stage III: n=16 **Ulcer duration:** range: new to five years ≤ 2 months: n=20 > 2 months: n=14	**Group 1:** foam dressing (Epi-Lock™). Epi-Lock™: a sterile, non-adherent, semi-occlusive polyurethane foam wound dressing with an adhesive cover. **Group 2:** saline moistened gauze dressing. **Both groups:** Standardized dressing procedures were performed in all patients.	**Outcome 1:** Proportion of patients/ulcers completely healed	**Group 1:** 10/24 **Group 2:** 3/14	**Funding:** funding by Calgon Vestal Labaratories **Limitations:** no report on sequence allocation; no report on allocation concealment; no report on blinding; a priory sample size calculation unclear; small sample size and high drop-out (ITT); no measurement of statistical difference between groups at baseline; no information on statistical analysis; no information on ulcer assessment; little information on dressing and standardized procedure.

healing. Data were analyzed using regression analysis. **Baseline differences: Difference was not statistically measured.** **Study power/sample size: Unclear if a priory sample size calculation was performed. Sample size was targeted to allow for drop-outs. The sample size was adequate to permit statistical analysis to detect difference in healing between groups, stages and over time.** **Setting: tertiary care veteran's hospital in the Midwest consisting of a spinal cord injury centre and an extended care centre.** **Length of study: 24 days of treatment** **Assessment of PUs:** **PU were classified according to the Enterstomal Therapy definition (1987).** **All subjects were**	**Group 1** **Randomised N:** 24 **Completed N:** 11 **Dropouts:** 13 (1 withdrew, staff requested withdrawal for 5 patients, 1 had special bed treatment, 4 had a reaction to RX) **Group 2** **Randomised N:** 14 **Completed N:** 6 **Dropouts:** 8 (2 died, 1 withdrew, staff requested withdrawal for 1 patients, 1 had surgery, 1 had a reaction to RX) **Inclusion criteria:** / **Exclusion criteria:** PU stage I or IV; clinically infected ulcer; patient on special bed; unstable insulin-dependent diabetes; serum albumin < 2gm; hemoglobin < 12gm; class IV congestive heart failure; chronic renal insufficiency; documented severe		**Additional outcomes:** Cost (nursing time and dressing cost): G1: $20.48 versus G2: $74.97 Correlation (variables: medication, cultures, age, smoking, serum albumin, TIBC, CBC, fasting blood sugar, electrolytes, CO_2 levels): serum albumin was inversely related to patients age **Notes:** /

assessed by the same rater who noted stage, tissue color, drainage, odor and condition of the skin surrounding the ulcer. **Multiple ulcers: Indirect: one ulcer per patient.**	peripheral vascular disease; documented COPD				

Table 116 – KUCAN 1981

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Kucan (1981)** **Title: Comparison of silver sulfadiazine, povidone-iodine and physiologic saline in the treatment of chronic pressure ulcers.** **Journal: Journal of the American geriatric Society, 29 (5); 232-235** **Study type: randomized controlled trial** **Sequence generation: a computer-generated**	**Patient group:** Hospitalized patients with an infected PU. **All patients** **Randomised N:** 45 **Completed N:** 40 **Drop-outs:** 5 (reason not reported) **Age (range years):** 16-102 **Group 1** **Randomised N:** not reported **Completed N:** 15 **Dropouts:** not reported	**Group 1:** Silver sulfazidine cream 1% (Silvadene® cream). Ulcers were cleansed with a sterile saline solution. The cream was applied to the ulcer every eight hours with a gloved hand and worked into the crypts and crevices. The ulcer was then covered with two layers of fine mesh gauze. **Group 2:** Povidone-iodine solution (Betadine®). Ulcers were cleansed with a sterile saline solution. The ulcers were dressed with a coarse-mesh gauze fluffed dressing saturated with the solution. The dressing was changed every six hours.	**Outcome 1:** Proportion of patient clinically responding within three weeks **Outcome 2:** Mean values of bacterial levels	**P value G1 versus G2:** ≤ 0.022 **P value G1 versus G2:** < 0.01 **P value G1 versus G3:** < 0.10	**Funding:** / **Limitations:** no report on allocation concealment; no report on blinding; no ITT analysis; no report on statistical analysis; no a priory sample size calculation. **Additional outcomes:** / **Notes:** /

randomized table was used **Allocation concealment: not reported** **Blinding: not reported.** **Addressing incomplete outcome data: drop-outs were excluded** **Statistical analysis: Not reported.** **Baseline differences: No statistical difference between groups.** **Study power/sample size: No a priory sample size calculation.** **Setting: hospital** **Length of study: three weeks of treatment or until the ulcer was deemed microbiologically clean, clinically ready for closure or the medical regimen was considered a failure.** **Assessment of PUs:** **PU classification not reported.**	**Group 2** **Randomised N:** not reported **Completed N:** 11 **Dropouts:** not reported **Group 3** **Randomised N:** not reported **Completed N:** 14 **Dropouts:** not reported **Inclusion criteria:** Infected PU (bacterial count >10^5 bacteria per gram tissue); no sensitivity to sulfa or iodine preparations; not pregnant; no severe concomitant systemic disease; no severe concomitant infection outside the ulcer; no acute cellulitis in the area surrounding the ulcer; no radiographic bone involvement beneath the ulcer **Exclusion criteria:** /	**Group 3:** Physiologic saline 0.9% NaCl. Ulcers were cleansed with a sterile saline solution. The ulcers were dressed with a coarse-mesh gauze fluffed dressing saturated with the saline. The dressing was changed every four hours. **Both groups:** Debridement of the necrotic tissue was performed was indicated. Systemic antibiotic therapy was started only for the treatment of intercurrent infections. No other topical agents were applied on the ulcers. All patients received supportive treatment consisting of nutritional, postural, surgical and nursing care.

Ulcers were clinically and microbiologically evaluated. The microbiologic examination was conducted as described by Robson and Heggers (1969 and 1970). A reduction in total microbial count per gram of tissue to 10^5 or fewer and the absence of β-hemolytic streptococci. The clinical evaluation was based on the investigators judgment. **Multiple ulcers: Only one ulcer per patient was evaluated.**		

Table 117 – Kuflik 2001

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Kuflik (2001)** **Title: Petrolatum versus Resurfix® ointment in the treatment of pressure ulcers.** **Journal: Ostomy/wound Management, 47 (2); 52-56** **Study type: randomized controlled trial** **Sequence generation: tubes were randomly numbered** **Allocation concealment: not reported** **Blinding: patients, physicians and nursing staff were blinded. Blinding of outcome assessor (investigator) was not reported.** **Addressing incomplete outcome**	**Patient group:** Elderly patients with a stage I or II PU (according to the AHCPR classification). **All patients** **Randomised N:** 19 patient with 20 ulcers **Completed N:** 15 patients with 16 ulcers **Drop-outs:** 4 patients with 4 ulcers (1 medical condition, 1 non-improvement, 2 worsening) **Group 1** **Randomised N:** 10 patients with 11 ulcers **Completed N:** 8 patients with 9 ulcers **Dropouts:** 2 patients with 2 ulcers (1 medical condition, 1 non-improvement) **Ulcer stage:** Stage I: 6 Stage II: 5 **Ulcer size (mean cm**	**Group 1:** Ointment (Resurfix®, Topix Pharamceuticals Inc., North Amityville, NY). Treatment was applied twice-daily. Resurfix®: contains petrolatum, live yeast cell derivates, shark liver oil, catechins in green tea extract and vitamin E, benzyl alcohol, ceramides and yucca extract. **Group 2:** Base component petrolatum. Treatment was applied twice-daily. **Both groups:** No patient received a pressure-reducing device (was judged as not necessary by the investigator). All patients received adequate nutrition. No other treatments or dressings could be used	**Outcome 1:** Proportion of ulcers completely healed (all stages) **Outcome 2:** Proportion of ulcers completely healed (stage I) **Outcome 3:** Proportion of ulcers completely healed (stage II) **Outcome 4:** Proportion of ulcers improved (all stages) **Outcome 5:** Proportion of ulcers improved (stage I) **Outcome 6:** Proportion of ulcers improved (stage II)	**Group 1:** 5/10 **Group 2:** 2/9 **Group 1:** 4/5 **Group 2:** 2/7 **Group 1:** 1/5 **Group 2:** 0/2 **Group 1:** 4/10 **Group 2:** 0/9 **Group 1:** 1/5 **Group 2:** 0/6	**Funding:** Funded by Topix Pharmaceuticals, Inc. **Limitations:** insufficient information on sequence generation; no report on allocation concealment; no blinding of outcome assessor; no report on statistical analysis; little information on baseline characteristics and difference not measured statistically; no a priory sample size calculation; small sample size; no report on setting; little information on ulcer assessment.

data: not reported **Statistical analysis: Not reported.** **Baseline differences: No baseline characteristics reported except for ulcer stage and -size. No statistical measurement of differences between groups.** **Study power/sample size: No a priory sample size calculation.** **Setting: not reported** **Length of study: six weeks of treatment.** **Assessment of PUs:** **PU were classified according to the Agency for Healthcare Policy and Research Guidelines (1992).** **Ulcers area was measured using standard metric measurements and tested by the investigators. Before and after photographs were taken.**	**(SD); range):** 1.69 (1.01) **Group 2** **Randomised N:** 9 patients with 9 ulcers **Completed N:** 7 patients with 7 ulcers **Dropouts:** 7 patients with 7 ulcers (2 worsening) **Ulcer stage:** Stage I: 6 Stage II: 3 **Ulcer size (mean cm (SD); range):** 1.2 (1.13) **Inclusion criteria:** Stage I and II PU; **Exclusion criteria:** complex underlying etiologies such as venous stasis and severe diabetes	**Outcome 7:** Proportion of ulcers not changed (all stages) **Outcome 8:** Proportion of ulcers not changed (stage I) **Outcome 9:** Proportion of ulcers not changed (stage II) **Outcome 10:** Proportion of ulcers worsened (all stages) **Outcome 11:** Proportion of ulcers worsened (stage I) **Outcome 12:** Proportion of ulcers worsened (stage II)	**Group 1:** 3/5 **Group 2:** 0/3 **Group 1:** 1/10 **Group 2:** 1/9 **Group 1:** 0/5 **Group 2:** 1/6 **Group 1:** 1/5 **Group 2:** 0/3 **Group 1:** 0/10 **Group 2:** 6/9 **Group 1:** 0/5 **Group 2:** 3/6	**Additional outcomes:** change in erythema **Notes:** /

Multiple ulcers: One patient had two ulcers. Ulcer was unit of analysis.				**Group 1:** 0/5 **Group 2:** 3/3	

Table 118 – Landi 2003

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Landi (2003)** **Title: Topical Treatment of Pressure Ulcers with Nerve Growth Factor: A Randomized Clinical Trial.** **Journal: Annals of Internal Medicine, 139 (8); 635-642.** **Study type: randomized controlled trial** **Sequence generation: a computer-generated list was used.** **Allocation concealment: randomly stratified according to age group, sex, and ulcer**	**Patient group:** Nursing home patients a stage II or V PU to the foot (according to the Yarkony-Kirk classification). **All patients** **Randomised N:** 38 **Completed N:** 36 **Drop-outs:** 2 (1 died, and 1 lost to follow up) **Group 1** **Randomised N:** 19 **Completed N:** 18 **Dropouts:** 1 (died) **Age (mean years (SD); range):** 80.2 (3.0); 75-85 **Gender (m/f):** 5/13 **BMI (mean kg/m²):** 24.0	**Group 1:** topical nerve growth factor (2.5 S murine nerve growth factor). One mg of nerve growth factor was dissolved in 20 ml of balanced salt solution, with a final concentration of 50 µg/ml. The nerve growth factor solution was dropped daily on the lesion and allowed to dry for 2 to 3 minutes. **Group 2:** Balanced salt solution. The solution was dropped daily on the lesion and allowed to dry for 2 to 3 minutes. **Both groups:** All ulcers received daily local care: irrigation with normal saline, use of debriding enzymes, and application of opaque hydrocolloid occlusive	**Outcome 1:** Proportion of patients completely healed **Outcome 2:** Improvement by 3 or more stages **Outcome 3:** Improvement by 2 stages **Outcome 4:** Improvement by 1 stage **Outcome 5:** Reduction in ulcer area (mm²) **Outcome 6:**	**Group 1:** 8/18 **Group 2:** 1/18 **P value:** 0.009 **Group 1:** 5/18 **Group 2:** 0/18 **P value:** < 0.001 **Group 1:** 14/18 **Group 2:** 2/18 **P value:** < 0.001 **Group 1:** 18/18 **Group 2:** 8/18 **P value:** < 0.001 **Group 1:** 738 (393) **Group 2:** 485 (384) **P value:** < 0.034	**Funding:** Grant from the Progetto Finalizzato Invecchiamento of the Italian National Research Council. Support was also provided by inter*RAI*, an international group of clinicians and researchers who collaborate to promote research on resident assessment instruments and quality outcomes for elderly persons. Dr. Aloe (co-author) was supported by a grant from the Italian National

surface area **Blinding: double blind, nurses and outcome assessor** **Addressing incomplete outcome data: unclear** **Statistical analysis: Quantitative variables are presented as mean values** **(±SD). Differences in baseline characteristics between patients** **in the control and treatment groups were analyzed in several ways. Quantitative outcomes were tested by using the Student *t*-test after a pretest for homogeneity of variance.** **The Mann–Whitney test was used for cases in which the normality assumption was not reasonable. Categorical variables were analyzed by using the Fisher**	(1.4) **Duration of PU (mean days (SD)):** 13 (4) **Ulcer stage:** Stage II: n=3 Stage III: n=9 Stage IV: n=5 Stage V: n=1 **Ulcer location:** Heel: n=14 Lateral malleolus: n=4 **Surface area (mean mm² (SD)):** 1012 (633) **Group 2** **Randomised N:** 19 **Completed N:** 18 **Dropouts:** 1 (lost to follow-up) **Age (mean years (SD); range):** 80.2 (4.7); 73-93 **Gender (m/f):** 5/13 **BMI (mean kg/m²):** 23.8 (1.4) **Duration of PU (mean days (SD)):** 12 (5) **Ulcer stage:** Stage II: n=3 Stage III: n=13 Stage IV: n=1	barriers. Al patient received the same preventive skin regimen (turning, repositioning and use of pressure relieving mattress)	Reduction in ulcer area (mm²) (adjusted for baseline ulcer area, location and duration) **Outcome 7:** Proportion of patients with adverse events	**Group 1:** 6.5 (0.3) **Group 2:** 5.9 (0.3) **P value:** < 0.001 **Group 1:** 0/18 **Group 2:** 0/18	Institute of Health (ICG 120/4RA00-90) and by a grant from the Italian National Research Council, FISR/ Neurobiotechnology (192/03). **Limitations:**; inadequate allocation concealment; no patient blinding; no a priory sample size calculation; no ITT. **Additional outcomes:** / **Notes:** /

exact test. **Analysis of covariance was used to compare reduction in pressure ulcer area from baseline to 6-week follow-up after adjustment for baseline ulcer area, location, and duration.** **Because the distribution of reduction in pressure ulcer area was not normal, this analysis was performed after natural log transformation of this variable. Statistical analyses were performed by using SPSS, version 10.0 (SPSS Inc., Chicago, Illinois).** **Baseline differences: No statistical differences between group according to a p <0.2.** **Study power/sample size: No a priory sample size calculation.** **Setting: teaching nursing home of**	Stage V: n=1 **Ulcer location:** Heel: n=15 Lateral malleolus: n=3 **Surface area (mean mm² (SD)):** 1012 (655) **Inclusion criteria:** PU of the foot that ranged from 1 cm^2 to 30 cm^2 in total area **Exclusion criteria:** developed the lesion more than 1 month before admission; terminal illnesses; diabetes; peripheral vascular diseases				

Catholic University of the Sacred Heart, Fontecchio, Italy. **Length of study: 6 weeks of treatment or until completely healed** **Assessment of PUs:** **PU were classified according to the Yarkony-Kirk classification (1990).** **The ulcer perimeter was traced onto sterile, transparent block paper and the blocks were counted. Digital photographs were taken at baseline** **and every week during the follow-up period.** **Multiple ulcers: indirect: one ulcer per patient**					

Table 119 – Ijunberg 2009

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Ljungberg (1998)** **Title: Comparison of dextranomer paste**	**Patient group:** Male patients with a spinal cord injury, aged 18 years and older, and	**Group 1:** Dextranomer paste (Debrisan®, Pharmacia Pharmaceuticals, AB, Uppsala, Sweden). Ulcers	**Outcome 1:** Proportion of ulcer improved with 25%	**Group 1:** 11/15 **Group 2:** 2/15 **P value:** < 0.01	**Funding:** Grant from Pharmacia Pharmaceuticals AB, Sweden.

and saline dressings for management of decubital ulcers. **Journal: Clinical Therapeutics, 20 (4); 737-743.** **Study type: randomized controlled trial** **Sequence generation: not reported.** **Allocation concealment: not reported** **Blinding: not reported** **Addressing incomplete outcome data: intention to treat analysis** **Statistical analysis: Treatment comparisons** **were based on the change from study entry to day 15 or the end of the study (end point) and using the chi-square test. The level of significance for all tests was *p* < 0.05.** **Baseline differences:**	with exudative PUs (according to the Eltorai classification). **All patients** **Randomised N:** 23 patients with 30 ulcers **Completed N:** not reported **Drop-outs:** not reported **Age (range years):** 23-73 **Gender (m/f):** 23/0 **Group 1** **Randomised N:** 15 ulcers **Completed N:** not reported **Dropouts:** not reported **Duration of PU (mean months; median months; range):** 4.2; 4; 0.5-12 **Ulcer stage:** Stage II: n=10 Stage III: n=4 Stage IV: n=1 **Ulcer location:** Ischium: n=6 Sacrum: n=3 Hips: n=4	were cleaned with mild soap and water and rinsed with saline solution. Paste was applied on the wet ulcer and was covered with a dry sterile dressing. Debrisan®: contained 64% dextranomer, 30.5% polyethylene glycol 600 and 5.5% distilled water **Group 2:** Saline dressing. Ulcers were cleaned with mild soap and water and rinsed with saline solution. The saline soaked dressing was applied on the wet ulcer and was covered with a dry sterile dressing. **Both groups:** All ulcers were surgically debrided before application of the dressing.	**Outcome 2:** Proportion of ulcers with granulation after 15 days **Outcome 3:** Proportion of ulcers with epithelialization after 15 days **Outcome 4:** Proportion of patients with adverse events	**Group 1:** 10/15 **Group 2:** 8/15 **P value:** > 0.05 **Group 1:** 7/15 **Group 2:** 4/15 **P value:** > 0.05 **Group 1 and 2:** 0/23	**Limitations:**; no report on sequence allocation; no report on allocation concealment; no report on blinding; no a priory sample size calculation; no measurement of statistical difference between groups; little information on ulcer assessment; no information on number of patients per group. **Additional outcomes:** / **Notes:** /

Difference not statistically measured. Groups were comparable. **Study power/sample size: No a priory sample size calculation.** **Setting: Spinal cord injury service, Long Beach Veterans Administration Hospital, Long Beach, California.** **Length of study: 15 days of treatment.** **Assessment of PUs:** **PU were classified according to the Eltorai classification.** **Qualitative assessment of the ulcers was conducted with the aid of photographs. The extent of granulation was measured on a six-point scale. Ulcers were assessed each time the nurse changed the dressing.** **Multiple ulcers: 30 ulcers in 23 patients. Ulcers was unit of**	Ankle: n=2 Other: n=0 **Infected ulcers:** 6 **Group 2** **Randomised N:** 15 ulcers **Completed N:** not reported **Dropouts:** not reported **Duration of PU (mean months; median months; range):** 4.3; 4; 0.5-10 **Ulcer stage:** Stage II: n=12 Stage III: n=3 Stage IV: n=0 **Ulcer location:** Ischium: n=5 Sacrum: n=3 Hips: n=3 Ankle: n=1 Other: n=3 **Infected ulcers:** 9 **Inclusion criteria:** Aged 18 years and older; exudative PU **Exclusion criteria:** PU involving the bone

analysis.

Table 120 – Matzen 1999

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Matzen (1999)** **Title: A new amorphous hydrocolloid for the treatment of pressure sores: A randomised controlled study.** **Journal: Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery, 33 (1); 13-15.** **Study type: randomized controlled trial** **Sequence generation: not reported.** **Allocation concealment: not reported** **Blinding: not**	**Patient group:** Patients older than 18 years with a stage III or IV PU (according to the Lowthian classification). **All patients** **Randomised N:** 32 **Completed N:** 6 **Drop-outs:** 20 (8 had other illnesses, 3 died, 1 had a missing schedule, 2 withdrew, 6 had insufficient effect of the treatment). **Ulcer location:** Sacrum: n=21 Trochanter: n=11 **Group 1** **Randomised N:** 17 **Completed N:** 8 **Dropouts:** 9 (5 had other illnesses, 2 died, 1 had a missing schedule, 1 withdrew)	**Group 1:** Hydrocolloid dressing (Hydrogel®, Coloplast A/S, Denmark). The dressing was covered with a transparent hydrocolloid dressing (Comfeel®, Coloplast A/S, Denmark). The ulcers were cleaned and changed daily. **Group 2:** Saline gauze compresses. The dressing was covered with a transparent hydrocolloid dressing (Comfeel®, Coloplast A/S, Denmark). The ulcers were cleaned and changed daily. **Both groups:** All ulcers were debrided before application of the dressing as necessary.	**Outcome 1:** Mean relative volume reduction (%) **Outcome 2:** Proportion of patients completely healed **Outcome 3:** Median (range) pain during treatment **Outcome 4:** Median (range) smell during treatment **Outcome 5:** Median (range) comfort during treatment	**Group 1:** 26 (20) **Group 2:** 64 (16) **P value:** < 0.02 **Group 1:** 5/17 **Group 2:** 0/15 **Group 1:** 2 (1-4) **Group 2:** 2 (1-3) **Group 1:** 2 (1-4) **Group 2:** 2 (1-3) **Group 1:** 4 (3-4) **Group 2:** 3 (2-4)	**Funding:** /. **Limitations:**; no report on sequence allocation; no report on allocation concealment; no report on blinding; no a priory sample size calculation; no measurement of statistical difference between groups; setting not reported; little information on ulcer assessment, pain, smell, comfort **Additional outcomes:** Length of time dressing required

reported **Addressing incomplete outcome data: intention to treat analysis.** **Statistical analysis: The data were skewed and therefore assessed by the nonparametric** **Mann-Whitney test. Differences were** **accepted as significant if the probability was less than 0.05.** **Baseline differences: Difference not statistically measured.** **Study power/sample size: No a priory sample size calculation.** **Setting: not reported.** **Length of study: 12 weeks of treatment or until complete healing.** **Assessment of PUs:** **PU were classified according to the Lowthian classification (1994).**	**Age (mean years range):** 82; 32-97 **Gender (m/f):** 2/15 **Group 2** **Randomised N:** 15 **Completed N:** 4 **Dropouts:** 11 (3 had other illnesses, 1 died, 1 had a missing schedule, 1 withdrew, 6 had insufficient effect of the treatment) **Age (mean years range):** 84; 46-89 **Gender (m/f):** 3/12 **Inclusion criteria:** Stage III or IV PU; non-infected PU located in the sacral or trochanteric areas. **Exclusion criteria:** Patients with diseases or taking drugs known to impair healing		(days) **Notes:** /

Healing of ulcers was estimated by measuring the amount of water needed to fill the cavity. **Multiple ulcers: not reported**					

Table 121 – Moberg 1983

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Moberg (1983)** **Title: A randomized trial of Cadexomer Iodine in Decubitus Ulcers.** **Journal: Journal of the American geriatric Society, 31 (8); 462-465.** **Study type: randomized controlled trial** **Sequence generation: not reported** **Allocation concealment: not reported** **Blinding: not**	**Patient group:** Hospitalized patients with an deep or superficial PU. **All patients** **Randomised N:** 38 **Completed N:** 34 **Drop-outs:** 4 (2 worsened, 1 skin irritation and oedema, 1 transferred) **Group 1** **Randomised N:** 19 **Completed N:** 16 **Dropouts:** 3 (2 worsened and 1 skin irritation and oedema) **Characteristics for**	**Group 1:** Cadexomer iodine. The iodine was applied daily to the ulcer in a layer approximately 3mm thick and was removed after 24 hours under stream of water or saline or with a wet swab. Cadexomer iodine: a dry powder consisting of spherical microbeads that range in diameter from 100 to 315µm. Each microbead is a highly hydrophilic, three dimensional network of a modified starch polymer containing iodine, which is physically immobilized within the matrix at a concentration of 0.9%. One gram of powder can absorb as much as 7ml of fluid. **Group 2:** standard treatment. Individualized and	**Outcome 1:** Proportion of ulcers reduced with 50% after three weeks **Outcome 2:** Mean cm² (SEM) decrease in ulcer area after three weeks. **Outcome 3:** Mean percentage (SEM) decrease in ulcer area of three weeks.	**Group 1:** 8/16 **Group 2:** 1/18 **P-value:** <0.01 **Group 1:** 2.9 (1.3) **Group 2:** 2.5 (1.1) **P-value:** <0.05 **Group 1:** 30.9 (11.5) **Group 2:** 19.6 (7.4) **P-value:** <0.02	**Funding:** / **Limitations:** no report on sequence generation; no report on allocation concealment; no report on blinding; no ITT analysis; baseline difference not measured statistically; no a priory sample size calculation. **Additional outcomes:** / **Notes:** /

reported. **Addressing incomplete outcome data: drop-outs were excluded** **Statistical analysis: Change of ulcer area and change of pain, pus and debris scores were evaluated suing the t-test. Nominal response categories were evaluated using fisher's exact probability test.** **Baseline differences: Statistical difference between groups was not measured. Groups were comparable.** **Study power/sample size: No a priory sample size calculation.** **Setting: hospital** **Length of study: First, three weeks of treatment. If the ulcers were clearly not abating or were getting worse the patient could be switched to the other treatment group for a**	**completed N** **Age (mean years (SD); range):** 72.6 (3.3); 52-90 **Gender (m/f):** 3/13 **Ulcer duration (mean months (SD)):** 6.2 (2.5) **Depth of ulcer:** Deep: 10 Superficial: 6 **Ulcer area (mean cm² (SEM)):** 9.6 (1.8) **Group 2** **Randomised N:** 19 **Completed N:** 18 **Dropouts:** 1 (transferred) **Characteristics for completed N** **Age (mean years (SD); range):** 80.1 (2.9); 52-97 **Gender (m/f):** 5/13 **Ulcer duration (mean months (SD)):** 6.2 (2.8) **Depth of ulcer:** Deep: 8 Superficial: 10 **Ulcer area (mean cm² (SEM)):** 12.4 (4.3)	depending on appearance of ulcer and surrounding skin. It included saline dressings, enzyme-based debriding agents, and nonadhesive dressings. **Both groups:** All patients received attention to nutrition, improvement of hygiene and removal of localized pressure by use of decubitus mattress, turning of the patient every two to three hours and optimal mobilization	

period of five weeks. If a positive response was observed during the first three weeks, treatment was continued until the ulcers healed or for five weeks, whichever occurred first. **Assessment of PUs:** **PU were classified as deep or superficial.** **Ulcer area was measured by planimetry performed on a tracing of the outline of the ulcer and by measurement of the longest diameter.** **Pain was assessed by a 10cm vas scale (0 (painless) to 100 (extremely painful)).** **Multiple ulcers: not reported.**	**Inclusion criteria:** PU **Exclusion criteria:** be moribund; have a malignancy; history of iodine sensitivity; psychiatric illness; other condition that might make them unable to give informed consent: otherwise unsuitable for the clinical trial					

Table 122 – Mustoe 1994

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Mustoe (1994)** **Title: A phase II**	**Patient group:** Patients with a stage III or IV PU.	**Group 1:** Growth factor rPDGF-BB (100µg/ml). Ulcers were dressed daily	**Outcome 1:** of Proportion patients	**Group 1:** 2/16 **Group 2:** 0/14 **Group 2:** 1/14	**Funding:** Supported by Amgen Inc,

study to evaluate recombinant platelet-derived growth factor- BB in the treatment of stage 3 and 4 pressure ulcers. **Journal: Archives of Surgery, 129; 213-219.** **Study type: randomized controlled trial** **Sequence generation: not reported.** **Allocation concealment: not reported** **Blinding: double blind, no further information** **Addressing incomplete outcome data: drop-out excluded.** **Statistical analysis: Patient characteristics, ulcer size and depth, and stage were compared among groups using analysis of variance. The Tukey test was**	**All patients** **Randomised N:** 52 **Completed N:** 41 **Drop-outs:** 11 (3 illness unrelated to the study, 2 died, 1 non-compliant to study, 1 infection, 1 physician required withdrawal, 2 missing data on day 29, 1 not reported) **Group 1** **Randomised N:** unclear **Completed N:** 15 **Dropouts:** unclear **Age (mean years (SD)):** 73.5 (15.0) **Gender (m/f):** 4/11 **Duration of PU (median months; range):** 5.2; 1.7-56.7 **Ulcer stage:** Stage III: n=4 Stage IV: n=11 **Ulcer location:** Ischium: n=3 Sacrum: n=5 Trochanter: n=4 Other: n=3 **Ulcer volume (mean cm² (SD)):** 5.5 (6.1)	with moist saline gauze dressings. **Group 2:** Growth factor rPDGF-BB (300µg/ml). Ulcers were dressed daily with moist saline gauze dressings. **Group 3:** placebo **Both groups:** All patients were mechanically debrided as necessary. Intermittent pressure relief wads obtained through turning regimes according the routines. No specialized pressure-reducing mattress and beds were used in the study	completely healed by 29 days **Outcome 2:** Proportion of patients completely healed by 5 months **Outcome 3:** Ulcer volume (g) at 29 days (adjusted for initial volume)	**Group 1:** 6/16 **Group 2:** 3/12 **Group 2:** 2/14 **Group 1:** 1.75 **Group 2:** 2.00 **Group 2:** 3.50 **P-value:** 0.056 **P-value G1&2 vs G3:** 0.009	Thousand Oaks, Calif. **Limitations:**; no report on sequence allocation; no report on allocation concealment; double blinding, no additional information; no a priory sample size calculation; small sample size; no ITT analysis; no information on PU classification; no information on multiple ulcers **Additional outcomes:** Cost-effectiveness **Notes:** /

used to make pairwise comparisons among treatment means. The Kruskal-Wallis anova was used to compare initial ulcer volume, and duration of the ulcer prior to onset of treatment among groups. On day 29, ulcer volume was compared among the groups using ancova with the baseline volume as covariate. Ulcer volume was transformed using log10 transformation prior to analysis. Groups were compared using single linear contrast by a two tailed t-test. Actual life table analysis was used to summarize the time to 50% healing for each group. The Tarone-Ware test was used to compare the time to 50% healing **Baseline differences: No statistical difference between**	**Group 2** **Randomised N:** unclear **Completed N:** 12 **Dropouts:** unclear **Age (mean years (SD)):** 67.5 (17.7) **Gender (m/f):** 5/7 **Duration of PU (median months; range):** 3.9; 0.3-10.0 **Ulcer stage:** Stage III: n=3 Stage IV: n=9 **Ulcer location:** Ischium: n=2 Sacrum: n=5 Trochanter: n=2 Other: n=3 **Ulcer volume (mean cm² (SD)):** 7.1 (8.8) **Group 3** **Randomised N:** unclear **Completed N:** 14 **Dropouts:** unclear **Age (mean years (SD)):** 73.4 (17.7) **Gender (m/f):** 5/9 **Duration of PU (median months;**	

groups. **Study power/sample size: No a priory sample size calculation** **Setting: Three centers: nursing homes and hospitals** **Length of study: 29 days of treatment and up to 5 months of follow-up.** **Assessment of PUs:** **PU classification not reported.** **Ulcers were evaluated by serial photographs. Volume measurements were obtained from weighting alginate casts of the wounds. The area of the ulcer opening was measured by planimetry.** **Multiple ulcers: not reported**	**range):** 2.0; 0.3-29.9 **Ulcer stage:** Stage III: n=3 Stage IV: n=11 **Ulcer location:** Ischium: n=4 Sacrum: n=6 Trochanter: n=3 Other: n=1 **Ulcer volume (mean cm² (SD)):** 10.8 (13.2) **Inclusion criteria:** Stage III or IV PU; ulcer surface between 4 and 100 cm²; no evidence of cellulites; malignancy in the ulcer area **Exclusion criteria:** venous or arterial disorder directly implicated n the cause of the ulcer; existing endocrine disease; immunosuppressive disease, sepsis; pregnancy or lactation; active abuse of alcohol or drugs; unstable renal, hepatic, hematologic or cardiac disease; use of immunotherapy, cytotoxic chemotherapy or investigational drugs.	

Table 123 – Neill 1989

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Neill (1989)** **Title: Pressure Sore Response to a New Hydrocolloid Dressing.** **Journal: Wounds: A compendium of Clinical Research and Practice, 1 (3); 173-185.** **Study type: randomized controlled trial** **Sequence generation: not reported.** **Allocation concealment: not reported** **Blinding: not reported** **Addressing incomplete outcome data: drop-out excluded.** **Statistical analysis: Nonparametric test was used to compare**	**Patient group:** Patients 18 years and older with grade II or III PUs (according to the Shea classification). **All patients** **Randomised N:** 100 ulcers **Completed N:** 65 patients and 87 ulcers **Drop-outs:** 13 ulcers (11 intercurrent medical events and 2 violated protocol) **Group 1** **Randomised N:** not reported **Completed N:** 42 ulcers **Dropouts:** not reported **Ulcer grade:** Stage II: n=25 Stage III: n=17 **Ulcer volume (mean cm² (SD); range):** 8.3 (9.9); 0.43-43.93 **Presence of necrosis:** 34	**Group 1:** Hydrocolloid dressing (Tegasorb™). Ulcers (free of debris) were irrigated with 50cc of a 1:1 solution of 3% hydrogen peroxide and sterile normal saline followed by 50cc saline rinse. Ulcers (with necrotic tissue, debris or faeces) were irrigated with 50cc of a 1:1 solution of 1% povidone-iodine and sterile saline solution between the hydrogen peroxide solution and the saline rinse. The skin was dried and the dressing was applied and changed every 7 days unless escar was present (every three days), or the dressing became non-adherent or leaked. Tegasorb™: contains polysaccharide, gelatine, pectin, and polyisobutylene. It consists of a flexible oval mass with an adherent hydrocolloid inner face, and an outer water and bacteria impermeable, adhesive-coated, polyurethane film. **Group 2:** Wet to damp saline	**Outcome 1:** Proportion of ulcers completely healed **Outcome 2:** Proportion of ulcers completely healed (grade II PUs) **Outcome 3:** Proportion of ulcers enlarged (grade II PUs) **Outcome 4:** Proportion of ulcers completely healed (grade III PUs) **Outcome 5:** Proportion of ulcers enlarged (grade III PUs) **Outcome 6:** Median percentage	**Group 1:** 13/42 **Group 2:** 10/45 **Group 1:** 11/25 **Group 2:** 9/34 **P value:** > 0.05 **Group 1:** 7/25 **Group 2:** 11/34 **P value:** > 0.05 **Group 1:** 2/17 **Group 2:** 1/11 **P value:** > 0.05 **Group 1:** 7/17 **Group 2:** 4/11 **P value:** > 0.05	**Funding:** Funded by the 3M Company, Medical-Surgical Division. **Limitations:**; no report on sequence allocation; no report on allocation concealment; no report on blinding; no a priory sample size calculation; no ITT analysis; no information on PU classification **Additional outcomes:** Nursing time; Organism growth **Notes:** /

distribution of healing between groups. Anova with PU grade, treatment group, and interaction as factor in the model was applied to the data after transformation of the data into ranks. A p value less than 0.05 was considered significant. A logistic regression model was used to look at covariates of healing. **Baseline differences: No statistical difference between groups.** **Study power/sample size: No a priory sample size calculation.** **Setting: A tertiary care facility and its affiliated nursing home** **Length of study: eight weeks of treatment.** **Assessment of PUs:** **PU were classified according to the Shea classification.**	**Ulcers on hip, heel, or sacrum:** 31 **Group 2** **Randomised N:** not reported **Completed N:** 45 ulcers **Dropouts:** not reported **Ulcer grade:** Stage II: n=34 Stage III: n=11 **Ulcer volume (mean cm² (SD); range):** 7.6 (8.6); 0.23-35.16 **Presence of necrosis:** 28 **Ulcers on hip, heel, or sacrum:** 34 **Inclusion criteria:** 18 years and older; ulcer < 1.5cm in depth, <5.6cm by 10cm in width and length; Grade II or III **Exclusion criteria:** inability of patient or guardian to give informed consent; presence of diabetes mellitus; history of skin hypersensitivity, skin disease, allergies to	gauze dressing. Ulcers (free of debris) were irrigated with 50cc of a 1:1 solution of 3% hydrogen peroxide and sterile normal saline followed by 50cc saline rinse. Ulcers (with necrotic tissue, debris or faeces) were irrigated with 50cc of a 1:1 solution of 1% povidone-iodine and sterile saline solution between the hydrogen peroxide solution and the saline rinse. After an open wide mesh gauze pad was moistened with sterile gauze and applied to the ulcer. A sterile gauze was applied as second dressing and secured with paper tape. The dressing was changed every eight hours **Both groups:** All subject received standard treatment for PUs: a pressure-reducing air mattress, and air-fluidized bed or a low air loss bed; an eggcrate wheelchair; turning and repositioning et least every two hours; control of incontinence with an external urine catheter and fecal incontinence collector.	reduction in size (grade II PUs) **Outcome 7:** Median percentage reduction in size (grade III PUs) **Outcome 8:** Proportion of patients with adverse events	**Group 1:** 91 **Group 2:** 48 **P value:** > 0.05 **Group 1:** 0.3 **Group 2:** 30 **P value:** > 0.05 **Group 1:** 9/50 (skin irritation) **Group 2:** 1/50 (ulcer worsened **P value:** < 0.06

Ulcers edges were traced onto transparencies and photographs beside a metric ruler were taken using a Minolta Maxxum 7000 with a 50mm macro lens and a 80PX ring light with automated exposure. A Zeiss IBAS Image Analyzer was used to calculate the ulcer surface area. **Multiple ulcers: A maximum of 2 PU per patients were included. The second ulcer received the alternate therapy**	tape or adhesives; concurrent radiotherapy to PU area; medical condition that could interfere with study controls; pre-existing skin disease around the PU; clinical infection associated with PU; peripheral vascular ulcers evidenced by a Brachial Ankle Index ≤ 0.6; scars, contusions, abrasions, or open skin in the immediate PU area.				

Table 124 – Olekse 1986

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Oleske (1986)** **Title: A randomized clinical trial of two dressing methods for the treatment of low-grade pressure ulcers.** **Journal: Journal of**	**Patient group:** Patients older than 21 years with stage I or II PUs (according to the Enis and Sarmiento classification). **All patients** **Randomised N:** 16	**Group 1:** Polyurethane self-adhesive dressing. Cleansing of the ulcer and application of the dressing was according to a standardized protocol. The dressing was changed if it dislodged from the ulcer site. **Group 2:** Saline dressing. Cleansing of the ulcer and	**Outcome 1:** Proportion of ulcers completely healed **Outcome 2:** Proportion of ulcers worsened	**Group 1:** 1/9 **Group 2:** 0/10 **Group 1:** 1/9 **Group 2:** 2/10	**Funding:** the study was sponsored by the Department of Medical Nursing, Rush-Presbyterian-St.Luke's Medical Centre and the Chicago

Enterostomal Therapy, 13 (3); 90-98. **Study type: randomized controlled trial** **Sequence generation: not reported.** **Allocation concealment: not reported** **Blinding: not reported** **Addressing incomplete outcome data: drop-out was excluded.** **Statistical analysis: One-way analysis of variance was used to compare the two treatments. A paired t test was used to compare the largest axis and surface are changes within treatment group. A standard chi-square test was used to compare the PU grades before and after therapy end to compare the two treatment groups.**	patients **Completed N:** 15 patients and 19 ulcers **Drop-outs:** 1 (unanticipated transfer to nursing home). **Age (mean years (SD); range):** 69 (6); 52-93 **Ulcer location:** Gluteal and coccyx area **Group 1** **Randomised N:** not reported **Completed N:** 7 patients and 9 ulcers **Dropouts:** not reported **Ulcer grade:** Grade I: n=2 Grade II: n=7 **Ulcer area (mean cm² (SD):** 3.5 (1.2) **Group 2** **Randomised N:** not reported **Completed N:** 8 patients and 10 ulcers **Dropouts:** not reported **Ulcer grade:** Grade I: n=5 Grade II: n=5	application of the dressing was according to a standardized protocol. The dressing was changed every four hours around the clock **Both groups:** All patients received the standardized nursing skin care: repositioning every 3 hours, daily administration of multivitamin tablets, use of a convoluted foam mattress (without sleeves)	**Outcome 3:** Mean percentage surface area reduction	**Group 1:** 42.9 **Group 2:** 2.5	Community trust. **Limitations:**; no report on sequence allocation; no report on allocation concealment; no report on blinding; no a priory sample size calculation; small sample size **Additional outcomes:** / **Notes:** /

The significance of the calculated statistics was determined by a two-tailed test with the level of alpha = 0.05 **Baseline differences: No statistical difference in terms of age, sex and race.** **Study power/sample size: No a priory sample size calculation.** **Setting: inpatient medicine unit.** **Length of study: 10 days of treatment.** **Assessment of PUs:** **PU were classified according to the Enis and Sarmiento classification (1973).** **Wound healing was evaluated: ulcer grade, longest wound axis, total wound surface area. A transparent rule was used to measure the longest wound axis. Tracings of the ulcer surface were made onto sterile plastic sheets. Surface area were**	**Ulcer area (mean cm² (SD):** 7.7 (8.6) **Inclusion criteria:** Adults (21 years of age or over) with a PU grade I or II; afebrile (< 100°F orally or < 101°F rectally); confined to bed, wheelchair, or chair and expected to be so for at least two weeks: expected hospitalization of two weeks; ulcer caused by pressure; ulcer of at least 2cm diameter; not contained in an area currently being irradiated; no evidence of infection; hemoglobin level > 10g/dL **Exclusion criteria:** /	

than computed by means of compensating polar planimeter. **Multiple ulcers: 15 patients with 19 ulcers**					

Table 125 – Payne 2001

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Payne (2001)** **Title: Long-term outcome study of growth factor-treated pressure ulcers.** **Journal: The American Journal of Surgery, 181 (1); 81-86.** **Study type: randomized controlled trial** **Sequence generation: not reported.** **Allocation concealment: not reported** **Blinding: double blind, only blinding**	**Patient group:** Inpatients with a grade III or IV PU. **All patients** **Randomised N:** 61 **Completed N:** 54 **Drop-outs:** 7 (4 died and 3 were lost to follow-up). **Group 1** **Randomised N:** 15 **Completed N:** 14 **Dropouts:** 1 (lost to follow-up) **Age (mean years (SD)):** 18.8 (11.8) **Ulcer duration (mean months (SD)):** 6.8 (6.1) **Ulcer volume (mean**	**Group 1:** Growth factor: rhuGM-CSF (2.0µg/cm²) was topically applied. After 15 minutes of air-drying, the wounds were dressed with a nonadherent dressing next to the wound surface and dry gauze to fill the wound. **Group 2:** Growth factor: rhubFGF (5.0µg/cm²) was topically applied. After 15 minutes of air-drying, the wounds were dressed with a nonadherent dressing next to the wound surface and dry gauze to fill the wound. **Group 3:** Growth factor: rhuGM-CSF/rhubFGF (2.0µg/cm² GM-CSF for 10 days and 5.0µg/cm² bFGF the following 25 days) was topically applied. After 15 minutes of air-drying, the wounds were dressed with a	**Outcome 1:** Proportion of patients completely healed after 1 year **Outcome 1:** Proportion of patients which worsened at 1 year	**Group 1:** 8/14 **Group 2:** 10/14 **Group 3:** 9/13 **Group 4:** 10/13 **Group 1:** 2/14 **Group 2:** 4/14 **Group 3:** 1/13 **Group 4:** 0/13	**Funding:** grant from the National Institutes of Health (ROI-AR42967). Schering-Plough Research Institute and Scios, Inc. provided the cytokines used in this study **Limitations:**; no report on sequence allocation; no report on allocation concealment; no blinding of patient and nurses; missing data were excluded; no a

of assessor reported. **Addressing incomplete outcome data: excluded.** **Statistical analysis: Differences amongst various groups in the time to achieve complete healing during the follow-up phase were** **determined by survival analyses using the Kaplan-Meier method. Significances of differences in time to reach 100% closure was determined by the log-rank and Wilcoxon** ***P* values derived from the Kaplan-Meier method. All survival analyses were done using JMP software (SAS Institute,** **Inc., Cary, NC). Chi-square and Fisher exact analyses were used to compare proportions of various groups of patients healed. All proportion analyses**	**cm³ (SD)):** 32.77 (21.06) **Group 2** **Randomised N:** 15 **Completed N:** 14 **Dropouts:** 1 (lost to follow-up) **Age (mean years (SD)):** 18.8 (11.8) **Ulcer duration (mean months (SD)):** 6.8 (6.1) **Ulcer volume (mean cm³ (SD)):** 33.81 (26.12) **Group 3** **Randomised N:** 16 **Completed N:** 13 **Dropouts:** 3 (died) **Age (mean years (SD)):** 51.3 (11.2) **Ulcer duration (mean months (SD)):** 12.1 (14.6) **Ulcer volume (mean cm³ (SD)):** 38.16 (38.3) **Group 4** **Randomised N:** 15 **Completed N:** 13 **Dropouts:** 2 (1 died	nonadherent dressing next to the wound surface and dry gauze to fill the wound. **Group 4:** Placebo. After 15 minutes of air-drying, the wounds were dressed with a nonadherent dressing next to the wound surface and dry gauze to fill the wound. **All groups:** All ulcers were sharp debrided before application of the dressing as necessary. Initial drug administration was delayed for at least 24 hours after debridement. All patients were kept on pressure-relief surfaces		priory sample size calculation; little information on setting; little information on ulcer assessment; no report on multiple ulcers; PU classification not reported **Additional outcomes:** / **Notes:** This study is a follow-up (1 year) study from the study of Robson (2000). General information on the study are provided in the study by Robson (2000). Outcomes are different and are reported in the study by Payne (2001).

were performed using SigmaStat software (SPSS, Inc., Chicago, IL). **Baseline differences: No statistical difference between groups for age, ethnicity, smoking status, and duration of PU.** **Study power/sample size: No a priory sample size calculation.** **Setting: inpatients.** **Length of study: 35 days of treatment and 1 year of follow-up.** **Assessment of PUs:** **PU classification not reported. Grade III/IV PU were seen as PU involving any tissue from a bony prominence to the subcutaneous tissue.** **The PUs was measured on day 0 and weekly for** **5 weeks. After that they were seen at 3 weeks, 6 weeks, 3 months, 6 months**	and 1 lost to follow-up) **Age (mean years (SD)):** 47.1 (10.8) **Ulcer duration (mean months (SD)):** 13.1 (14.2) **Ulcer volume (mean cm³ (SD)):** 45.19 (34.79) **Inclusion criteria:** Age 28-70 years; PU on truncal area; PU grade III/IV; ulcer duration > 8 weeks; initial ulcer volume 10-200cm³ **Exclusion criteria:** Significant diabetes mellitus, renal insufficiency, vasculitis, or hepatic, immunologic, cardiac, or hemorrhagic disease; Malignant or neoplastic disease, except for adequately treated skin cancers; Significant malnutrition, systemic steroidal therapy, immunotherapy, or chemotherapy; Cytokine therapy within 90 days or investigational drug study within 30 days	

and 1 year. The planimetry was used to determine the ulcer opening and volume using alginate molds. At each follow-up visit the wounds were assesses as to whether they had achieved complete healing, were still less than 100% healed, or had recurred after a time of 100% closure **Multiple ulcers: not reported**					

Table 126 – Payne 2009

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Payne (2009)** **Title: A prospective, randomized clinical trial to assess the cost-effectiveness of a modern foam dressing versus a traditional saline gauze dressing in the treatment of stage II pressure ulcers.** **Journal:**	**Patient group:** Patients 18 years and older with a stage II PU (according to the NPUAP classification). **All patients** **Randomised N:** 36 **Completed N:** 27 **Drop-outs:** 9 (5 died, 1 ulcer infection, 1 abscess unrelated to	**Group 1:** Polyurethane self-adhesive foam dressing (Allevyn® Thin, Smith & Nephew Inc, Largo, FI). Ulcers were cleansed and dried. Ulcers were dressed with the dressing without secondary dressing or fixation. Dressing were changed determined by clinician. **Group 2:** Saline-soaked gauze dressing. Ulcers were	**Outcome 1:** Proportion of patients completely healed **Outcome 2:** Median (days) time to healing (time at which 50% of the patients achieved complete healing)	**Group 1:** 10/20 **Group 2:** 6/16 **Group 1:** 28 **Group 2:** 28	**Funding:** travel grand and funding from Smith & Nephew **Limitations:** no report on sequence allocation; no report on allocation concealment; no report on blinding;

Ostomy/wound management 55(2); 50-55. **Study type: randomized controlled trial** **Sequence generation: not reported.** **Allocation concealment: not reported.** **Blinding: not reported.** **Addressing incomplete outcome data: intention to treat analysis for all analysis except cost-effectiveness.** **Statistical analysis:** **An accelerated failure time model was used to test for differences between groups for time of healing after adjustment for study center, baseline ulcer area, and duration. Kaplan-Meier methods were used to estimate the median time to**	study ulcer, 1 became ineligible, 1 discharged) **Group 1** **Randomised N:** 20 **Completed N:** 14 **Dropouts:** 6 (3 died, 1 ulcer infection, 1 abscess unrelated to study ulcer, 1 became ineligible) **Age (mean years (SD); median years):** 72.5 (14.3); 74.0 **Gender (m/f):** 13/7 **Ulcer duration (mean weeks (SD); median weeks):** 56.1 (219.6); 3.5 **Ulcer area (mean cm² (SD); median cm²):** 5.6 (11.3); 1.8 **Ulcer location:** Hips/buttocks: n=7 Sacrum: n=8 Upper leg: n=1 Ankle/foot: n=4 Lower leg: n=0 **Group 2** **Randomised N:** 16 **Completed N:** 13	cleansed and dried. Ulcers were dressed with the dressing and with a secondary dry sterile gauze pad held in place with tape. Dressing were changed determined by clinician. **All groups:** /		no measurement of statistical difference between groups; no information on use of preventive measures. **Additional outcomes:** cost-effectiveness **Notes:** /

healing. **Baseline differences: No calculation of the statistical difference between groups.** **Study power/sample size: To detect a $10 per week difference in cost of dressing and other materials between groups assuming a standard deviation of $9.80. This was based on a two-sided unpaired t-test at the 5% level of significance and 80% power. A sample size of 19 patients per groups are required.** **Setting: three hospital wards, one outpatient hospital clinic, one long-term residential care, one community care clinic.** **Length of study: four weeks of treatment or until complete healed, whichever came first.** **Assessment of PUs:** **PU were classified according to the NPUAP**	**Dropouts:** 3 (2 died, 1 became ineligible) **Age (mean years (SD); median years):** 73.3 (12.4); 71.5 **Gender (m/f):** 9/7 **Ulcer duration (mean weeks (SD); median weeks):** 7.0 (9.4); 2.0 **Ulcer area (mean cm² (SD); median cm²):** 6.2 (7.2); 1.4 **Ulcer location:** Hips/buttocks: n=7 Sacrum: n=7 Upper leg: n=0 Ankle/foot: n=1 Lower leg: n=1 **Inclusion criteria:** 18 years and older; not pregnant or using contraception; stage II PU with light to moderate exudate. **Exclusion criteria:** Known history of poor compliance; presence of clinical infection in wound; previous participation in the evaluation	

classification. **Ulcers were measured at baseline and weekly using Visitrak (Smith&Nephew Inc. Largo, FL).** **Multiple ulcers: the largest ulcer was included in the study treatment.**					

Table 127 – Rees 1999

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Rees (1999)** **Title: Becaplermin gel in the treatment of pressure ulcers: A phase II randomized, double-blind, placebo-controlled study.** **Journal: Wound Repair and Regeneration, 7; 141-147.** **Study type: randomized controlled trial** **Sequence generation: not**	**Patient group:** Patients 18 years and older with a stage III or IV PU (according to the NPUAP classification). **All patients** **Randomised N:** 124 **Completed N:** unclear if patients with adverse events dropped the study **Drop-outs:** unclear **Group 1** **Randomised N:** 31 **Completed N:** unclear **Dropouts:** unclear	**Group 1:** Becaplermin gel (100 µg/g recombinant human PDGF-BB) (Regranex®) applied once daily alternated with placebo every 12 hours. A thin layer of study drug was placed on the entire ulcer and the ulcer was packed with saline-moistened gauze. The second daily dressing was applied in a similar fashion after gently rinsing the wound surface with saline or water. **Group 2:** Becaplermin gel (300 µg/g recombinant human PDGF-BB) (Regranex®) applied once daily alternated with placebo	**Outcome 1:** Proportion of patients completely healed **Outcome 2:** Proportion of patients healed ≥ 90% **Outcome 3:** Median percentage (range) reduction	**Group 1:** 7/31 **Group 2:** 6/32 **Group 3:** 1/30 **Group 4:** 0/31 **P value G1 vs G4:** 0.005 **P value G2 vs G4:** 0.008 **Group 1:** 18/31 **Group 2:** 19/32 **Group 3:** 12/30 **Group 4:** 9/31 **P value G1 vs G4:** 0.021 **P value G2 vs G4:** 0.014 **Group 1:** 99.6 **Group 2:** 99.7	**Funding:** sponsored by Office of Research and Development, Department of Veterans Affairs, Ann Arbor, MI. Funding from Johnson & Johnson, Inc.. **Limitations:** no report on sequence allocation; no report on allocation concealment; insufficient

reported. **Allocation concealment: not reported.** **Blinding: double blind; no further information.** **Addressing incomplete outcome data: intention to treat analysis.** **Statistical analysis:** **The primary endpoint, incidence of complete healing, was analyzed using the Cochran-Mantel Haenszel test, which evaluated the association between the response variable and treatments, while adjusting for the effects of study center. Because the incidence of complete healing in the control group was 0, the incidence of and time to 90% ulcer closure were also analyzed. The incidence of 90% closure was analyzed using the Cochran-**	**Age (mean years (SD)):** 48 (13.1) **Gender (m/f):** 26/5 **Ulcer duration (median weeks (IQR)):** 22 (32) **Ulcer volume (median ml (IQR)):** 16.6 (15.1) **Group 2** **Randomised N:** 32 **Completed N:** unclear **Dropouts:** unclear **Age (mean years (SD)):** 49 (12.5) **Gender (m/f):** 27/5 **Ulcer duration (median weeks (IQR)):** 33 (40) **Ulcer volume (median ml (IQR)):** 17.2 (19.7) **Group 3** **Randomised N:** 30 **Completed N:** unclear **Dropouts:** unclear **Age (mean years (SD)):** 51 (18.3) **Gender (m/f):** 26/4 **Ulcer duration (median weeks (IQR)):** 22 (52) **Ulcer volume (median ml (IQR)):** 17.6 (33.8)	every 12 hours. A thin layer of study drug was placed on the entire ulcer and the ulcer was packed with saline-moistened gauze. The second daily dressing was applied in a similar fashion after gently rinsing the wound surface with saline or water. **Group 3:** Becaplermin gel (100 µg/g recombinant human PDGF-BB) (Regranex®) applied twice daily. A thin layer of study drug was placed on the entire ulcer and the ulcer was packed with saline-moistened gauze. The second daily dressing was applied in a similar fashion after gently rinsing the wound surface with saline or water. **Group 4:** Placebo twice daily. **All groups:** Ulcers were debrided prior to randomization and when necessary.	in ulcer volume **Outcome 4:** Proportion of patients with non-treatment related adverse events **Outcome 5:** Proportion of patients with condition aggravated **Outcome 6:** Proportion of patients with osteomyelitis **Outcome 7:** Proportion of patients with infection **Outcome 8:** Proportion of patients with sepsis **Outcome 9:** Proportion of patients with other adverse events	**Group 3:** 98.6 **Group 4:** 99.1 **P value G1 vs G4:** 0.013 **P value G2 vs G4:** 0.011 **Group 1:** 2/31 **Group 2:** 6/32 **Group 3:** 9/30 **Group 4:** 4/31 **Group 1:** 0/31 **Group 2:** 1/32 **Group 3:** 1/30 **Group 4:** 0/31 **Group 1:** 2/31 **Group 2:** 1/32 **Group 3:** 0/30 **Group 4:** 1/31 **Group 1:** 0/31 **Group 2:** 0/32 **Group 3:** 1/30 **Group 4:** 1/31 **Group 1:** 0/31 **Group 2:** 1/32 **Group 3:** 0/30	information on blinding; no a priory sample size calculation; drop-out unclear; no measurement of statistical difference between groups; no information on setting; no information on use of preventive measures. **Additional outcomes:** / **Notes:** /

Mantel Haenszel test, and the significance of differences in time to 90% closure was assessed using the Cox proportional hazards model with baseline ulcer volume as a covariate. **The relative ulcer volume, defined as the ulcer volume at the end of the study divided by the ulcer volume at baseline, was analyzed using an analysis of covariance** **model with terms for treatment effect, center effect, and baseline ulcer volume effect, with tests for** **the relevant interactions. All hypotheses regarding interactions were tested at a significance level of 0.10.** **All hypotheses regarding comparisons of the**	**Group 4** **Randomised N:** 31 **Completed N:** unclear **Dropouts:** unclear **Age (mean years (SD)):** 50 (13.6) **Gender (m/f):** 25/6 **Ulcer duration (median weeks (IQR)):** 30 (43) **Ulcer volume (median ml (IQR)):** 19.6 (21.9) **Inclusion criteria:** Age > 18 years; having between one and three chronic full thickness (stage III or IV) Pus; target ulcer was the ulcer with the longest time to heal; primary or recurrent PU not involving the bone tissue; ulcer with a volume between 10ml and 150ml, following debridement at baseline; ulcer present for at least 4 weeks; ulcer located where pressure could be off-loaded; albumin concentration > 2.5g/dl, total lymphocyte count > 1000; normal range for vitamin A and C.	**Group 4:** 0/31 **Group 1:** 2/31 **Group 2:** 3/32 **Group 3:** 2/30 **Group 4:** 2/31

active treatment to the vehicle control were 2-sided, performed at the 0.05 level of significance. To ascertain the dose–response relationship, the Cochran-Armitage trend test was used for complete and 90% **wound closure parameters. The trend test was one-sided** **at the 0.025 level against the alternative of a linearly increasing dose-response.** **Baseline differences: No calculation of the statistical difference only calculated. Groups were comparable.** **Study power/sample size: No a priory sample size calculation.** **Setting: not reported.** **Length of study: 16 weeks of treatment or until complete**	**Exclusion criteria:** Osteomyelitis affecting the area of the target ulcer was present; after debridement, a target ulcer volume (measured by Jeltrate mold) of < 10 ml or > 150 ml; topical antibiotics, antiseptics, enzymatic debriding agents, or other agents that would interfere with study evaluations had been used within the 7 days preceding randomization; patients with ulcers resulting from electrical, chemical, or radiation insult; patients with cancer; concomitant diseases (e.g., connective tissue disease); treatment (e.g., radiation therapy); medication (e.g., corticosteroids, chemotherapy, or immunosuppressive agents); pregnant, nursing, childbearing potential woman, not using acceptable method of birth control.				

healed, whichever came first.. **Assessment of PUs:** **PU were classified according to the NPUAP classification (1989).** **Ulcers were assessed for complete healing (completely healed or < completely** **healed, scored as 1 or 2, respectively).** **Ulcer volume was measured (determined by Jeltrate mold) and ulcer area was measured (determined by planimetric analyses of acetate tracings).** **Multiple ulcers: target ulcer was the ulcer needing the longest tile to heal.**					

Table 128 – Rhodes 2001

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Rhodes (2001)** **Title: Topical**	**Patient group:** Nursing home patients with a stage II PU (according	**Group 1:** Phenytoin. Ulcers were cleansed with NaCl 0.9% and hydroxide, dried,	**Outcome 1:** Mean time (days; range) to healing	**Group 1:** 35.3 (14.3); 15-64 **Group 2:** 51.8 (19.6); 27-90 **Group 3:** 53.8 (8.5); 42-67	**Funding:** / **Limitations:**; no

phenytoin treatment of stage II decubitus ulcers in the elderly. **Journal: The Annals of Pharmacotherapy, 35 (6); 675-681.** **Study type: randomized controlled trial** **Sequence generation: Patients were matched for age, gender, size and severity of the ulcers and were placed in one of the three groups based on the treatment preference of the randomly assigned physician prescribing the treatment plan.** **Allocation concealment: not reported** **Blinding: not reported.** **Addressing incomplete outcome data: drop-outs were excluded.** **Statistical analysis: Statistical analysis included the Levine**	to the AHCPR classification). **All patients** **Randomised N:** 47 **Completed N:** 39 **Drop-outs:** 8 (1 continually recurrent ulcers, 5 died, 2 were discharged) **Group 1** **Randomised N:** 18 **Completed N:** 15 **Dropouts:** 3 (1 continually recurrent ulcers, 2 died) **Age (mean years):** 75.5 **Gender (m/f):** 16/2 **Group 2** **Randomised N:** 16 **Completed N:** 13 **Dropouts:** 3 (2 died, 1 was discharged) **Age (mean years):** 78.7 **Gender (m/f):** 15/1 **Group 3** **Randomised N:** 13 **Completed N:** 11	and covered with 100mg phenytoin suspension daily. A sterile gauze was soaked in the suspension and placed on the ulcer, followed by a layer of dry sterile gauze. Phenytoin suspension: a single 100 mg phenytoin cup containing 5ml of sterile NaCl 0.9% to form a suspension. **Group 2:** Hydrocolloid dressing (DuoDerm®). Ulcers were cleansed with NaCl 0.9% and hydroxide, dried, and covered with dressing with the edges extending 1¼ inch beyond the wound. The dressing was changed every seven days or when it became uncomfortable, leaked, or the presence of infection signs. **Group 3:** Triple antibiotic ointment. Ulcers were cleansed with NaCl 0.9% and hydroxide, dried, and covered with a layer of TAO. Followed a sterile gauze was applied as cover. The dressing was changed every day. **All groups:** All ulcers were surgically debrided as necessary. All patients received preventive	**Outcome 2:** Proportion of patients with treatment related adverse events **Outcome 2:** Proportion of patients pain	**P-value G1 vs G2:** 0.020 **P-value G1 vs G3:** 0.011 **Group 1:** 0/15 **Group 2:** 0/13 **Group 3:** 0/11 Minimal pain was reported in all groups	report on sequence allocation; no report on allocation concealment; no report on blinding; no ITT analysis; no a priory sample size calculation; small sample size; little information on setting; little information on statistical analysis; no report on multiple ulcers **Additional outcomes:** / **Notes:** Hydrocolloid dressings was defined as a collagen dressing in this article

test for homogeneity of variance, anova, and a post hoc Bonferroni adjustment for multiple pairs. **Baseline differences: Difference was not statistically different.** **Study power/sample size: No a priory sample size calculation.** **Setting: veteran administration nursing home.** **Length of study: not reported** **Assessment of PUs:** **PU were classified according to the Agency Health Care Research and Quality's Pressure Ulcer Guideline Panel classification (1992).** **Ulcers were measured with a MediRule, which was centred over the area to be measured. This transparent, disposable ruler consists of concentric circles**	**Dropouts:** 2 (1 died, 1 was discharged) **Age (mean years):** 76.5 **Gender (m/f):** 12/1 **Inclusion criteria:** Age > 60 years; stage II PU **Exclusion criteria:** signs and symptoms of ulcer infection; anaemia; malnutrition; folate deficiency; chronic use of immunosuppressive treatment; immobility; those receiving oral phenytoin; history of adverse events caused by phenytoin.	measures such as maximum mobilisation, adequate nutrition and hydration, and incontinence care.

measured in centimetres around a cross hair ruled in millimetres. Photographs using a Polaroid Spectra AF were taken once weekly. Two light beams were placed at eight inches from the object. **Multiple ulcers: not reported**					

Table 129 – Robson 1992a

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Robson (1992a)** **Title: The safety and effect of topically applied recombinant basic fibroblast growth factor on the healing of chronic pressure sores.** **Journal: Annals of surgery, 216 (4); 401-406.** **Study type: randomized controlled trial** **Sequence**	**Patient group:** Hospitalized patients denervated in the ulcer area (congenital or acquired spinal cord pathology) with a grade III or IV PU. **All patients** **Randomised N:** 50 **Completed N:** 49 **Drop-outs:** 1 (removed due to suspicion of cancer) **Group 1**	**Group 1:** Growth factor: bFGF (1.0µg/cm^2) Administration schedule were: (1) 1.0 µg/cm^2 bFGF administered on days 1 and 13. Placebo on day 4, 7 and 10. No treatment on day 16, 19, and 22. (2) 1.0 µg/cm^2 bFGF administered on days 1, 4, 7, 10, and 13. No treatment on day 16, 19, and 22. (3) 1.0 µg/cm^2 bFGF administered on days 1, 4, 7, 10, 13, 16, 19, and 22. (4) 10.0 µg/cm^2 bFGF	**Outcome 1:** Change in volume (cc) (regression curve) **Outcome 2:** Mean percentage decrease in volume **Outcome 3:** Proportion of patients >70% decrease in 30 days	**Group 1:** / **Group 2:** / **P value:** <0.05 **Group 1:** 69 **Group 2:** 59 **Group 1:** 21/35 **Group 2:** 4/14 **P value:** 0.047	**Funding:** grant from California Biotechnology, Inc. **Limitations:**; no report on sequence allocation; inadequate allocation; no blinding of patient and nurses; missing data were excluded; no a priory sample size calculation; no information on

generation: not reported. **Allocation concealment: not reported; unequal allocation to different schedules.** **Blinding: blinding of observer.** **Addressing incomplete outcome data: not reported.** **Statistical analysis: Descriptive statistics were computed for demographic** **characteristics such as age, gender, ethnicity, and pressure sore duration. The patients' ages and sore durations were** **compared using the Wilcoxon two-sample test, whereas gender and ethnicity were compared using the Fisher's exact test. Both parametric and nonparametric analyses were used** **to determine efficacy of bFGF, depending on the apparent normality of the data.**	**Randomised N:** 35 **Completed N:** 35 **Dropouts:** 0 **Age (mean years (SD)):** 37.8 (13.2) **Gender (m/f):** 30/5 **Ulcer duration (mean months (SD)):** 17.7 (21.6) **Group 2** **Randomised N:** 15 **Completed N:** 14 **Dropouts:** 1 (removed due to suspicion of cancer) **Age (mean years (SD)):** 37.9 (12.8) **Ulcer duration (mean months (SD)):** 25.9 (46.3) **Inclusion criteria:** Age 28-65 years; initial ulcer volume 10-200cm³ measured by alginate mold; hospitalized; mechanical debridement (at least 24 hours before initiation of treatment); normal or clinically insignificant laboratory findings.	administered on days 1 and 13. Placebo on day 4, 7 and 10. No treatment on day 16, 19, and 22. (5) 10.0 µg/cm^2 bFGF administered on days 1, 4, 7, 10, and 13. No treatment on day 16, 19, and 22. (6) 10.0 µg/cm^2 bFGF administered on days 1, 4, 7, 10, 13, 16, 19, and 22. (7) 5.0 µg/cm^2 bFGF administered daily for 21 days. (8) 5.0 µg/cm^2 administered on days 1-5, 7, 14, and 21. **Group 2:** Placebo Administration schedule were: (1) placebo on days 1, 4, 7, 10, and 13. (2) placebo daily for 21 days. (3) placebo on days 1-5, 7, 14, and 21. **All groups:** All ulcers were sharp debrided before application of the dressing as necessary. Initial drug administration was delayed for at least 24 hours after debridement. Pressure-relieving devices were used as appropriate.		setting; no report on multiple ulcers; PU classification not reported **Additional outcomes:** / **Notes:** /

Percentage decrease in volume over 30 days was compared in each bFGF dosage regimen patient group with the placebo-treated patients, using analysis of variance. To assess for response rate relationships to initial pressure sore size, actual decrease in volume was compared with initial wound size and regression analyses were performed. The slopes of the regression curves then were compared with the F test. **Because previous trials with the pressure sore model used in this study showed a placebo response of up to 50% decrease in volume, and a topical antimicrobial response** **of 60% reduction over a 4-week period,'4 an arbitrary response rate of 70%**	**Exclusion criteria:** Arterial or venous disorder, or vasculitis as cause for ulcerated wound; clinically significant systemic disease; significant malnutrition; recent use of steroidal therapy; penicillin allergy	Patients not on air-fluidized beds were repositioned rigorously at 2-hour intervals throughout the treatment period.

wound closure over 30 days was chosen as indicative of a responder. Categorical responders by this definition were compared between bFGF treated patients and placebo-treated patients using analysis of variance. Baseline differences: No statistical difference between groups. Study power/sample size: No a priory sample size calculation. Setting: not reported. Length of study: 30 days of treatment and 5 months of follow up. Assessment of PUs: PU classification not reported. Grade III/IV PU were seen as PU extending from the bone to the subcutaneous tissue.							

The PUs was measured on day 0, 8, 16, 23 and 30 using planimetry; maximum perpendicular diameters of the surface opening and maximum depth of the crater; volume determination using alginate molds; color photography of the ulcer at a set focal distance; quantitative and qualitative microbiology of wound tissue biopsies; and histologic analyses of wound tissue. **Multiple ulcers: not reported**					

Table 130 – Robson 1992b

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Robson (1992b)** **Title: Recombinant human platelet-derived growth factor-BB for the**	**Patient group:** Hospitalized patients denervated in the ulcer area (congenital or acquired spinal cord pathology) with a grade III or IV PU.	**Group 1:** Growth factor: rPDGF-BB (1.0 µg/ml). Wound were cleansed with saline and then bottled dry with sterile gauze, before application of the GF. After application the wound was	**Outcome 1:** Mean percentage (SEM) change in ulcer depth at day 29	**Group 1:** not reported; figure unclear **Group 2:** not reported; figure unclear **Group 3:** 85.9 (7.4) **Group 4:** 65.1 (6.7)	**Funding:** / **Limitations:**; no report on sequence allocation;

treatment of chronic pressure ulcers. **Journal: Annals of Plastic Surgery, 29 (3); 193-201.** **Study type: randomized controlled trial** **Sequence generation: not reported; unequal allocation to different schedules.** **Allocation concealment: not reported** **Blinding: blinding of patients and investigator** **Addressing incomplete outcome data: no drop out.** **Statistical analysis: The primary endpoints were evaluated as a percentage of initial wound size to adjust for differences in baseline ulcer sizes. A two-way analysis of variance with repeated measures was performed to	**All patients** **Randomised N:** 20 **Completed N:** 20 **Drop-outs:** 0 **Group 1** **Randomised N:** 4 **Completed N:** 4 **Dropouts:** 0 **Age (mean years (SD); range):** 37.8 (13.2); 21-56 **Ulcer duration (mean months (SD); range):** 11.6 (5.5); 3-27 **Ulcer depth (mean cm (SD); range):** 1.7 (0.5); 0.5-2.7 **Ulcer volume (mean cm³ (SD); range):** 13.8 (4.8); 5-26 **Group 2** **Randomised N:** 4 **Completed N:** 4 **Dropouts:** 0 **Age (mean years (SD); range):** 43 (5); 32-54 **Ulcer duration (mean months (SD); range):** 16.0 (7.1); 4-36	left open for 15 minutes to permit absorption of the GF. The ulcer crater was packed with fresh sterile gauze and sealed closed with Biobrane attached to the healthy surface of the wound margins. **Group 2:** Growth factor: rPDGF-BB (10.0 µg/ml). Wound were cleansed with saline and then bottled dry with sterile gauze, before application of the GF. After application the wound was left open for 15 minutes to permit absorption of the GF. The ulcer crater was packed with fresh sterile gauze and sealed closed with Biobrane attached to the healthy surface of the wound margins. **Group 3:** Growth factor: rPDGF-BB (100.0 µg/ml). Wound were cleansed with saline and then bottled dry with sterile gauze, before application of the GF. After application the wound was left open for 15 minutes to permit absorption of the GF. The ulcer crater was packed with fresh sterile gauze and sealed closed with Biobrane attached to the healthy surface of the wound	**Outcome 2:** Mean percentage (SEM) change in ulcer volume at day 29 **Outcome 3:** Proportion of patients with invasive infections **Outcome 3:** Proportion of patients completely healed	**Group 1:** not reported; figure unclear **Group 2:** not reported; figure unclear **Group 3:** 93.6 (4.0) **Group 4:** 78.2 (5.6) **P value:** 0.16 **Group 1:** 0/4 **Group 2:** 0/4 **Group 3:** 0/5 **Group 4:** 0/7 **Group 1:** 0/4 **Group 2:** 0/4 **Group 3:** 2/5 **Group 4:** 0/7	inadequate allocation; no blinding of nurses; no a priory sample size calculation; small sample size; no information on setting; no report on multiple ulcers; PU classification not reported **Additional outcomes:** / **Notes:** /

compare healing among treatment groups over time. Significant anova effects were further analyzed using the Tukey-Kramer multiple comparisons procedure (alpha 0.05, two tailed). **Baseline differences: No statistical difference between groups.** **Study power/sample size: No a priory sample size calculation.** **Setting: hospital.** **Length of study: 4 weeks of treatment and 5 months of follow-up.** **Assessment of PUs:** **PU classification not reported. Grade III/IV PU were seen as PU trough the subcutaneous tissue.** **Measurements of PU were perfomed on days 0, 7, 14, 21, and 29 using (1) maximum perpendicalr**	**Ulcer depth (mean cm (SD); range):** 1.6 (0.6); 0.8-3.5 **Ulcer volume (mean cm³ (SD); range):** 15.8 (4.0); 9-28 **Group 3** **Randomised N:** 5 **Completed N:** 5 **Dropouts:** 0 **Age (mean years (SD); range):** 29 (4); 21-45 **Ulcer duration (mean months (SD); range):** 17.3 (12.4); 4-67 **Ulcer depth (mean cm (SD); range):** 2.8 (1.0); 1.6-6.8 **Ulcer volume (mean cm³ (SD); range):** 11.6 (5.5); 4-33 **Group 4** **Randomised N:** 7 **Completed N:** 7 **Dropouts:** 0 **Age (mean years (SD); range):** 27 (2); 22-35 **Ulcer duration (mean months (SD); range):** 14.2 (6.2); 1-37 **Ulcer depth (mean cm**	margins. **Group 4:** Placebo. **All groups:** All ulcers were sharp debrided if necessary. Initial drug administration was delayed for at least 24 hours after debridement. Pressure-relieving devices were used as appropriate. Patients were repositioned rigorously at 2-hour intervals throughout the treatment period.	

diameters of the surface and maximum depth of the crater (Kudin wound gauge), (2) volume determination using alginate mold weight, and volumetric displacement, and (3) color photography of the ulcer at a set focal distance. The ulcer area opening was quantitated from the tracing using a macrolens and digitized planimetry. **Multiple ulcers: not reported**	**(SD); range):** 2.8 (0.4); 1.5-5.2 **Ulcer volume (mean cm³ (SD); range):** 12.9 (3.8); 5-33 **Inclusion criteria:** PU surface area between 25 and 95 cm² if grade III or IV); no past/present malignancy; mechanical debridement of necrotic tissue at least 2 days before initiation of treatment; normal or clinically insignificant laboratory results **Exclusion criteria:** Arterial or venous disorder cause for ulcerated wound; clinically significant systemic disease; significant malnutrition; recent use of steroidal therapy, immunotherapy or cytotoxic chemotherapy	

Table 131 – Robson 1994

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Robson (1994)** **Title: Safety and effect of topical recombinant human interleukin-1 beta in the management of pressure sores.** **Journal: Wound Repair and Regeneration, 2; 177-181.** **Study type: randomized controlled trial** **Sequence generation: not reported** **Allocation concealment: not reported** **Blinding: double blinding; no further information** **Addressing incomplete outcome data: two patients were excluded.** **Statistical analysis:**	**Patient group:** Hospitalized patients denervated in the ulcer area (congenital or acquired spinal cord pathology) with a grade III or IV PU. **All patients** **Randomised N:** 24 **Completed N:** 22 **Drop-outs:** 2 (1 was discharge, 1 had osteomyelitis) **Group 1** **Randomised N:** 6 **Completed N:** 5 **Dropouts:** 1 (discharged) **Group 2** **Randomised N:** 6 **Completed N:** 6 **Dropouts:** 0 **Group 3** **Randomised N:** 6	**Group 1:** Topical recombinant human IL-1β (0.01 µg/cm^2/day – 1.0 µg/ml). Wound were cleansed with normal saline and then bottled spray with the IL-1β. After application the wound was left open for 20 minutes to permit absorption of the GF. Then a saline solution-moistened gauze dressing was applied. The gauze dressing was changed 12 hours later. **Group 2:** Topical recombinant human IL-1β (0.1 µg/cm^2/day – 10.0 µg/ml). Wound were cleansed with normal saline and then bottled spray with the IL-1β. After application the wound was left open for 20 minutes to permit absorption of the GF. Then a saline solution-moistened gauze dressing was applied. The gauze dressing was changed 12 hours later. **Group 3:** Topical recombinant human IL-1β (1.0 µg/cm^2/day – 100.0 µg/ml). Wound were	**Outcome 1:** Proportion of patients completely healed **Outcome 2:** Percentage reduction in wound size at 29 days	**Group 1:** 0/6 **Group 2:** 0/6 **Group 3:** 0/6 **Group 4:** 0/6 **Group 1:** not reported; figure unclear **Group 2:** not reported; figure unclear **Group 3:** not reported; figure unclear **Group 4:** not reported; figure unclear	**Funding:** Grant from Immunex Corportation, Seattle Wahsington **Limitations:**; no report on sequence allocation; no report on allocation concealment; no information on blinding; no a priory sample size calculation; small sample size; no information on setting; no report on multiple ulcers; PU classification not reported **Additional outcomes:** / **Notes:** /

The Cochrane-Mantel Haenszel to compare baseline difference between groups. Percentage of change between the groups was compared by means of an analysis of variance model with factors for the group only and adjusted for percentage change. **Baseline differences: No statistical difference between groups.** **Study power/sample size: No a priory sample size calculation.** **Setting: hospital.** **Length of study: 28 days of treatment and 3 months of follow-up.** **Assessment of PUs:** **PU classification not reported. Grade III/IV PU were seen as PU from the bone to the subcutaneous tissue.** **Measurements of PU were performed on days 0, 7, 14, 29, and 1 and 3 months after**	**Completed N:** 5 **Dropouts:** 1 (osteomyelitis) **Group 4** **Randomised N:** 5 **Completed N:** 5 **Dropouts:** 0 **Inclusion criteria:** Men, non-pregnant, non-lactating women; 18 years and older; 28 days of hospitalization; wound volume ranging from 10 to 100 cm^3 or to the bone prominence; PU located on the sacrum, ischium or trochanter; PU stage III or IV. **Exclusion criteria:** Arterial or venous disorder cause for ulcerated wound; significant endocrine disease such as diabetes mellitus; systemic sepsis from the PU; lack of cooperation or unsuitability; inability o provide informed consent; whirlpool therapy requirements; testing positive for HIV;	cleansed with normal saline and then bottled spray with the IL-1β. After application the wound was left open for 20 minutes to permit absorption of the GF. Then a saline solution-moistened gauze dressing was applied. The gauze dressing was changed 12 hours later. **Group 4:** Placebo **All groups:** All ulcers were sharp debrided before application of the dressing as necessary. Initial drug administration was delayed for at least 24 hours after debridement. Pressure-relieving devices were used as appropriate. Patients not on air-fluidized beds were repositioned rigorously at 2-hour Intervals.	

drug application using (1) color photography of the ulcer at a set focal distance, (2) maximum length, width and depth crater diameter, (3) planimetry of the ulcer opening, and (4) volume determination **Multiple ulcers: not reported**	use of investigational drugs within 1 month before study entry; treatment of the target ulcer with cytokines within 3 months before study entry.				

Table 132 – Robson 2000

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Robson (2000)** **Title: Sequential cytokine therapy for pressure ulcers: Clinical and mechanistic response.** **Journal: Annals of surgery, 231 (4); 600-611.** **Study type: randomized controlled trial** **Sequence**	**Patient group:** Inpatients with a grade III or IV PU. **All patients** **Randomised N:** 61 **Completed N:** 61 **Drop-outs:** 0 **Group 1** **Randomised N:** 15 **Completed N:** 15 **Dropouts:** 0 **Age (mean years range):** 18.8 (11.8)	**Group 1:** Growth factor: rhuGM-CSF (2.0µg/cm²) was topically applied. After 15 minutes of air-drying, the wounds were dressed with a nonadherent dressing next to the wound surface and dry gauze to fill the wound. **Group 2:** Growth factor: rhubFGF (5.0µg/cm²) was topically applied. After 15 minutes of air-drying, the wounds were dressed with a nonadherent dressing next to the wound surface and dry gauze to fill the wound. **Group 3:** Growth factor:	**Outcome 1:** Mean percentage wound closure on day 36 **Outcome 2:** Median (range) percentage wound closure on day 36	**Group 1:** 67 (24) **Group 2:** 75 (19) **Group 3:** 68 (21) **Group 4:** 71 (11) **Group 1:** 70 (3-93) **Group 2:** 79 (42-99) **Group 3:** 73 (29-98) **Group 4:** 72 (39-84) **P-value:** 0.69	**Funding:** grant from the National Institutes of Health (ROI-AR42967). Schering-Plough Research Institute and Scios, Inc. provided the cytokines used in this study **Limitations:**; no report on sequence allocation; no report on

generation: not reported. **Allocation concealment: not reported** **Blinding: double blind, only blinding of assessor reported.** **Addressing incomplete outcome data: excluded.** **Statistical analysis: Descriptive statistics were computed for demographic** **characteristics such as age, ethnicity, smoking status, and pressure ulceration duration. The patients' ages and ulcer duration were compared by analysis of variance, whereas** **ethnicity and smoking status were compared using chi-square** **analysis (Sigma Stat 2.03, SPSS, Chicago, IL). Both parametric and nonparametric analyses were used to determine the efficacy of GM-CSF**	**Ulcer duration (mean months (SD)):** 6.8 (6.1) **Ulcer volume (mean cm³ (SD)):** 32.77 (21.06) **Group 2** **Randomised N:** 15 **Completed N:** 15 **Dropouts:** 0 **Age (mean years range):** 18.8 (11.8) **Ulcer duration (mean months (SD)):** 6.8 (6.1) **Ulcer volume (mean cm³ (SD)):** 33.81 (26.12) **Group 3** **Randomised N:** 16 **Completed N:** 16 **Dropouts:** 0 **Age (mean years range):** 51.3 (11.2) **Ulcer duration (mean months (SD)):** 12.1 (14.6) **Ulcer volume (mean cm³ (SD)):** 38.16 (38.3) **Group 4** **Randomised N:** 15	rhuGM-CSF/rhubFGF (2.0μg/cm² GM-CSF for 10 days and 5.0μg/cm² bFGF the following 25 days) was topically applied. After 15 minutes of air-drying, the wounds were dressed with a nonadherent dressing next to the wound surface and dry gauze to fill the wound. **Group 4:** Placebo. After 15 minutes of air-drying, the wounds were dressed with a nonadherent dressing next to the wound surface and dry gauze to fill the wound. **All groups:** All ulcers were sharp debrided before application of the dressing as necessary. Initial drug administration was delayed for at least 24 hours after debridement. All patients were kept on pressure-relief surfaces	allocation concealment; no blinding of patient and nurses; missing data were excluded; no a priory sample size calculation; little information on setting; little information on ulcer assessment; no report on multiple ulcers; PU classification not reported **Additional outcomes:** cost: G1: $2200, G2: $800 to $1000; G3: $1700, G4: $3000 **Notes:** /

treatment alone, bFGF treatment alone, or sequential GM-CSF/bFGF treatment, depending on the apparent normality of the data. The percentage decrease in volume during the 35 days was compared among patient groups using the Kruskal-Wallis method of analysis of variance on ranks (Sigma Stat). Patients achieving various percentages of healing versus time were compared across treatment groups by Kaplan-Meier survival analysis (JMP software, SAS, Cary, NC). All data obtained longitudinally on ulcer measurements, cytokine levels and changes, and fibroblast activity in FPCLs were evaluated for	**Completed N:** 15 **Dropouts:** 0 **Age (mean years range):** 47.1 (10.8) **Ulcer duration (mean months (SD)):** 13.1 (14.2) **Ulcer volume (mean cm³ (SD)):** 45.19 (34.79) **Inclusion criteria:** Age 28-70 years; PU on truncal area; PU grade III/IV; ulcer duration > 8 weeks; initial ulcer volume 10-200cm³ **Exclusion criteria:** Significant diabetes mellitus, renal insufficiency, vasculitis, or hepatic, immunologic, cardiac, or hemorrhagic disease; Malignant or neoplastic disease, except for adequately treated skin cancers; Significant malnutrition, systemic steroidal therapy, immunotherapy, or chemotherapy; Cytokine therapy within 90 days or investigational drug study within 30 days	

possible correlations using the Spearman rank order correlation (Sigma Stat). With this test, pairs of variables with positive correlation coefficients and *p* values , 0.05 tend to increase together. For pairs with negative correlation coefficients and *p* values , 0.05, one variable tends to decrease while the other increases. Baseline differences: No statistical difference between groups for age, ethnicity, smoking status, and duration of PU. Study power/sample size: No a priory sample size calculation. Setting: inpatients. Length of study: 35 days of treatment. Assessment of PUs: PU classification not reported. Grade III/IV PU were seen as PU					

involving any tissue from a bony prominence to the subcutaneous tissue. The PUs was measured on day 0 and weekly for 5 weeks. After that they were seen at 3 weeks, 6 weeks, 3 months, 6 months and 1 year. The planimetry was used to determine the ulcer opening and volume using alginate molds. At each follow-up visit the wounds were assesses as to whether they had achieved complete healing, were still less than 100% healed, or had recurred after a time of 100% closure Multiple ulcers: not reported	

Table 133 – Shamimi 2008

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Shamimi (2008)** **Title: Topical application of Semelil (ANGIPARS™) in treatment of pressure ulcers: a randomized clinical trial.** **Journal: DARU, 16 (Supplement 1); 54-57.** **Study type: randomized controlled trial** **Sequence generation: not reported** **Allocation concealment: not reported** **Blinding: not reported.** **Addressing incomplete outcome data: no drop-outs** **Statistical analysis: not reported.**	**Patient group:** Hospitalized patients with a PU. **All patients** **Randomised N:** 18 **Completed N:** 18 **Drop-outs:** 0 **Group 1** **Randomised N:** 9 **Completed N:** 9 **Dropouts:** 0 **Age (mean years (SD)):** 47.9 (21.2) **Gender (m/f):** 7/2 **Ulcer area (mean cm² (SD)):** 56.1 (93.3) **Number of ulcers (mean number (SD)):** 1.2 (0.4) **Group 2** **Randomised N:** 9 **Completed N:** 9 **Dropouts:** 0 **Age (mean years (SD)):** 46.0 (22.7)	**Group 1:** Naïve herbal extract (Semelil (Angipars™). 3% gel daily. **Group 2:** conventional treatment **Both groups:** Debridement if necessary	**Outcome 1:** Mean cm² decrease in ulcer area **Outcome 2:** Mean rate of healing (%) **Outcome 4:** Proportion of patients healed > 80% **Outcome 5:** Proportion of patients healed 50-80% **Outcome 6:** Proportion of patients healed 20-50% **Outcome 7:** Proportion of patients healed < 20% **Outcome 8:**	**Group 1:** 48.2 (85.3) **Group 2:** 2.8 (6.2) **P-value:** 0.000 **Group 1:** 78.3 (12.5) **Group 2:** 6.3 (22.7) **P-value:** 0.000 **Group 1:** 6/9 **Group 2:** 0/9 **Group 1:** 3/9 **Group 2:** 1/9 **Group 1:** 0/9 **Group 2:** 0/9 **Group 1:** 0/9 **Group 2:** 8/9	**Funding:** / **Limitations:** no report on sequence generation; no report on allocation concealment; no report on blinding; no a priory sample size calculation; no report on PU classification; little information on intervention and comparison **Additional outcomes:** / **Notes:** /

Baseline differences: No statistical difference between groups. **Study power/sample size: No a priory sample size calculation.** **Setting: Vali-e-Asr hospital, Medical Sciences/University of Tehran (Iran)** **Length of study: two months** **Assessment of PUs:** **PU classification not reported.** **Ulcers were photographed and measured to assess the ulcer diameter, steadiness or regression per 2 weeks till 2 months.** **Multiple ulcers: patients had a mean number of ulcers of 1.2 (0.4) for G1 and 1.2 (0.7) for G2**	**Gender (m/f):** 7/2 **Ulcer area (mean cm² (SD)):** 19.5 (16.1) **Number of ulcers (mean number (SD)):** 1.2 (0.7) **Inclusion criteria:** > 18 years; PU resulting from spinal complications, amputation of the lower limbs, chronic diseases like brain vessel disorders or factures due to osteoporosis; ulcer size > 1cm²; occurred within the last 2 weeks **Exclusion criteria:** acute infection of ulcer; ulcer with bone exposure; disease or situation that impairs ulcer improvement; alcohol or drug abuse; dialysis and renal failure; corticosteroid consumption; use of immune suppressive agents; radiotherapy or chemotherapy; any known drug hypersensitivity	Proportion of patients with adverse events	**Group 1:** 0/9 **Group 2:** 0/9

Table 134 – Sipponen 2008

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Sipponen (2008)** **Title: Beneficial effect of resin salve in treatment of severe pressure ulcers: A prospective, randomized and controlled multicentre trial.** **Journal: British Journal of Dermatology, 158 (5); 1055-1062.** **Study type: randomized controlled trial** **Sequence generation: permuted block sizes of four according to a random list designed by a specialist in biometrics.** **Allocation concealment: closed envelopes** **Blinding: no blinding**	**Patient group:** Hospitalized patients with a grade II to IV PU (according to the EPUAP). **All patients** **Randomised N:** 37 patients and 45 ulcers **Completed N:** 22 patients and 29 ulcers **Drop-outs:** 15 patients and 16 ulcers (7 deaths, 2 operated, 1 allergic skin reaction, 1 misdiagnosed, 4 patients-based refusal) **Group 1** **Randomised N:** 21 patients and 27 ulcers **Completed N:** 13 patients and 18 ulcers **Dropouts:** 8 patients and 9 ulcers (3 deaths, 2 operated, 1 allergic skin reaction, 1 misdiagnosed, 1 patients-based refusal) **Age (mean years (SD);**	**Group 1:** Resin salve (from the Norway spruce (Picea abies). An even layer of resin +/- 1 mm thick was spread between loose sterile cotton gauze. The gauze was placed on both infected and noninfected areas of the pressure ulcer to cover the ulcer area with resin fully. The resin–gauze dressing was changed daily if the ulcer was infected or produced a discharge; if this were not the case, the dressing was changed every third day. **Group 2:** sodium carboxymethylcellulose hydrocolloid polymer without or with ionic silver (Aquacel® or Aquacel Ag®; ConvaTec Ltd, London, U.K.). The Aquacel–hydrocolloid dressing was changed daily if the ulcer produced excessive discharge, but if there was no secretion the dressing was changed every third day, as for the resin–gauze.	**Outcome 1:** Proportion of patients completely healed **Outcome 2:** Proportion of ulcers completely healed **Outcome 3:** Proportion of ulcers improved **Outcome 4:** Proportion of ulcers worsened **Outcome 5:** Mean percentage reduction in ulcer width **Outcome 6:** Mean percentage reduction in ulcer depth **Outcome 7:** speed of healing	**Group 1:** 12/13 **Group 2:** 4/9 **P-value:** 0.003 **Group 1:** 17/18 **Group 2:** 4/11 **P-value:** 0.003 **Group 1:** 18/18 **Group 2:** 10/11 **Group 1:** 0/18 **Group 2:** 1/11 **P-value:** 0.003 **Group 1:** 93.75 **Group 2:** 57.14 **Group 1:** 88.46 **Group 2:** -1.89	**Funding:** grant to A.s. in support of this investigation and the Lappish Resin project **Limitations:** no blinding; no ITT analysis; final sample size lower than calculated **Additional outcomes:** bacterial cultures **Notes:** /

Addressing incomplete outcome data: drop-outs were excluded **Statistical analysis: Differences between parallel groups were compared with the $\chi 2$ test or Fisher's exact test, as appropriate.** **Mean and SD were computed for continuous variables and proportions were compared after distribution analysis with the nonparametric Mann–Whitney U-test or Student's t-test, as appropriate. The healing of the ulcers over time was assessed by Kaplan–Meier analysis and the log-rank test was used to estimate the differences in the final outcome and healing time between the parallel groups. P < 0.05 was considered statistically significant. SPSS 14.0 was used for the**	**range):** 80 (10); 58-98 **Gender (m/f):** 6/7 **BMI (mean kg/m² (SD); range):** 21.8 (7.1); 15.9-35.5 **Diabetes:** 6 **Ulcer width (mean cm (SD)):** 3.2 (2.4) **Ulcer depth (mean mm (SD)):** 5.2 (10.3) **Ulcer location:** Calcaneus: 8 Trochanter: 3 Sacrum: 1 Ischium: 1 Other: 5 **Ulcer grade:** Grade II: 7 Grade III: 9 Grade IV: 2 **Group 2** **Randomised N:** 16 patients and 18 ulcers **Completed N:** 9 patients and 11 ulcers **Dropouts:** 7 patients and 7 ulcers (4 deaths, 3 patients-based refusal) **Age (mean years (SD); range):** 74 (8); 60-88	**Both groups:** 3 patients received a pressure ulcer mattress.	(days) (log-rank-test) **Outcome 8:** Proportion of patients allergic skin reaction	**P-value:** 0.013 **Group 1:** 1/21 **Group 2:** 0/16

statistical calculations **(SPSS, Chicago, IL, U.S.A.).** **Baseline differences: No statistical difference between groups.** **Study power/sample size: A two group** **χ2 test with a 0.05 two-sided significance level will have 80% power to detect the difference between a group 1 proportion of 0.900 and a group 2 proportion of** **0.500 (odds ratio 0.111) when the sample size in each group is 20.** **Setting: 11 primary care hospitals in Finland** **Length of study: six months** **Assessment of PUs:** **PU were classified according to the EPUAP classification.** **Ulcer localization, ulcer grade, color,**	**Gender (m/f):** 3/6 **BMI (mean kg/m² (SD); range):** 21.9 (6.6); 16.9-34.7 **Diabetes:** 1 **Ulcer width (mean cm (SD)):** 4.2 (2.8) **Ulcer depth (mean mm (SD)):** 5.3 (6.5) **Ulcer location:** Calcaneus: 2 Trochanter: 1 Sacrum: 2 Ischium: 5 Other: 1 **Ulcer grade:** Grade II: 5 Grade III: 5 Grade IV: 1 **Inclusion criteria:** One or several severe PU (grade II to IV); with or without an infection **Exclusion criteria:** Life expectancy < 6 months; advanced malignant disease				

width and depth were measured at the beginning of the study and thereafter monthly for 6 months. All ulcers were photographed and planimetry analysis was performed. **Multiple ulcers: 37 patients and 45 ulcers**					

Table 135 – Subbanna 2007

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Subbanna (2008)** **Title: Topical phenytoin solution for treating pressure ulcers: A prospective, randomized, double-blind clinical trial.** **Journal: Spinal Cord, 45 (11); 739-743.** **Study type: randomized controlled trial** **Sequence generation:**	**Patient group:** Patients with a spinal cord injury and a grade II PU (according to the NPUAP). **All patients** **Randomised N:** 28 **Completed N:** 26 **Drop-outs:** 2 (discharged) **Group 1** **Randomised N:** 14 **Completed N:** 12 **Dropouts:** 2	**Group 1:** Phenytoin solution. Sterile gauge soaked with phenytoin solution dressing once daily. Injection phenytoin solution (50 mg/ml, Park-Davis) was diluted using normal saline (0.9% NaCl, CMC pharmacy) to prepare phenytoin solution (5 mg/ml). At this concentration the pH was 7.3–7.4. **Group 2:** Saline solution. Sterile gauge soaked with normal saline once daily. **Both groups:** /	**Outcome 1:** Mean percentage reduction in ulcer size **Outcome 2:** Mean percentage reduction in ulcer volume **Outcome 3:** Mean percentage reduction in PUSH score **Outcome 4:** Proportion of	**Group 1:** 47.83 (20.94) **Group 2:** 36.03 (17.63) **P-value:** 0.132 **Group 1:** 53.94 (31.20) **Group 2:** 55.76 (27.75) **P-value:** 0.777 **Group 1:** 19.53 (17.70) **Group 2:** 11.39 (11.09) **P-value:** 0.261	**Funding:** fund from the CMC fluid research grants committee **Limitations:** no report on allocation concealment; no report on blinding of the patients; no ITT analysis; no report on the sample size calculation; small sample size; no information on preventive

computer-generated randomized list. **Allocation concealment: not reported** **Blinding: nursing staff and outcome assessor were blinded. No report on blinding of patient.** **Addressing incomplete outcome data: drop-outs were excluded** **Statistical analysis: Values were expressed as mean+/-SD and number** **(percentage) for continuous and categorical variables,** **respectively. The differences in the PUSH scores, ulcer** **volume and ulcer size between the two groups were** **analyzed using independent t-test and Mann–Whitney U** **test (for normally and non-normally distributed data).** **P-values less than**	(discharged) **Age (mean years (SD)):** 34.25 (18.12) **Gender (m/f):** 13/1 **Ulcer volume (mean ml (SD)):** 3.70 (2.85) **Ulcer duration (mean days (SD)):** 71.81 (48.12) **PUSH score (mean (SD)):** 13.5 (1.16) **Ulcer location:** Gluteal: 2 Trochanter: 2 Sacrum: 9 Lumbar: 1 **Group 2** **Randomised N:** 14 **Completed N:** 14 **Dropouts:** 0 **Age (mean years (SD)):** 31.64 (12.27) **Gender (m/f):** 12/2 **Ulcer volume (mean ml (SD)):** 4.85 (3.75) **Ulcer duration (mean days (SD)):** 68.18 (40.45) **PUSH score (mean (SD)):** 13.21 (1.42) **Ulcer location:**	patients with adverse events	**Group 1:** 0/14 **Group 2:** 0/14	measures **Additional outcomes:** / **Notes:** /

0.05 were considered statistically significant. All analyses were carried out using Statistical Package for Social Sciences (SPSS version 11.5 Inc., Chicago, IL). **Baseline differences: No difference between groups. Unclear if it was measured statistically.** **Study power/sample size: Sample size was based on the study results form a pilot study with 14 patients. No report on the sample size calculation.** **Setting: tertiary care teaching hospital in South India, Department of Physical Medicine and Rehabilitation, Christian Medical College, Vellore.** **Length of study: 15 days of treatment** **Assessment of PUs:** **PU were classified according to the**	Gluteal: 1 Trochanter: 2 Sacrum: 10 Knee: 1 **Inclusion criteria:** PU stage II without necrotic tissue; paraplegic; age between 10 and 55 **Exclusion criteria:** anemia; hypoalbuminemia; elevated serum creatinine; abnormal liver function tests; history of smoking; peripheral vascular disease; diabetes mellitus; malignancy; connective tissue disorder; psychiatric illness	

NPUAP classification (1989). The ulcer healing rate was assessed using the Pressure Ulcer Scale for Healing (PUSH 3.0). PUSH 3.0 scores pressure ulcers from 0 to 17 based on ulcer surface area (length X width), exudate amount and tissue type. Reduction in PUSH 3.0 indicates ulcer healing. To assess the ulcer size, tracings of ulcer perimeter were taken on transparent sheets. Images were scanned And ulcer size was determined using a computer software developed by the Department of Bioengineering, Christian Medical College, Vellore. To measure ulcer volume, ulcers were initially filled with normal saline up to	

the brim and then normal saline was withdrawn using a calibrated syringe. PUSH 3.0 scores, ulcer size and volume measurements were estimated on day 1 before starting the treatment and on day 16. Multiple ulcers: not reported					

Table 136 – Thomas 1998

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Thomas (1998)** **Title:** **Acemannan hydrogel dressing versus saline dressing for pressure ulcers. A randomized, controlled trial.** **Journal: Advances in Wound Care, 11 (6); 273-276.** **Study type:**	**Patient group:** Patients older than 18 years with stage II, III or IV PU. **All patients** **Randomised N:** 41 **Completed N:** 30 **Drop-outs:** 11 (6 died, 2 worsened, 2 hospitalized, 1 violated protocol) **Age (mean years (SD); range):** 77 (12); 35-97 **Gender (m/f):** 19/22	**Group 1:** Amorphous hydrogel dressing (Carrasyn® gel, Carrington Laboratories, Inc., Irving, TX). Ulcers were cleansed with saline and gently mechanical wiped with gauze. Ulcers were treated with a 1/8 inch layer of hydrogel and covered with a dry sterile nonwoven gauze, held in place with a thick gauze dressing. Dressings were changed daily. Carrasyn®: the active ingredient is thought to be	**Outcome 1:** Proportion of patients completely healed **Outcome 2:** Percentage healing rate **Outcome 3:** Mean time to healing (weeks)	**Group 1:** 10/16 **Group 2:** 9/14 **Odds ratio:** 0.93 (95% CI: 0.16-5.2) **P-value:** 0.92 **Group 1:** 63 **Group 2:** 64 **Group 1:** 5.3 (2.3) **Group 2:** 5.2 (2.4) **P-value:** 0.87	**Funding:** grant from Carrington Labaratories, Inc. Irving, Tx. **Limitations:** no report on sequence generation; no report on allocation concealment; no report on blinding; no ITT analysis; no a priory

randomized controlled trial **Sequence generation: not reported** **Allocation concealment: not reported** **Blinding: not reported.** **Addressing incomplete outcome data: drop-outs were excluded.** **Statistical analysis: Comparison of dichotomous variables was performed by chi-square test. Fischer's exact test was used when a cell value was less than 5. Distributions of continuous variables were compared by the Kruskal-Wallis test for groups. Data were analysed using EPI6..** **Baseline differences: No statistical difference between groups for the characteristics of the patients after**	**Ulcer stage:** Stage II: 15 Stage III: 20 Stage IV: 6 **Group 1** **Randomised N:** 22 **Completed:** 16 **Dropouts:** 6 (4 died, 1 worsened, 1 hospitalized) **Characteristics are form completed N** **Age (mean years (SD)):** 79 (9) **Gender (m/f):** 7/9 **Ulcer stage:** Stage II: 8 Stage III: 6 Stage IV: 2 **Ulcer area (mean cm² (SD)):** 8.9 (9.3) **Incontinence:** Urine: 9 Faecal: 12 **Group 2** **Randomised N:** 19 **Completed N:** 14 **Drop-outs:** 5 (2 died, 1	acemannan, a complex carbohydrate derived from the aloe vera plant. **Group 2:** Moist saline gauze dressing. Ulcers were cleansed with saline and gently mechanical wiped with gauze. Ulcers were covered with a sterile nonwoven saline soaked gauze and a dry sterile nonwoven gauze, held in place with a thick gauze dressing. Dressings were changed daily. **All groups:** Pressure relieving devices were used in 26.7% of the patients	**Outcome 4:** Proportion of patients worsened	**Group 1:** 1/22 **Group 2:** 1/19	sample size calculation; no report on classification of PU **Additional outcomes:** healing rate and subject characteristics (odds ratio's) **Notes:** /

exclusion of drop-outs **Study power/sample size: The study had a power of 80% to detect 25% difference at alpha significance 0.05. Unclear if a priory calculation.** **Setting: skilled nursing facilities and home health care agencies.** **Length of study: 10 weeks of treatment or until complete healing, whichever came first.** **Assessment of PUs:** **PU classification not reported.** **Ulcers were photographed and tracing were made.** **Multiple ulcers: only one ulcer par subject was evaluated**	worsened, 1 hospitalized, 1 violated protocol) **Characteristics are form completed N** **Age (mean years (SD)):** 72 (13) **Gender (m/f):** 9/5 **Ulcer stage:** Stage II: 6 Stage III: 7 Stage IV: 1 **Ulcer area (mean cm² (SD)):** 5.9 (6.0) **Incontinence:** Urine: 7 Faecal: 12 **Inclusion criteria:** Age 18 years and older; stage II, III or IV PU; ulcer area ≥ 1.0cm² **Exclusion criteria:** venous or arterial insufficiency or other non-pressure etiology; ulcers with sinus tracts and/or undermining greater than 1 cm; clinically infected ulcers; concomitant use of other topical medication or systemic steroid therapy; severe medical	

	condition; estimated survival of less than 6 months ; HIV, currently abusing alcohol or drugs; pregnant, breast feeding or not on acceptable means of anti- contraception; diagnose of cancer; receiving chemotherapy				

Table 137 – Van Ort 1976

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Gerber (1979)** **Title: Topical application of insulin in decubitus ulcers: a pilot study** **Journal: Nursing Research, 25 (1): 9-12.** **Study type:** **Randomized controlled trial, pilot study** **Sequence generation: table of random numbers.** **Allocation concealment: not reported**	Patient group: Nursing home patients with a pressure ulcer. All patients Randomised N: 14 Completed N: 14 Drop-outs: 0 Age (mean years (SD); median years): 72.5 (20.22); 77.5 Gender (m/f): 12/2 Group 1 Randomised N: 6 Completed N: 6 Dropouts: 0 Age (mean years):	Group 1: Insulin (10 units of U-40 regular insulin (U.S.P.). The insulin was dropped from a syringe to the ulcer. The ulcer was then allowed to dry. No dressing was applied. Insulin therapy was applied twice a day for five days. Group 2: Standard care determined by physician or nursing home standing order. Both groups: All patients received routine supportive nursing care: position change, increased fluid intake, high protein diet, and local massage.	Outcome 1: Mean rate of healing	P-value: p=0.05	Funding: funded by the University of Arizona College of Nursing Limitations: a random list was used for sequence generation; no report on allocation concealment; no report n blinding; no a priory sample size calculation; little information of baseline characteristics of

Blinding: not reported **Addressing incomplete outcome data: no drop outs** **Statistical analysis:** **The t-test was used to determine effect of independent variable on dependent variable. Tests to determine the influences of extraneous variables included the Pearson correlation coefficient and the t-test for difference in means. For the t-test, level of significance was set at 0.05.** **Baseline differences: Difference in baseline characteristics (age and gender) was not measured statistically.** **Study power/sample size: A priory sample size calculation unclear. A sample size of 20 patients was anticipated but not reached** **Setting: nursing**	79.83 Group 2 Randomised N: 8 Completed N: 8 Dropouts: 0 Age (mean years): 67.0 Inclusion criteria: as a break in skin continuity as evidenced by epidermal or dermal injury involving erythema, pallor, cyanosis, and superficial erosion; size of the ulcer at time of admission was between 1.0 and 7.0 cm; skin breakdown had been in existence 14 days or less prior to the tie the subject was admitted to the study Exclusion criteria: /		individual groups; baseline difference not measured statistically Additional outcomes: / Notes: larger study was reported by Gerber and Van Ort 1979 (no outcome of interest were reported in this study)

home residents **Length of study:** **15 days** **Assessment of PUs:** **PU were defined as a break in skin continuity as evidenced by epidermal or dermal injury involving erythema, pallor, cyanosis, and superficial erosion.** **The size of the decubitus was measured using a transparent scale, the B.W.Co.Measure, which was placed on the lesion. Ulcers were also photographed.** **The ulcer was measured and photographed once a day.** **Multiple ulcers:** **Patients had multiple ulcers. Mean (SD) number of ulcers: 1.14 (0.36)**	

Table 138 – Xakellis 1992

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Xakellis (1992)** **Title:** **Hydrocolloid versus saline-gauze dressings in treating pressure ulcers: A cost-effectiveness analysis.** **Journal: Archives of Physical Medicine and Rehabilitation, 73; 463-469.** **Study type: randomized controlled trial** **Sequence generation: not reported** **Allocation concealment: not reported** **Blinding: not reported.** **Addressing incomplete outcome data: intention to treat analysis** **Statistical analysis:**	**Patient group:** Patients with a stage II or III PU (according to the Shea classification). **All patients** **Randomised N:** 39 **Completed N:** 34 **Drop-outs:** 5 (1 hospitalized, 1 withdrawal of consent, 3 died) **Group 1** **Randomised N:** 18 **Completed:** 16 **Dropouts:** 2 (1 hospitalized, and 1 withdrawal of consent) **Age (mean years (SD)):** 77.3 (16.9) **Gender (m/f):** 2/16 **Ulcer location:** Sacrum: 6 Pelvic area: 8 Other: 4 **Ulcer grade:** Grade II: 18	**Group 1:** Hydrocolloid dressing (DuoDermCGF®, ConvaTec, Princeton, NJ). Ulcers were cleansed with normal saline only. The dressing was applied and rimmed with tape. The dressing was changed twice weekly or if non-occlusive. **Group 2:** Saline wet-to-moist gauze dressing. The gauze consists of a non-sterile eight ply gauze dressing moistened with saline and placed on the ulcer. This was covered with an additional gauze dressing and rimmed with tape. The dressing was remoistened with 3cc saline after four hours and changed after eight hours. **All groups:** All patients with necrotic tissue were sharp debrided as necessary All patient received routine care: repositioning every two hours, cleaning of incontinence with warm water, placing on an air-mattress and air-filled	**Outcome 1:** Proportion of patients completely healed **Outcome 2:** Median time to healing (days)	**Group 1:** 16/18 **Group 2:** 18/21 **Group 1:** 9 **Group 2:** 11 **P-value:** 0.12	**Funding:** supported by ConvaTec Princeton, NJ and Family Health Foundation of America. **Limitations:** no report on sequence generation; no report on blinding; no a priory sample size calculation; small sample size; little information on ulcer assessment **Additional outcomes:** Cost; multivariate analysis **Notes:** /

Two-tailed chi-square or Fisher exact tests were performed for all categorical variables. Continuous and ordinal data were analysed with the Wilcoxon rank-sum test using the t-approximation for the significance level. The Cox proportional-hazards regression model for survival data was used to determine the factors related to healing time. Logrank statistics were calculated to test the univariate associations between baseline characteristics and healing time. Multivariate analysis was performed using Cox proportional-hazard regression analysis to determine the factors associated independently and significantly (p≤0.05) with healing time. **Baseline differences:**	Grade III: 0 **Ulcer area (mean cm²; range):** 0.66; 0.12-13.4 **Incontinence:** Occasionally: 1 Usually: 5 Urine and faeces: 12 **BMI (mean kg/m² (SD)):** 20.2 (5) **Norton score (mean score (SD)):** 11.4 (2.8) **Group 2** **Randomised N:** 21 **Completed:** 18 **Dropouts:** 3 (died) **Age (mean years (SD)):** 83.5 (10.6) **Gender (m/f):** 1/20 **Ulcer location:** Sacrum: 8 Pelvic area: 6 Other: 7 **Ulcer grade:** Grade II: 19 Grade III: 2 **Ulcer area (mean cm²; range):** 0.38; 0.04-24.6 **Incontinence:** Occasionally: 0	wheelchair cushion, and record of diet.

No statistical difference between groups. **Study power/sample size: No a priory sample size calculation.** **Setting: long-term care facility.** **Length of study: six months of treatment.** **Assessment of PUs:** **PU were classified according to the Shea classification (1975).** **Ulcer circumference was traced on clear plastic film two times weekly.** **Multiple ulcers: only one ulcer determined by coin toss was included in the study**	Usually: 3 Urine and faeces: 13 **BMI (mean kg/m² (SD)):** 21.1 (5) **Norton score (mean score (SD)):** 12.8 (3.0) **Inclusion criteria:** Grade II or III **Exclusion criteria:** rapidly fatal disease; anticipated discharge within one week: ulcers from other causes than pressure such as venous stasis				

Table 139 – Yastrub 2004

Reference	Patient Characteristics	Intervention Comparison	Outcome measures	Effect sizes	Comments
Author and year: **Yastrub (2004)** **Title:** **Relationship between type of**	**Patient group:** Patients with a stage II PU (according to the AHCPR classification).	**Group 1:** Polymeric membrane dressing (Polymen®). Dressing were changed as per protocol. **Group 2:** Dry clean dressing and antibiotic ointment.	**Outcome 1:** Proportion of patients improved **Outcome 2:**	**Group 1:** 18/21 **Group 2:** 15/23 **Group 1:** 3.24	**Funding:** Partial funding by NPUAP award. **Limitations:** no

treatment and degree of wound healing among institutionalized geriatric patients with stage II pressure ulcers. **Journal: Care Management Journal, 5 (4); 213-218.** **Study type: randomized controlled trial** **Sequence generation: not reported** **Allocation concealment: not reported** **Blinding: not reported.** **Addressing incomplete outcome data: not reported** **Statistical analysis: The t-test was used to determine the difference between PUSH scores of the different groups. Descriptive statistics were computed using SPSS.**	**All patients** **Randomised N:** 50 **Completed N:** 44 **Drop-outs:** 6 (reason not reported) - unclear **Group 1** **Randomised N:** 21 **Completed:** 19 **Dropouts:** 2 missings **Group 2** **Randomised N:** 23 **Completed:** 23 **Dropouts:** 0 **Inclusion criteria:** > 65 years; limitation in ADL; PU stage II **Exclusion criteria:** /	**All groups:** All patient received: nutritional supplements, vitamin C and zinc sulphate, pressure relief mattress, foam cushion and repositioning every 2 hours	Mean PUSH score	**Group 2:** 1.61 **P-value:** > 0.05	report on sequence generation; no report on allocation concealment; no report on blinding; ITT analysis unclear; drop-outs unclear; no baseline characteristics reported, comparison between groups unclear; no a priory sample size calculation; little information on ulcer assessment; multiple ulcers not reported; little information on dressings. **Additional outcomes:** / **Notes:** /

Baseline differences: Baseline characteristics not reported. **Study power/sample size: No a priory sample size calculation.** **Setting: long-term care facility in Queens, New York.** **Length of study: four weeks** **Assessment of PUs:** **PU were classified according to the AHCPR classification (1994).** **Ulcer were weekly assessed using the Pressure Ulcer Scale for Healing (PUSH).** **Multiple ulcers: not reported**	

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