

Antimicrobial wound dressings (AWDs) for chronic wounds HTA Supplementary material

Strategies for literature searches

Secondary and grey literature

Internet searches were undertaken to identify HTAs, systematic reviews and other evidence based reports.

Clinical effectiveness

The following sources were searched in January 2014:

- Adelaide Health Technology Assessment
<http://www.adelaide.edu.au/ahta/>
- Agency for Healthcare Research and Quality (AHRQ)
<http://www.ahrq.gov/>
- AHRQ National Guideline Clearing House
<http://www.guideline.gov/>
- Aggressive Research Intelligence Facility (ARIF)
<http://www.arif.bham.ac.uk/>
- Alberta Heritage Foundation for Medical Research
<http://www.ahfmr.ab.ca/>
- American Academy of Dermatology
<http://www.aad.org/>
- American Academy of Family Physicians
<http://www.aafp.org/>
- American College of Certified Wound Specialists
<http://www.theccws.org/>
- American College of Physicians
<http://www.acponline.org/>
- American Professional Wound Care Association
<http://www.apwca.org/>
- American Society of Dermatology
<http://www.asd.org/>
- Association for the Advancement of Wound Care
<http://www.aawconline.org/>
- Australasian College of Dermatologists
<http://www.dermcoll.asn.au/>
- Australasian Wound and Tissue Repair Society
<http://www.awtrs.org/>
- Australian National Health and Medical Research Council
<http://www.nhmrc.gov.au/guidelines/index.htm>
- Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S)
<http://www.surgeons.org/racs/research-and-audit/asernip-s/asernip-s-publications>
- Australian Wound Management Association
<http://www.awma.com.au/>
- Bandolier
<http://www.jr2.ox.ac.uk/bandolier>

- Belgian Healthcare Knowledge Centre (KCE)
<https://kce.fgov.be/>
- British Association of Dermatologists
<http://www.bad.org.uk/>
- British Society for Paediatric Dermatology
<http://www.bspd.org/>
- Canadian Agency for Drugs and Technologies in Health (CADTH)
<http://www.cadth.ca/>
- Canadian Association of Wound Care
<http://www.cawc.net/>
- Canadian Dermatology Association
<http://www.dermatology.ca/>
- Canadian Institutes of Health Research
<http://www.cihr-irsc.gc.ca/e/43989.html>
- Centers for Medicare and Medicaid Services
<http://www.cms.gov/medicare-coverage-database/indexes/technology-assessments-index.aspx?TAId=85&bc=AAAQAAAAAAAA&>
- Centre for Clinical Effectiveness (Monash)
http://www.southernhealth.org.au/page/Health_Professionals/CCE/Evidence_reviews/
- NICE Clinical Knowledge Summaries
<http://www.cks.nhs.uk/home>
- CMA Infobase
http://www.cma.ca/index.cfm/ci_id/54316/la_id/1.htm
- Cochrane Database of Systematic Reviews
<http://onlinelibrary.wiley.com/cochranelibrary/search/advanced>
- Database of Abstracts of Reviews of Effects (DARE)
<http://onlinelibrary.wiley.com/cochranelibrary/search/advanced>
- Dermatology Nurses Association
<http://www.dnanurse.org/>
- Dynamed
<http://web.a.ebscohost.com/dynamed>
- ECRI
<http://www.ecri.org/>
- eGuidelines
<http://www.eguidelines.co.uk/>
- European Pressure Ulcer Advisory Panel (EPUAP)
<http://www.epuap.org/>
- European Tissue Repair Society
<http://www.etrso.org/>
- European Wound Management Association (EWMA)
<http://www.ewma.org/>
- Euroscan
<http://www.euroscan.org.uk/>
- EVIDENT database
<https://evident.has-sante.fr/has/login.xhtml>
- EVIP Net
<http://global.evipnet.org/search/evipnet/index.php>
- Google
<http://www.google.co.uk/>
- Guidelines and Audit Implementation Network (GAIN)
<http://www.gain-ni.org/index.php/audits/guidelines>
- Guidelines International Network (GIN)

- <http://www.g-i-n.net/>
- Health Evidence Network
<http://www.euro.who.int/hen>
- Health Information and Quality Authority (HIQA)
<http://www.hiqa.ie/>
- Health Quality Ontario
<http://www.hqontario.ca/>
- Health Services Assessment Collaboration (HSAC)
<http://www.healthsac.net/>
- Health Systems Evidence
<http://www.mcmasterhealthforum.org/healthsystemsevidence/>
- HTA database
<http://onlinelibrary.wiley.com/cochranelibrary/search/advanced>
- Institute for Clinical Evaluative Sciences (ICES)
<http://www.ices.on.ca/webpage.cfm>
- International Society of Dermatology
<http://www.intsocderm.org/>
- Japanese Society for Wound Healing
http://www.jswh.com/english2/index_e.html
- Liverpool Reviews and Implementation Group (LRIG)
<http://www.liv.ac.uk/lrig/>
- Madox Horizon Scanning Reports
<http://madox.org/horizon-scanning-reports>
- McGill University Health Center Technology Assessment Unit
<http://www.mcgill.ca/tau/>
- Medicaid Evidence Based Decisions Project (MED)
<http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/med/index.cfm>
- Medical Dermatology Society
<http://www.meddermsociety.org/>
- Medical Research Council (MRC)
<http://www.mrc.ac.uk/>
- Medical Services Advisory Committee (Australia)
<http://www.msac.gov.au/>
- National Health and Medical Research Council (NHMRC)
<http://www.nhmrc.gov.au/publications/index.htm>
- National Horizon Scanning Centre
<http://www.nhsc-healthhorizons.org.uk/>
- National Institute for Health and Clinical Excellence (NICE)
<http://www.nice.org.uk/>
- National Pressure Ulcer Advisory Panel (NPUAP)
<http://www.npuap.org/>
- New Zealand Dermatological Society
<http://www.dermnetnz.org/>
- New Zealand Guidelines Group
<http://www.nzgg.org.nz/>
- New Zealand Wound Care Society
<http://www.nzwcs.org.nz/>
- NHS Evidence
<https://www.evidence.nhs.uk/>
- NIHR HTA Programme
<http://www.nchta.org/>
- Ottawa Hospital Research Institute

- <http://www.ohri.ca/hta/>
- Peel Health Library
<http://www.peelregion.ca/health/library/literature-reviews.asp>
- Peninsula Technology Assessment Group (PenTAG)
<http://medicine.exeter.ac.uk/pentag/>
- Primary Care Dermatology Society
<http://www.pcds.org.uk/>
- Public Health Wales
<http://www.wales.nhs.uk/sitesplus/888/home>
- PubMed Clinical Queries
<http://www.ncbi.nlm.nih.gov/pubmed/clinical>
- Royal College of Nursing Clinical Guidelines
<http://www.rcn.org.uk/development/practice/clinicalguidelines>
- Sax Institute
<http://www.saxinstitute.org.au/>
- Scottish Dermatological Society
<http://www.scottish-dermatology.org.uk/>
- Scottish Intercollegiate Guidelines Network (SIGN)
<http://www.sign.ac.uk/>
- Sheffield Technology Assessment Group
<https://www.shef.ac.uk/scharr/sections/heds/collaborations/tag>
- Southampton Health Technology Assessment Centre
<http://www.southampton.ac.uk/shtac>
- Tissue Viability Online
<http://www.tissueviabilityonline.com/>
- Tissue Viability Society
<http://www.tvs.org.uk/>
- TRIP Database
<http://www.tripdatabase.com/>
- UpToDate
<http://www.uptodate.com/home/index.html>
- US National Institutes of Health
<http://www.nih.gov/>
- VA Technology Assessment Program
<http://www.va.gov/vatap/>
- West Midlands Health Technology Assessment Collaboration
<http://www.wmhtac.bham.ac.uk/>
- World Union of Wound Healing Societies
<http://www.wuwhs.org/>
- Wound Healing Society
<http://www.woundheal.org/>
- Wound Ostomy and Continence Nurses Society
<http://www.wocn.org/>

Manufacturer websites

Websites of the following manufacturers of antimicrobial wound dressings were searched in January 2014:

- Molnlycke Health Care
- Smith & Nephew
- Convatec

- Johnson & Johnson Medical
- Systagenix Wound Management Ltd
- Unomedical Ltd
- Coloplast
- Urogo Ltd
- Hartmann (Paul)
- 3M Healthcare
- Braun Medical
- Crawford Pharm
- Derma Sciences Europe Ltd
- Activa Healthcare
- BSN
- Lohmann Raucher
- Schulke
- Advancis
- Danetre
- Medihoney
- Aspen Medica
- Medlogic
- Covidien
- Archimed

Cost effectiveness

The following sources were searched for economic studies and reports in January 2014:

- Audit Scotland
<http://www.audit-scotland.gov.uk/>
- CEA registry
<https://research.tufts-nemc.org/cear4/default.aspx>
- Centre for Health Economics
<http://www.york.ac.uk/inst/che/>
- Centre for Health Economics and Policy Analysis
<http://www.chepa.org/>
- EconLIT
<http://www.econlit.org/>
- ESHER (University of Newcastle)
<http://www.ncl.ac.uk/nubs/research/centres/esher/>
- Health and Social Care Information Centre
<http://www.hscic.gov.uk/>
- Health Economic Evaluations Database (HEED)
<http://www3.interscience.wiley.com/cgi-bin/mrwhome/114130635/HOME>
- Health Economics and Decision Science (University of Sheffield)
<http://www.shef.ac.uk/scharr/sections/heds>
- Health Economics Group (University of East Anglia)
http://www.med.uea.ac.uk/research/research_econ/welcome.htm
- Health Economics Research Centre (University of Oxford)
<http://www.herc.ox.ac.uk/>
- Health Economics Research Group (Brunel University)

- <http://www.brunel.ac.uk/about/acad/herg>
- Health Economics.com
<http://www.healtheconomics.com/>
- Institute of Health Economics (Canada)
<http://www.ihe.ca/>
- International Health Economics Association
<https://www.healtheconomics.org/>
- London School of Economics and Political Science
<http://www.lse.ac.uk/>
- NHS Economic Evaluations Database (NHS EED)
<http://onlinelibrary.wiley.com/cochranelibrary/search/advanced>
- NHS Finance Manual
<http://www.info.doh.gov.uk/doh/finman.nsf>
- Paediatric Economic Database Evaluation (PEDE) database
<http://pede.ccb.sickkids.ca/pede/index.jsp>
- Prescription Services, NHS Business Services Authority
<http://www.nhsbsa.nhs.uk/PrescriptionServices/810.aspx>
- RePEc
<http://repec.org/>
- Southampton University Economics Department
<http://www.economics.soton.ac.uk/>
- University of Melbourne Centre for Health Policy Programs and Economics
<http://healthprograms.unimelb.edu.au/>
- University of Sydney Health Economics Research and Evaluation
<http://www.chere.uts.edu.au/>
- WHO-CHOICE
<http://www.who.int/choice/en/>
- York Health Economics Consortium
<http://www.yhec.co.uk/>

Patient and organisational issues (including safety issues)

The following sources were searched in April 2014:

- Australian Commission on Safety and Quality in Health Care
<http://www.safetyandquality.gov.au/>
- Australian Patient Safety Foundation
<http://www.apsf.net.au/>
- Better Together (Scottish Patient Experience Programme)
http://www.bettertogetherscotland.com/bettertogetherscotland/CCC_FirstPage.jsp
- Campbell Collaboration
<http://www.patientsafetyinstitute.ca/English/Pages/default.aspx>
- Canadian Patient Safety Institute
<http://www.patientsafetyinstitute.ca/English/Pages/default.aspx>
- Centre for Qualitative Research
<http://www.bournemouth.ac.uk/cqr/>
- Centre for Research Excellence in Patient Safety
<http://www.crepatientsafety.org.au/>
- Cochrane Consumer Network (CCNet)
<http://www.cochrane.org/consumers/homepage.htm>

- Community Health Exchange (CHEX)
<http://www.chex.org.uk/>
- Developing Patient Partnerships
<http://dpp.org.uk/>
- Equality Evidence Finder
<http://www.scotland.gov.uk/Topics/People/Equality/Equalities/DataGrid>
- Equality in Health Managed Knowledge Network
<http://www.equalityinhealth.scot.nhs.uk/home.aspx?referer=AAS&un=nousername>
- Federal Drugs Administration
<http://www.fda.gov/>
- Health Talk Online
<http://www.healthtalkonline.org/>
- Institute for Safe Medication Practices
<http://www.ismp.org/>
- Institute of Medicine
<http://www.iom.edu/>
- International Alliance of Patients' Organizations
<http://www.patientsorganizations.org/index.pl>
- Involve
<http://www.invo.org.uk/>
- James Lind Alliance
<http://www.lindalliance.org/>
- Joint Commission: Patient Safety
http://www.jointcommission.org/topics/patient_safety.aspx
- King's Patient Safety and Service Quality Research Centre
<http://www.kingspssq.org.uk/>
- MedlinePlus: Patient Safety
<http://www.nlm.nih.gov/medlineplus/patientsafety.html>
- MHRA
http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=5
- National Association for Patient Participation
<http://www.napp.org.uk/>
- National Coordinating Council for Medication Error Reporting and Correction
<http://www.nccmerp.org/>
- National Patient Safety Agency (NPSA)
<http://www.npsa.nhs.uk/>
- National Patient Safety Foundation
<http://www.npsf.org/>
- National Voices
<http://www.nationalvoices.org.uk/>
- NHS Centre for Involvement
<http://www.nhscentreforinvolvement.nhs.uk/>
- NHS Improving Quality
<http://www.england.nhs.uk/ourwork/qual-clin-lead/nhsiq/>
- NHS Surveys
<http://www.nhssurveys.org/>

- Patient Opinion
<http://www.patientopinion.org.uk/>
- Patient Safety Board, Royal College of Surgeons (Edinburgh)
<http://www.patientsafetyboard.org/>
- Patient Safety Research Group
<http://www.abdn.ac.uk/psrg/>
- Patient UK Discussion Forums
<http://www.patient.co.uk/forums/>
- Patient Views
<http://www.patient-view.com/>
- Patients Accelerating Change
http://www.cgsupport.nhs.uk/Programmes/Patients_Accelerating_Change_Program
- Patients Association
<http://www.patients-association.org.uk/>
- Picker Institute
<http://www.pickereurope.org/>
- Royal College of Nursing: Patient Safety
http://www.rcn.org.uk/development/practice/patient_safety
- Scottish Patient Safety Alliance
<http://www.patientsafetyalliance.scot.nhs.uk/>
- Scottish Patient Safety Research Network
<http://www.spsrn.ac.uk/>
- Veterans Association National Center for Patient Safety
<http://www.patientsafety.gov/>
- World Alliance for Patient Safety
<http://www.who.int/patientsafety/en/>
- Youth Talk Online
<http://www.youthhealthtalk.org/>

Organisational issues

The following sources were searched in June 2014:

- Chief Scientist Office
<http://www.cso.scot.nhs.uk/>
- Healthcare Improvement Scotland
http://www.healthcareimprovementscotland.org/welcome_to_healthcare_improvem.a.spx
- Health Services Research Unit (Aberdeen)
<http://www.abdn.ac.uk/hsru/>
- ISD Scotland
http://www.isdscotland.org/isd/CCC_FirstPage.jsp
- National Procurement Scotland
<http://www.nhsscotlandprocurement.scot.nhs.uk/>
- NHS Education for Scotland
<http://www.nes.scot.nhs.uk/>
- Scottish Government

- <http://www.scotland.gov.uk/Topics/Health>
- Scottish Public Health Observatory (ScotPHO)
<http://www.scotpho.org.uk/>
 - Scottish Health On the Web (SHOW)
<http://www.show.scot.nhs.uk/>
 - Health Facilities Scotland
<http://www.hfs.scot.nhs.uk/>
 - Health Protection Scotland
<http://www.hps.scot.nhs.uk/>
 - Health Scotland
<http://www.healthscotland.com/>
 - Health Foundation
<http://www.health.org.uk/>
 - King's Fund
<http://www.kingsfund.org.uk/>
 - NHS Improving Quality
<http://www.england.nhs.uk/ourwork/qual-clin-lead/nhsiq/>
 - NIHR Service Delivery and Organisation Programme
<http://www.sdo.nihr.ac.uk/>

Bibliographic database searches

The following databases were searched to identify additional systematic reviews and primary studies:

- MEDLINE (Ovid)
- MEDLINE in Process (Ovid)
- EMBASE (Ovid) [*Not searched for cost effectiveness*]
- CINAHL (EBSCOHost)
- PsychInfo (EBSCOHost) [*Patient issues searches only*]
- Web of Science (ISI)
- Cochrane Central Register of Controlled Trials (CENTRAL, Cochrane Library)

Search 1: AWD systematic reviews

Database: MEDLINE

Database coverage: 1946 to present with daily update

Platform: Ovid

Date of search: 20 January 2014

1. exp "Wounds and Injuries"/
2. wound*.tw.
3. Chronic Disease/
4. (chronic illness* or chronically ill or chronic disease*).tw.

5. exp Skin Ulcer/
6. ulcer*.tw.
7. exp Venous Insufficiency/
8. Varicose Ulcer/
9. ((venous or varicose) adj3 ulcer*).tw.
10. Diabetic Foot/
11. "diabetic foot".tw.
12. or/1-11
13. exp Anti-Infective Agents/
14. (antimicrobial* or "anti-microbial*").tw.
15. (antibacterial* or "anti-bacterial*").tw.
16. (antiseptic* or "anti-septic*" or antiinfective or "anti-infective").tw.
17. (bacteri?cidal or bacteri?static).tw.
18. Chlorhexidine/
19. (chlorhexidine or chlorhexidene or dialkylcarbomoyl chloride or "di-alkylcarbomoyl chloride").tw.
20. (glucose oxidase or lactoperoxidase or microcid).tw.
21. Honey/
22. honey.tw.
23. Iodine/
24. iodine.tw.
25. octenidine.tw.
26. (PHMB or polihexanide or polyhexanide).tw.
27. "polymethylene biguanide".tw.
28. Silver/
29. exp Silver Compounds/
30. silver.tw.
31. or/13-30
32. exp Bandages/
33. Alginates/
34. Ointments/
35. Hydrogel/
36. (bandage* or dressing*).tw.
37. (alginate* or carboxymethylcellulose).tw.
38. (foam* or gauze*).tw.
39. (hydrocolloid* or hydrogel*).tw.
40. "low adher* acetate*".tw.
41. (ointment* or paste* or gel*).tw.
42. (pad or tulle or viscose net or viscose mesh).tw.
43. topical*.tw.
44. or/32-43
45. 31 and 44
46. 12 and 45
47. Meta-Analysis as Topic/
48. meta analy\$.tw.
49. metaanaly\$.tw.
50. Meta-Analysis/
51. (systematic adj (review\$1 or overview\$1)).tw.
52. exp Review Literature as Topic/
53. or/47-52
54. cochrane.ab.
55. embase.ab.
56. (psyclit or psychlit).ab.
57. (psycinfo or psychinfo).ab.
58. (cinahl or cinhal).ab.

59. science citation index.ab.
60. bids.ab.
61. cancerlit.ab.
62. or/54-61
63. reference list\$.ab.
64. bibliograph\$.ab.
65. hand-search\$.ab.
66. relevant journals.ab.
67. manual search\$.ab.
68. or/63-67
69. selection criteria.ab.
70. data extraction.ab.
71. 69 or 70
72. Review/
73. 71 and 72
74. Comment/
75. letter/
76. Editorial/
77. animal/
78. human/
79. 77 not (77 and 78)
80. or/74-76,79
81. 53 or 62 or 68 or 73
82. 81 not 80
83. 46 and 82
84. limit 83 to (yr="1990 -Current" and english)

Search 2: AWD systematic reviews (company name)

Database: MEDLINE

Database coverage: 1946 to present with daily update

Platform: Ovid

Date of search: 20 January 2014

1. exp "Wounds and Injuries"/
2. wound*.tw.
3. Chronic Disease/
4. (chronic illness* or chronically ill or chronic disease*).tw.
5. exp Skin Ulcer/
6. ulcer*.tw.
7. exp Venous Insufficiency/
8. Varicose Ulcer/
9. ((venous or varicose) adj3 ulcer*).tw.
10. Diabetic Foot/
11. "diabetic foot".tw.
12. or/1-11
13. "3M healthcare".tw.
14. activa.tw.
15. advancis.tw.
16. archimed.tw.

17. "aspen medica".tw.
18. braun.tw.
19. BSN.tw.
20. convatec.tw.
21. covidien.tw.
22. "crawford pharma".tw.
23. danetre.tw.
24. "derma sciences".tw.
25. hartmann.tw.
26. "johnson and johnson".tw.
27. "lohmann raucher".tw.
28. medlogic.tw.
29. molnlycke.tw.
30. schulke.tw.
31. "smith and nephew".tw.
32. systagenix.tw.
33. unomedical.tw.
34. urgo.tw.
35. or/13-34
36. 12 and 35
37. Meta-Analysis as Topic/
38. meta analy\$.tw.
39. metaanaly\$.tw.
40. Meta-Analysis/
41. (systematic adj (review\$1 or overview\$1)).tw.
42. exp Review Literature as Topic/
43. or/37-42
44. cochrane.ab.
45. embase.ab.
46. (psyclit or psychlit).ab.
47. (psycinfo or psychinfo).ab.
48. (cinahl or cinhal).ab.
49. science citation index.ab.
50. bids.ab.
51. cancerlit.ab.
52. or/44-51
53. reference list\$.ab.
54. bibliograph\$.ab.
55. hand-search\$.ab.
56. relevant journals.ab.
57. manual search\$.ab.
58. or/53-57
59. selection criteria.ab.
60. data extraction.ab.
61. 59 or 60
62. Review/
63. 61 and 62
64. Comment/
65. letter/
66. Editorial/
67. animal/
68. human/
69. 67 not (67 and 68)
70. or/64-66,69
71. 43 or 52 or 58 or 63

72. 71 not 70
73. 36 and 72
74. 36 and 72
75. 36 and 72

Search 3: AWD systematic reviews (brand-names)

Database: MEDLINE

Database coverage: 1946 to present with daily update

Platform: Ovid

Date of search: 20 January 2014

1. exp "Wounds and Injuries"/
2. wound*.tw.
3. Chronic Disease/
4. (chronic illness* or chronically ill or chronic disease*).tw.
5. exp Skin Ulcer/
6. ulcer*.tw.
7. exp Venous Insufficiency/
8. Varicose Ulcer/
9. ((venous or varicose) adj3 ulcer*).tw.
10. Diabetic Foot/
11. "diabetic foot".tw.
12. or/1-11
13. (acticoat or actisorb).tw.
14. (coloplast or cutimed sorbact).tw.
15. flaminol.tw.
16. (inadine or iodasorb or iodoflex or iodozyme).tw.
17. octenilin.tw.
18. (physiotulle ag or polymem silver or prontosan).tw.
19. "vliwaktiv ag".tw.
20. (urgocell or urgisorb or urgotul or urgotul SSD).tw.
21. (suprasorb or tegaderm or telfa or therabond).tw.
22. (algicel or algisite).tw.
23. (algivon or allevyn or aquacel).tw.
24. (askina or atrauman).tw.
25. (bactigras or biatain).tw.
26. (kendal AMD or kendal antimicrobial dressing* or kendal anti-microbial dressing*).tw.
27. (medihoney or melgisorb or mepilex or mesalt or mesitran).tw.
28. (seasorb or silvercel or silverseal or sorbact or sorbsan).tw.
29. or/13-28
30. 12 and 29
31. Meta-Analysis as Topic/
32. meta analy\$.tw.
33. metaanaly\$.tw.
34. Meta-Analysis/
35. (systematic adj (review\$1 or overview\$1)).tw.
36. exp Review Literature as Topic/
37. or/31-36

38. cochrane.ab.
39. embase.ab.
40. (psyclit or psychlit).ab.
41. (psycinfo or psychinfo).ab.
42. (cinahl or cinhal).ab.
43. science citation index.ab.
44. bids.ab.
45. cancerlit.ab.
46. or/38-45
47. reference list\$.ab.
48. bibliograph\$.ab.
49. hand-search\$.ab.
50. relevant journals.ab.
51. manual search\$.ab.
52. or/47-51
53. selection criteria.ab.
54. data extraction.ab.
55. 53 or 54
56. Review/
57. 55 and 56
58. Comment/
59. letter/
60. Editorial/
61. animal/
62. human/
63. 61 not (61 and 62)
64. or/58-60,63
65. 37 or 46 or 52 or 57
66. 65 not 64
67. 30 and 66
68. limit 67 to (yr="1990 -Current" and english)

Search 4: AWD cost effectiveness

Database: MEDLINE

Database coverage: 1946 to present with daily update

Platform: Ovid

Date of search: 30 January 2014

1. exp "Wounds and Injuries"/
2. wound*.tw.
3. Chronic Disease/
4. (chronic illness* or chronically ill or chronic disease*).tw.
5. exp Skin Ulcer/
6. ulcer*.tw.
7. exp Venous Insufficiency/
8. Varicose Ulcer/
9. ((venous or varicose) adj3 ulcer*).tw.
10. Diabetic Foot/
11. "diabetic foot".tw.

12. or/1-11
13. exp Anti-Infective Agents/
14. (antimicrobial* or "anti-microbial*").tw.
15. (antibacterial* or "anti-bacterial*").tw.
16. (antiseptic* or "anti-septic*" or antiinfective or "anti-infective").tw.
17. (bacteri?cidal or bacteri?static).tw.
18. Chlorhexidine/
19. (chlorhexidine or chlorhexidene or dialkylcarbomoyl chloride or "di-alkylcarbomoyl chloride").tw.
20. (glucose oxidase or lactoperoxidase or microcid).tw.
21. Honey/
22. honey.tw.
23. Iodine/
24. iodine.tw.
25. octenidine.tw.
26. (PHMB or polihexanide or polyhexanide).tw.
27. "polymethylene biguanide".tw.
28. Silver/
29. exp Silver Compounds/
30. silver.tw.
31. or/13-30
32. exp Bandages/
33. Alginates/
34. Ointments/
35. Hydrogel/
36. (bandage* or dressing*).tw.
37. (alginate* or carboxymethylcellulose).tw.
38. (foam* or gauze*).tw.
39. (hydrocolloid* or hydrogel*).tw.
40. "low adher* acetate*".tw.
41. (ointment* or paste* or gel*).tw.
42. (pad or tulle or viscose net or viscose mesh).tw.
43. topical*.tw.
44. or/32-43
45. 31 and 44
46. 12 and 45
47. ECONOMICS/
48. "Costs and Cost Analysis"/
49. Cost Allocation/
50. Cost-Benefit Analysis/
51. Cost Control/
52. Cost Savings/
53. Cost of Illness/
54. Cost Sharing/
55. "Deductibles and Coinsurance"/
56. Medical Savings Accounts/
57. Health Care Costs/
58. Direct Service Costs/
59. Drug Costs/
60. Employer Health Costs/
61. Hospital Costs/
62. Health Expenditures/
63. Capital Expenditures/
64. Value of Life/
65. exp Economics, Hospital/

66. exp Economics, Medical/
67. Economics, Nursing/
68. Economics, Pharmaceutical/
69. exp "Fees and Charges"/
70. exp BUDGETS/
71. (low adj cost).mp.
72. (high adj cost).mp.
73. (health?care adj cost\$).mp.
74. (fiscal or funding or financial or finance).tw.
75. (cost adj estimate\$).mp.
76. (cost adj variable).mp.
77. (unit adj cost\$).mp.
78. (economic\$ or pharmaco-economic\$ or price\$ or pricing).tw.
79. or/47-78
80. 46 and 79
81. Economics/
82. exp "Costs and Cost Analysis"/
83. Economics, Dental/
84. exp Economics, Hospital/
85. Economics, Medical/
86. Economics, Nursing/
87. Economics, Pharmaceutical/
88. (economic* or cost or costs or costly or costing or price or prices or pricing or pharmaco-economic*).tw.
89. (expenditure* not energy).tw.
90. (value adj1 money).ti,ab.
91. budget*.tw.
92. or/81-91
93. ((energy or oxygen) adj cost).tw.
94. (metabolic adj cost).tw.
95. ((energy or oxygen) adj expenditure).tw.
96. 93 or 94 or 95
97. 92 not 96
98. 46 and 97
99. 80 or 98
100. limit 99 to (yr="1990 -Current" and english)

Search 5: AWD patient issues

Database: MEDLINE

Database coverage: 1946 to present with daily update

Platform: Ovid

Date of search: 7 April 2014

1. exp "Wounds and Injuries"/
2. wound*.tw.
3. Chronic Disease/
4. (chronic illness* or chronically ill or chronic disease*).tw.
5. exp Skin Ulcer/
6. ulcer*.tw.

7. exp Venous Insufficiency/
8. Varicose Ulcer/
9. ((venous or varicose) adj3 ulcer*).tw.
10. Diabetic Foot/
11. "diabetic foot".tw.
12. or/1-11
13. exp Anti-Infective Agents/
14. (antimicrobial* or "anti-microbial").tw.
15. (antibacterial* or "anti-bacterial").tw.
16. (antiseptic* or "anti-septic*" or antiinfective or "anti-infective").tw.
17. (bacteri?cidal or bacteri?static).tw.
18. Chlorhexidine/
19. (chlorhexidine or chlorhexidene or dialkylcarbomoyl chloride or "di-alkylcarbomoyl chloride").tw.
20. (glucose oxidase or lactoperoxidase or microcid).tw.
21. Honey/
22. honey.tw.
23. Iodine/
24. iodine.tw.
25. octenidine.tw.
26. (PHMB or polihexanide or polyhexanide).tw.
27. "polymethylene biguanide".tw.
28. Silver/
29. exp Silver Compounds/
30. silver.tw.
31. or/13-30
32. exp Bandages/
33. Alginates/
34. Ointments/
35. Hydrogel/
36. (bandage* or dressing*).tw.
37. (alginate* or carboxymethylcellulose).tw.
38. (foam* or gauze*).tw.
39. (hydrocolloid* or hydrogel*).tw.
40. "low adher* acetate*".tw.
41. (ointment* or paste* or gel*).tw.
42. (pad or tulle or viscose net or viscose mesh).tw.
43. topical*.tw.
44. or/32-43
45. 31 and 44
46. 12 and 45
47. limit 46 to (yr="1990 -Current" and english)
48. exp Consumer Participation/
49. ((patient\$ or consumer\$) adj3 (participat\$ or decisi\$ or decid\$)).ti,ab.
50. "Patient Acceptance of Health Care"/
51. exp attitude to health/
52. consumer satisfaction/
53. exp *Consumer Satisfaction/
54. Patient Preference/
55. "patient-focused".ti,ab.
56. "patient-centered".ti,ab.
57. "patient-centred".ti,ab.
58. (patient adj3 (attitude\$ or preference\$)).ti,ab.
59. "patient satisfaction".ti.
60. cooperative behavior/

61. exp self-efficacy/
62. self-efficacy.ti,ab.
63. exp adaptation, psychological/
64. coping.ti,ab.
65. ("self-perception" or "self-concept").ti,ab.
66. exp health education/
67. patient education as topic/
68. exp attitude to health/
69. health knowledge, attitudes, practice/
70. "informed choice".ti,ab.
71. "shared decision making".ti,ab.
72. empowerment.tw.
73. ("focus group" adj3 (patient\$ or parent\$ or famil\$ or spouse\$)).ti,ab.
74. *"Quality of Life"/
75. "Quality of Life"/px [Psychology]
76. (QoL or "quality of life").ti.
77. personal autonomy/
78. self concept/
79. Consumer Advocacy/
80. freedom/
81. needs assessment/
82. patient advocacy/
83. self-help groups/
84. life change events/
85. attitude to death/
86. patient-centered care/
87. exp professional-patient relations/
88. self care/
89. self-management.ti.
90. ((patient\$ or consumer\$ or parent\$ or famil\$ or spouse\$) adj (attitude\$ or involvement or desir\$ or perspective\$ or activation or view\$ or preference\$)).ti,ab.
91. "expert patient".ti,ab.
92. or/48-91
93. exp decision making/
94. exp communication/
95. stress, psychological/
96. emotions/
97. vignette*.ti,ab.
98. or/93-97
99. exp Patients/px [Psychology]
100. (patient\$ or consumer\$).ti.
101. or/99-100
102. 98 and 101
103. "focus group\$".ti,ab.
104. focus groups/
105. narration/
106. qualitative.ti.
107. or/103-106
108. 92 or 102 or 107
109. 47 and 108
110. from 109 keep 1-114
111. exp Mortality/
112. Morbidity/
113. (mortality or morbidity).ti.
114. Incidence/

115. Prevalence/
116. (inciden* or prevalen*).ti.
117. Demography/
118. Censuses/
119. exp Population Surveillance/
120. "age of onset"/
121. age distribution/
122. Age Factors/
123. age.ti.
124. exp sex distribution/
125. Sex Factors/
126. (sex or gender).ti.
127. "Emigration and Immigration"/
128. Minority Groups/
129. culture/ or cultural characteristics/
130. exp Population Groups/
131. (ethnic* or cultur* or minorit*).ti.
132. epidemiologic factors/
133. Income/
134. (income or salar* or earning*).ti.
135. ep.fs.
136. eh.fs.
137. burden.ti.
138. "Quality of Life"/
139. (sociodemographic* or socio-demographic* or social demographic* or "social and demographic").tw.
140. (socioeconomic or socio-economic or (social and economic)).ti.
141. "Activities of Daily Living"/
142. px.fs.
143. (psychological or psychosocial or emotional).ti.
144. exp Socioeconomic Factors/
145. Work/
146. employment/ or unemployment/
147. Occupations/
148. (employment or earning* or workplace or productivity).tw.
149. work.ti.
150. or/111-149
151. 47 and 150
152. exp Great Britain/
153. ("great britain" or "united kingdom" or UK or GB).tw.
154. (London or Birmingham or Bristol or Oxford or Cambridge or Manchester or Leeds or York or Newcastle or Sheffield or Liverpool or Coventry or Leicester or Nottingham).tw.
155. (Cardiff or Swansea or Belfast).tw.
156. (england or english or wales or welsh or "northern ireland" or irish).tw.
157. (scotland or scottish or scots).tw.
158. (Glasgow or Edinburgh or Stirling or Dundee or Perth or Inverness or Aberdeen).tw.
159. (Argyll or Ayresshire or Arran or Dumfries or Galloway or Lothian or Highland or Clyde or Fife or "Forth valley" or Orkney or Hebride* or Borders or Shetland or "Western isles" or Grampian or Lanarkshire or Tayside).tw.

Search 6: AWD adverse effects

Database: MEDLINE

Database coverage: 1946 to present with daily update

Platform: Ovid

Date of search: 18 June 2014

1. exp "Wounds and Injuries"/
2. wound*.tw.
3. Chronic Disease/
4. (chronic illness* or chronically ill or chronic disease*).tw.
5. exp Skin Ulcer/
6. ulcer*.tw.
7. exp Venous Insufficiency/
8. Varicose Ulcer/
9. ((venous or varicose) adj3 ulcer*).tw.
10. Diabetic Foot/
11. "diabetic foot".tw.
12. or/1-11
13. exp Anti-Infective Agents/
14. (antimicrobial* or "anti-microbial*").tw.
15. (antibacterial* or "anti-bacterial*").tw.
16. (antiseptic* or "anti-septic*" or antiinfective or "anti-infective").tw.
17. (bacteri?cidal or bacteri?static).tw.
18. Chlorhexidine/
19. (chlorhexidine or chlorhexidene or dialkylcarbomoyl chloride or "di-alkylcarbomoyl chloride").tw.
20. (glucose oxidase or lactoperoxidase or microcid).tw.
21. Honey/
22. honey.tw.
23. Iodine/
24. iodine.tw.
25. octenidine.tw.
26. (PHMB or polihexanide or polyhexanide).tw.
27. "polymethylene biguanide".tw.
28. Silver/
29. exp Silver Compounds/
30. silver.tw.
31. or/13-30
32. exp Bandages/
33. Alginates/
34. Ointments/
35. Hydrogel/
36. (bandage* or dressing*).tw.
37. (alginate* or carboxymethylcellulose).tw.
38. (foam* or gauze*).tw.
39. (hydrocolloid* or hydrogel*).tw.
40. "low adher* acetate*".tw.
41. (ointment* or paste* or gel*).tw.
42. (pad or tulle or viscose net or viscose mesh).tw.

43. topical*.tw.
44. or/32-43
45. 31 and 44
46. 12 and 45
47. limit 46 to (yr="1990 -Current" and english)
48. *Patient Safety/
49. Patient Harm/
50. (safe or safety).ti,ab.
51. (side effect* or undesirable effect*).ti,ab.
52. harm*.ti,ab.
53. (tolerability or toxicity).ti,ab.
54. (adverse adj2 (effect* or reaction* or event* or outcome*)).ti,ab.
55. or/48-54
56. ae.fs.
57. (pain* or discomfort).ti.
58. (bleed* or blood loss or h?emorrhag*).ti.
59. (dermatitis or skin inflammation or skin irritation).ti.
60. ((skin or ulcer or wound or dermat* or tissue) adj2 deteriorat*).ti.
61. (erythema or (red* adj2 skin)).ti.
62. (edema or oedema).ti.
63. (edema or oedema).ti.
64. exudate*.ti.
65. (pruritis or itch*).ti.
66. (exanthema or (skin rash* or dermat* rash*)).ti.
67. eczema.ti.
68. sting*.ti.
69. (allergy or allergies or allergic or hypersensitiv* or hyper-sensitiv*).ti.
70. ((wound or ulcer or skin or dermat* or tissue) adj2 (erosion or erod*)).ti.
71. burning.ti.
72. ((local* or wound or ulcer or tissue or dermat*) adj3 infect*).ti.
73. ((wound or ulcer or tissue) adj3 contaminat*).ti.
74. or/57-73
75. human/ not animal/
76. 55 or 56 or 74
77. 47 and 76
78. 75 and 77

Search 7: AWD qualitative studies (patient issues)

Database: MEDLINE

Database coverage: 1946 to present with daily update

Platform: Ovid

Date of search: 2 July 2014

1. exp "Wounds and Injuries"/
2. wound*.tw.
3. Chronic Disease/
4. (chronic illness* or chronically ill or chronic disease*).tw.
5. exp Skin Ulcer/
6. ulcer*.tw.

7. exp Venous Insufficiency/
8. Varicose Ulcer/
9. ((venous or varicose) adj3 ulcer*).tw.
10. Diabetic Foot/
11. "diabetic foot".tw.
12. or/1-11
13. exp Anti-Infective Agents/
14. (antimicrobial* or "anti-microbial").tw.
15. (antibacterial* or "anti-bacterial").tw.
16. (antiseptic* or "anti-septic*" or antiinfective or "anti-infective").tw.
17. (bacteri?cidal or bacteri?static).tw.
18. Chlorhexidine/
19. (chlorhexidine or chlorhexidene or dialkylcarbomoyl chloride or "di-alkylcarbomoyl chloride").tw.
20. (glucose oxidase or lactoperoxidase or microcid).tw.
21. Honey/
22. honey.tw.
23. Iodine/
24. iodine.tw.
25. octenidine.tw.
26. (PHMB or polihexanide or polyhexanide).tw.
27. "polymethylene biguanide".tw.
28. Silver/
29. exp Silver Compounds/
30. silver.tw.
31. or/13-30
32. exp Bandages/
33. Alginates/
34. Ointments/
35. Hydrogel/
36. (bandage* or dressing*).tw.
37. (alginate* or carboxymethylcellulose).tw.
38. (foam* or gauze*).tw.
39. (hydrocolloid* or hydrogel*).tw.
40. "low adher* acetate*".tw.
41. (ointment* or paste* or gel*).tw.
42. (pad or tulle or viscose net or viscose mesh).tw.
43. topical*.tw.
44. (fabric or polyester* or soft polymer).ti,ab.
45. ((silicone or starch based) adj2 dress*).tw.
46. or/32-45
47. 31 and 46
48. 12 and 47
49. exp Interviews as Topic/
50. exp Attitude to Health/
51. exp Observation/
52. qualitative research/
53. Narration/
54. exp Nursing Research/
55. exp Tape Recording/
56. experience*.ti,ab.
57. interview*.ti,ab.
58. qualitative*.ti,ab.
59. theme*.ti,ab.
60. analytic memo.ti,ab.

61. anecdote*.ti,ab.
62. audiotape*.ti,ab.
63. (conceptual adj2 (categor* or framework*)).ti,ab.
64. (concurrent adj2 (analys* or data)).ti,ab.
65. confirmability.ti,ab.
66. content analys*.ti,ab.
67. (comparative adj2 (analys* or method*)).ti,ab.
68. convenience sampl*.ti,ab.
69. data saturation.ti,ab.
70. ((descriptive or document) adj2 analys*).ti,ab.
71. emergent theor*.ti,ab.
72. ((semistructured or semi-structured or unstructured or informal or in-depth or indepth or face-to-face or structured or guided*) adj3 (discussion* or questionnaire*)).ti,ab.
73. (ethnograph* or ethnological or ethnomethodol* or ethnonsursing research).ti,ab.
74. exploratory design.ti,ab.
75. (field notes or fieldwork or field work or key informant*).ti,ab.
76. focus group*.ti,ab.
77. grounded theor*.ti,ab.
78. hermeneutic.ti,ab.
79. (inductive adj2 (analys* or grounded or reasoning)).ti,ab.
80. informational redundancy.ti,ab.
81. (iterative adj2 approach*).ti,ab.
82. interpretive.ti,ab.
83. life histor*.ti,ab.
84. maximum variation sampl*.ti,ab.
85. (meta-ethnography or metaethnography).ti,ab.
86. (narrative* or narration or metanarrative* or meta-narrative*).ti,ab.
87. naturalistic.ti,ab.
88. observation*.ti,ab.
89. (open-ended or open coding).ti,ab.
90. phenomen*.ti,ab.
91. ((purposeful or purposive or quota) adj2 sampl*).ti,ab.
92. saturation.ti,ab.
93. selective coding.ti,ab.
94. (semistructured or semi-structured).ti,ab.
95. snowball sampling.ti,ab.
96. symbolic interactionism.ti,ab.
97. (tape record* or taped discussion*).ti,ab.
98. thematic.ti,ab.
99. (theoretical adj2 (grounding or sampl* or model* or saturation)).ti,ab.
100. transcendental phenomenology.ti,ab.
101. (transcrib* or transcript*).ti,ab.
102. triangulation.ti,ab.
103. verbatim.ti,ab.
104. (video tape* or videotap*).ti,ab.
105. or/49-104
106. 12 and 46 and 105
107. 12 and 47 and 105
108. 106 or 107

Search 8: AWD primary studies (venous ulcers)

Database: MEDLINE

Database coverage: 1946 to present with daily update

Platform: Ovid

Date of search: 7 July 2014

1. Varicose Ulcer/
2. exp Venous Insufficiency/
3. ((venous or varicose or stasis) adj3 ulcer*).ti,ab.
4. "venous insufficien*".ti,ab.
5. or/1-4
6. Iodine/
7. exp Iodine Compounds/
8. iodine.ti,ab.
9. or/6-8
10. Honey/
11. honey*.ti,ab.
12. 10 or 11
13. Silver/
14. exp Silver Compounds/
15. silver*.ti,ab.
16. or/13-15
17. exp Bandages/
18. Alginates/
19. Ointments/
20. Hydrogel/
21. (bandage* or dressing*).ti,ab.
22. (alginate* or carboxymethylcellulose).ti,ab.
23. (foam* or gauze*).ti,ab.
24. (hydrocolloid* or hydrogel*).ti,ab.
25. "low adher* acetate*".ti,ab.
26. (ointment* or paste* or gel*).ti,ab.
27. (pad or tulle or viscose net or viscose mesh).ti,ab.
28. topical*.ti,ab.
29. (fabric* or polyester* or soft polymer).ti,ab.
30. (silicone or starch based).ti,ab.
31. or/17-30
32. 5 and 9 and 31
33. limit 32 to (yr="2009 -Current" and english)
34. 5 and 12 and 31
35. limit 34 to (yr="1990 -Current" and english)
36. 5 and 16 and 31
37. limit 36 to (yr="1990 -Current" and english)
38. randomized controlled trial.pt.
39. controlled clinical trial.pt.
40. randomized.ab.
41. placebo.ab.
42. clinical trials as topic.sh.
43. randomly.ab.

44. trial.ti.
45. or/38-44
46. exp animals/ not humans.sh.
47. 45 not 46
48. 33 and 47
49. 35 and 47
50. 37 and 47

Search 9: AWD primary studies (pressure ulcers)

Database: MEDLINE

Database coverage: 1946 to present with daily update

Platform: Ovid

Date of search: 7 July 2014

1. Pressure Ulcer/
2. (pressure adj3 ulcer*).ti,ab.
3. (pressure adj3 sore*).ti,ab.
4. (bed sore* or bedsore*).ti,ab.
5. (decubitus adj3 ulcer*).ti,ab.
6. or/1-5
7. Iodine/
8. exp Iodine Compounds/
9. iodine.ti,ab.
10. or/7-9
11. Honey/
12. honey*.ti,ab.
13. 11 or 12
14. Silver/
15. exp Silver Compounds/
16. silver*.ti,ab.
17. or/14-16
18. exp Bandages/
19. Alginates/
20. Ointments/
21. Hydrogel/
22. (bandage* or dressing*).ti,ab.
23. (alginate* or carboxymethylcellulose).ti,ab.
24. (foam* or gauze*).ti,ab.
25. (hydrocolloid* or hydrogel*).ti,ab.
26. "low adher* acetate*".ti,ab.
27. (ointment* or paste* or gel*).ti,ab.
28. (pad or tulle or viscose net or viscose mesh).ti,ab.
29. topical*.ti,ab.
30. (fabric* or polyester* or soft polymer).ti,ab.
31. (silicone or starch based).ti,ab.
32. or/18-31
33. randomized controlled trial.pt.
34. controlled clinical trial.pt.
35. randomized.ab.

36. placebo.ab.
37. clinical trials as topic.sh.
38. randomly.ab.
39. trial.ti.
40. or/33-39
41. exp animals/ not humans.sh.
42. 40 not 41
43. 6 and 10 and 32
44. limit 43 to (yr="2013 -Current" and english)
45. 42 and 44
46. 6 and 13 and 32
47. limit 46 to (yr="2013 -Current" and english)
48. 42 and 47
49. 6 and 17 and 32
50. limit 49 to (yr="2013 -Current" and english)
51. 42 and 50

Search 10: AWD primary studies (diabetic ulcers)

Database: MEDLINE

Database coverage: 1946 to present with daily update

Platform: Ovid

Date of search: 7 July 2014

1. Diabetic Foot/
2. (diabetic foot or diabetic feet).ti,ab.
3. (diabet* adj3 ulcer*).ti,ab.
4. (diabet* adj5 wound*).ti,ab.
5. or/1-4
6. Iodine/
7. exp Iodine Compounds/
8. iodine.ti,ab.
9. or/6-8
10. Honey/
11. honey*.ti,ab.
12. 10 or 11
13. Silver/
14. exp Silver Compounds/
15. silver*.ti,ab.
16. or/13-15
17. exp Bandages/
18. Alginates/
19. Ointments/
20. Hydrogel/
21. (bandage* or dressing*).ti,ab.
22. (alginate* or carboxymethylcellulose).ti,ab.
23. (foam* or gauze*).ti,ab.
24. (hydrocolloid* or hydrogel*).ti,ab.
25. "low adher* acetate*".ti,ab.
26. (ointment* or paste* or gel*).ti,ab.

27. (pad or tulle or viscose net or viscose mesh).ti,ab.
28. topical*.ti,ab.
29. (fabric* or polyester* or soft polymer).ti,ab.
30. (silicone or starch based).ti,ab.
31. or/17-30
32. randomized controlled trial.pt.
33. controlled clinical trial.pt.
34. randomized.ab.
35. placebo.ab.
36. clinical trials as topic.sh.
37. randomly.ab.
38. trial.ti.
39. or/32-38
40. exp animals/ not humans.sh.
41. 39 not 40
42. 5 and 9 and 31
43. limit 42 to (yr="2009 -Current" and english)
44. 41 and 43
45. 5 and 12 and 31
46. limit 45 to (yr="1990 -Current" and english)
47. 41 and 46
48. 5 and 16 and 31
49. limit 48 to (yr="2005 -Current" and english)
50. 41 and 49

Search 11: AWD primary studies (surgical wounds and all ulcer types)

Database: MEDLINE

Database coverage: 1946 to present with daily update

Platform: Ovid

Date of search: 5 August 2014

1. Varicose Ulcer/
2. exp Venous Insufficiency/
3. ((venous or varicose or stasis) adj3 ulcer*).ti,ab.
4. "venous insufficien*".ti,ab.
5. or/1-4
6. Pressure Ulcer/
7. (pressure adj3 ulcer*).ti,ab.
8. (pressure adj3 sore*).ti,ab.
9. (bed sore* or bedsore*).ti,ab.
10. (decubitus adj3 ulcer*).ti,ab.
11. or/6-10
12. Diabetic Foot/
13. (diabetic foot or diabetic feet).ti,ab.
14. (diabet* adj3 ulcer*).ti,ab.
15. (diabet* adj5 wound*).ti,ab.
16. or/12-15
17. exp Skin Ulcer/
18. ulcer*.ti,ab.

19. Surgical Wound Dehiscence/
20. exp Wound Infection/
21. ((chronic* or surg* or postoperat* or "post-operat*") adj3 wound*).ti,ab.
22. (wound* adj3 dehisc*).ti,ab.
23. or/17-22
24. 5 or 11 or 16 or 23
25. Chlorhexidine/
26. (chlorhexidine or chlorhexidene).ti,ab.
27. (dialkylcarbomoyl chloride or "di-alkylcarbomoyl chloride" or dialkylcarbomoyl chloride or "di-alkylcarbomoyl chloride" or DACC).ti,ab.
28. (glucose oxidase or lactoperoxidase or microcid or flaminol or "enzyme alginogel*").ti,ab.
29. (octenidine or octenidene).ti,ab.
30. (PHMB or polihexanide or polyhexanide or polyhexamide or polihexamide).ti,ab.
31. or/25-30
32. 24 and 31
33. randomized controlled trial.pt.
34. controlled clinical trial.pt.
35. randomized.ab.
36. placebo.ab.
37. clinical trials as topic.sh.
38. randomly.ab.
39. trial.ti.
40. or/33-39
41. exp animals/ not humans.sh.
42. 40 not 41
43. 32 and 42
44. limit 43 to (yr="1990 -Current" and english)

Before publishing, need guidance on whether we should be listing preferred brands etc

Introduction

A questionnaire was distributed throughout NHSScotland, targeting staff that would use AWDs. The main aims were to:

- understand current practice and opinions around the use of AWDs;
- find out what/who influences clinicians decision making;
- find out if there are preferred dressings;
- learn about any adverse events/side effects associated with the use of AWDs;
- find out if clinicians feel adequately trained/supported in their use of AWDs;
- give clinicians the opportunity to tell us where consensus guidance would be most useful.

The questionnaire was designed in Survey Monkey, and was open for responses from 02/12/2014 until 05/01/2015. It was sent to the following clinical groups for circulation:

- Scottish Association of Medical Directors (SAMD)
- Academy of Medical Royal Colleges & Faculties in Scotland (Scottish Academy)
- Royal College of General Practitioners – Scottish Council
- Scottish Medical & Scientific Advisory Committee (SMASAC)
- Directors of Public Health
- Faculty of Public Health
- Scottish Executive Nurse Directors (SEND)
- AHP Directors & Leads
- Royal College of Nursing
- Royal College of Paramedics / Scottish Ambulance Service
- Directors of Pharmacy
- Royal Pharmaceutical Society (Scotland)

Contact was also made with certain key individuals, asking them to distribute the questionnaire. It was also circulated by members of the HTA topic group.

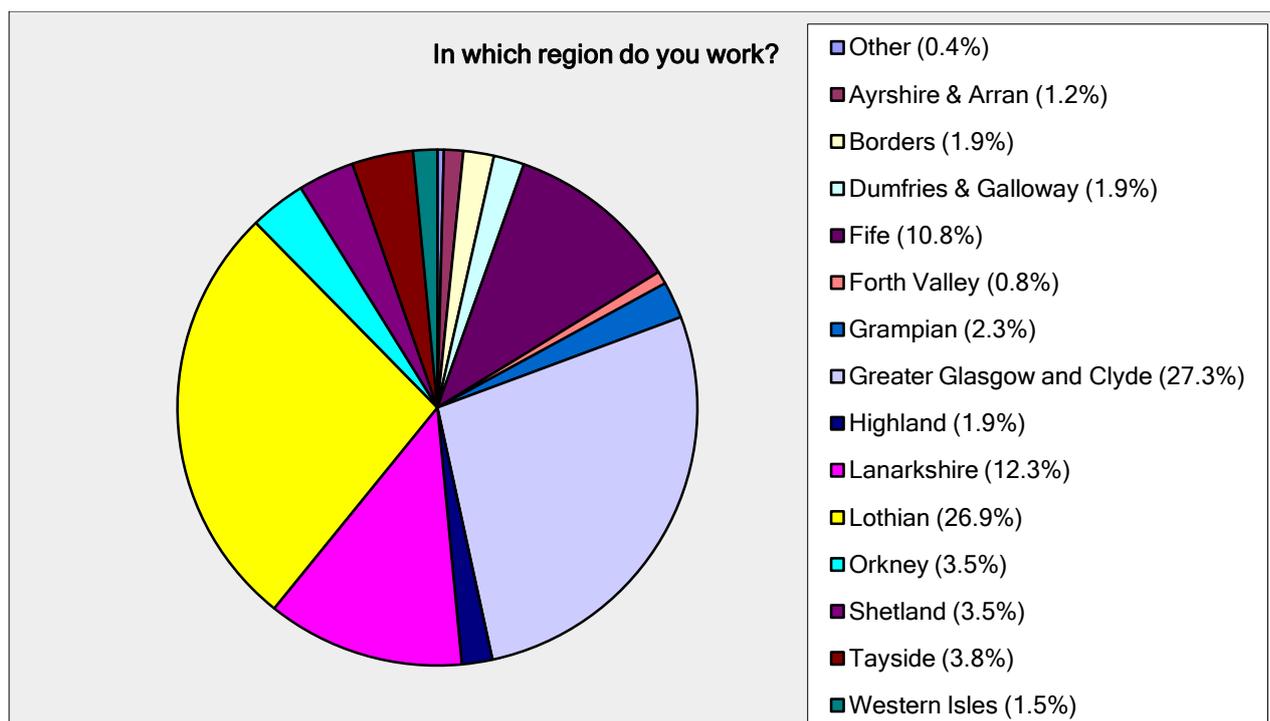
The questionnaire was advertised on the Healthcare Improvement Scotland website, the front page of the SIGN website and the NHS SHOW website. It was also ‘tweeted’ about on the Healthcare Improvement Scotland twitter account, and ‘re-tweeted’ by colleagues and associates.

Results

A total of 263 people responded, including all of the health boards. While it was made clear in the questionnaire that the focus was on the use of AWDs in chronic wounds, some people responded regarding their use of AWDs in other wound types. These responses have still been included.

In which region do you work? 260 out of 263 respondents answered this question (figure 1). Most of the responses came from Lothian (70/254 responses; 27%) and Greater Glasgow and Clyde (71/254 responses; 27%).

Figure 1: In which region do you work?



What is your job role? All respondents answered this question. Most were district nurses (84/263; 31.9%) or podiatrists (54/263; 20.5%) (figure 2).

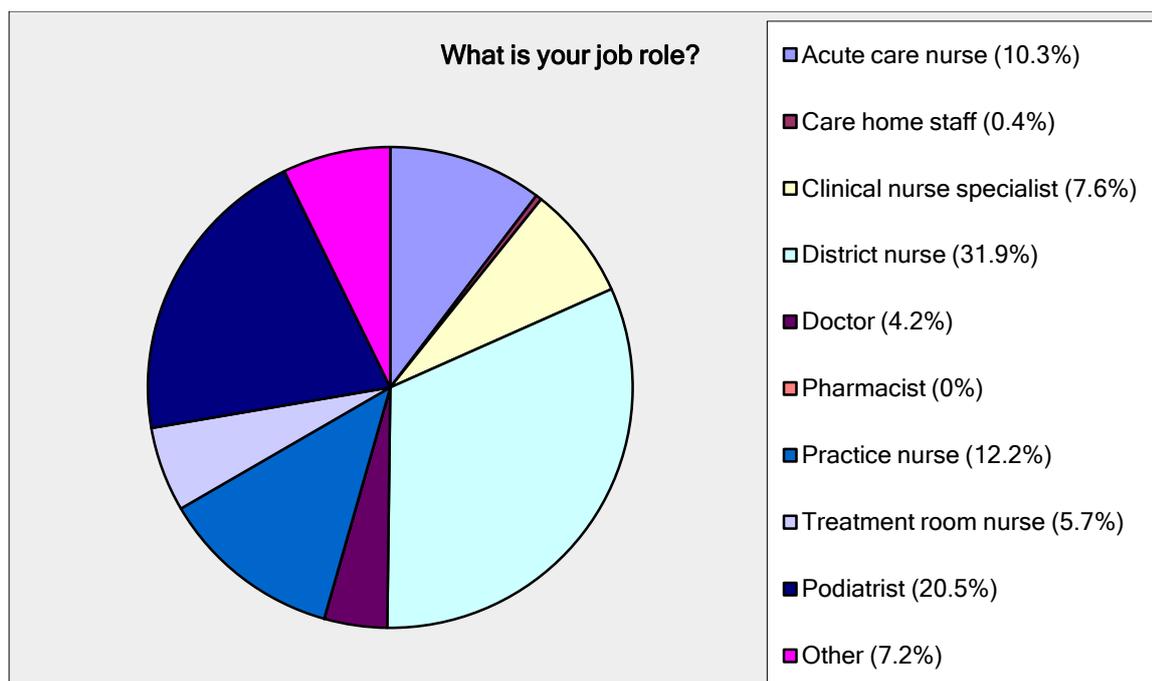
Twenty people (7.6%) responded that they were clinical nurse specialists. Thirteen said they were tissue viability nurses, with the remaining seven detailing their specialism as: infection control, leg ulcer, wound care, dermatology, lead staff nurse, vascular and lymphoedema.

Eleven responses were from doctors (two general practice; one general surgery; one microbiology; one remote and rural surgery; one hospice; one consultant; one orthopaedics, foot and ankle; one maxillofacial, head and neck surgery; one consultant oncologist; and one emergency medicine)

Nineteen people responded 'other' to this question. Eighteen people specified their role: community staff nurse (five); paramedic (two); community hospital (one); clinical nurse manager – prescribing lead (one); outpatient care (one); rehab nurse (one); outpatient charge nurse (one); care home liaison nurse (one); nursing lecturer (one); police custody health care (one); nurse practitioner (one); professional adviser – health (one); clinical support worker (one).

No responses were received from pharmacists.

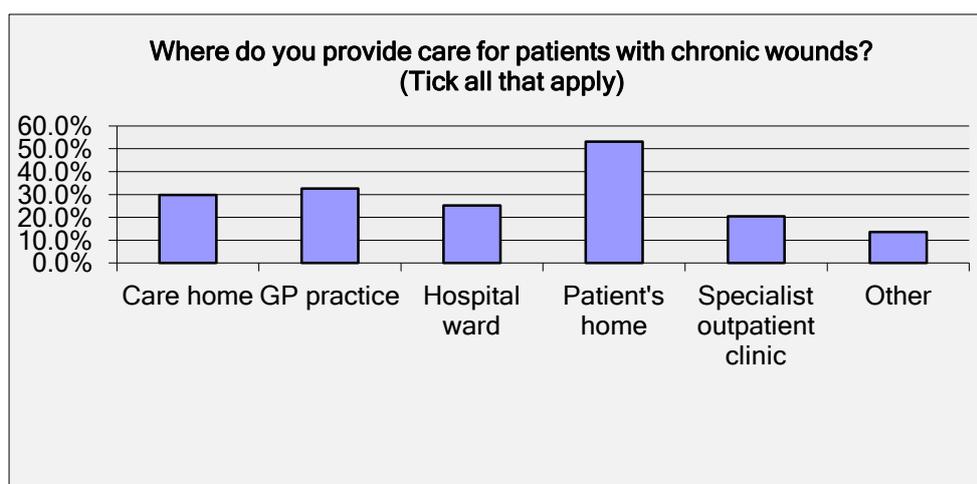
Figure 2: What is your job role?



Are you an independent/community formulary nurse/non-medical prescriber?: 257 people responded to this question, with 121 answering 'yes' (47.1%) and 136 answering 'no' (52.9%).

Where do you provide care for patients with chronic wounds? (Tick all that apply): 262 out of 263 people responded to this question. The most commonly selected answer was 'patient's home' (53.1%) (figure 3). In the comments box, respondents also mentioned a number of other settings, most commonly: podiatry clinics, plastics and burns outreach, diabetes MDT clinics (including diabetic foot clinics), care of the elderly wards and community clinics/hospices.

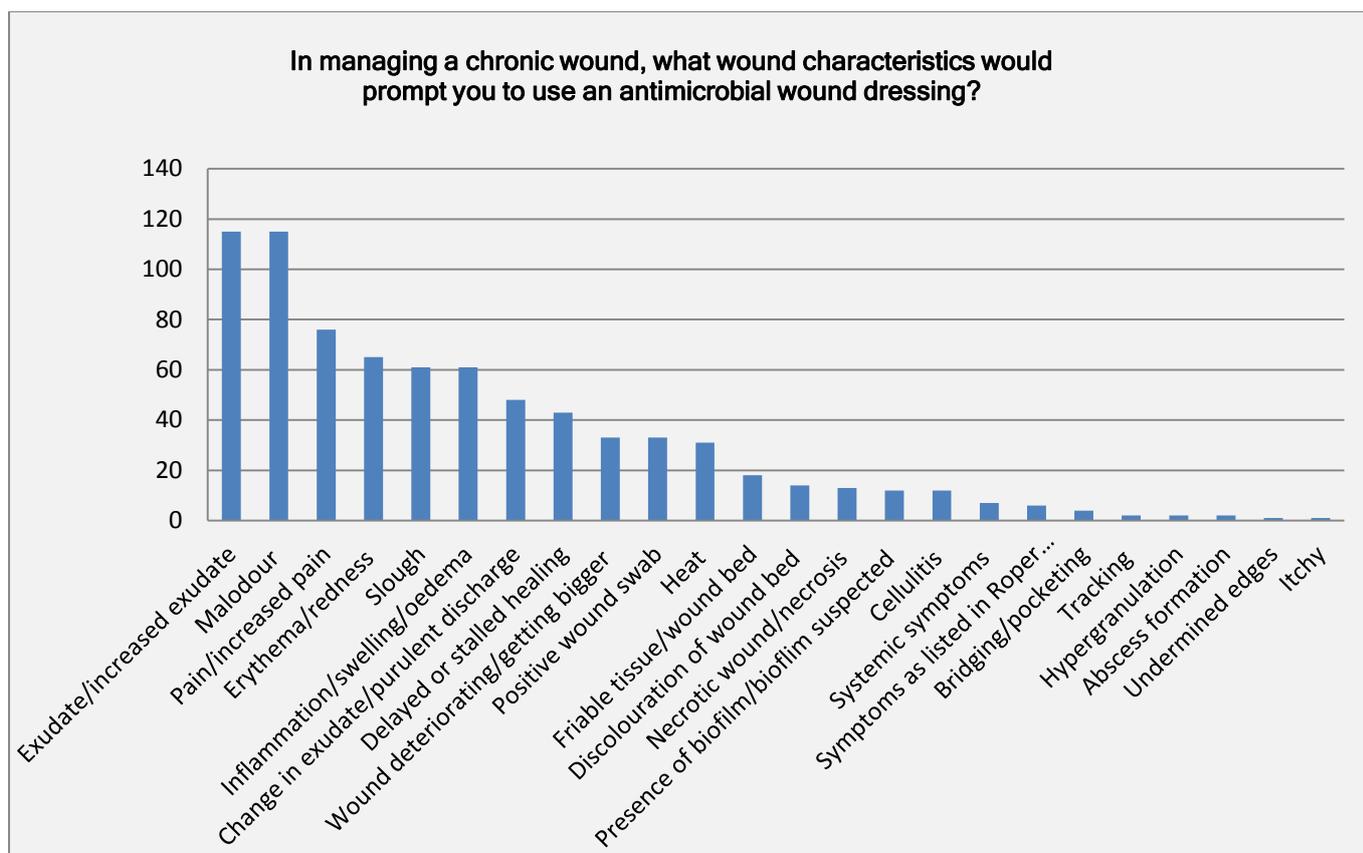
Figure 3: Where do you provide care for patients with chronic wounds?



In managing a chronic wound, what wound characteristics would prompt you to use an antimicrobial wound dressing?

- 257 out of 263 respondents answered this question, with most listing more than one wound characteristic.
- The vast majority of respondents (246/257; 96%) said they would use an AWD if a wound was showing signs of infection. Some (47/257; 18%) simply stated that signs of infection would prompt them to use AWDs, without giving further details. However, most respondents listed symptoms of infection. The symptoms reported, in order of frequency, were (see figure 4 also):
 - Exudate/increased exudate (115/257; 45%)
 - Malodour (115/257; 45%)
 - Pain/increased pain (76/257; 30%)
 - Erythema/redness (65/257; 25%)
 - Slough (61/257; 24%)
 - Inflammation/swelling/oedema (61/257; 24%)
 - Change in exudate/colour of exudates/purulent discharge/pus (48/257; 19%)
 - Delayed or stalled healing (43/257; 17%)
 - Wound deteriorating/getting bigger (33/257; 13%)
 - Positive wound swab (33/257; 13%)
 - Heat (31/257; 12%)
 - Friable tissue/wound bed (18/257; 7%)
 - Discolouration of wound bed (14/257; 5%)
 - Necrotic wound/necrosis (13/257; 5%)
 - Presence of biofilm/biofilm suspected (12/257; 5%)
 - Cellulitis (12/257; 5%)
 - Systemic symptoms (seven respondents)
 - Symptoms as listed in Ropper ladder/algorithm/wound formulary guidelines (six respondents)
 - Bridging/pocketing (four respondents)
 - Tracking (two respondents)
 - Hypergranulation (two respondents)
 - Abscess formation (two respondents)
 - Undermined edges (one respondent)
 - Itchy (one respondent)

Figure 4: Symptoms of infection that would prompt use of an AWD



- Most of the respondents referred to 'infection' and symptoms of 'infection'. Other terminology used included: 'critical colonisation', 'invasive infection', 'local and systemic infection'; 'colonisation'; 'contamination'; 'acute infection'; 'severe infection'; and 'biofilm'.
- Other reasons that prompted the use of AWDs were also given:
 - 13 respondents (5%) said that they would consider the prophylactic use of AWDs. The reasons given included the patient having underlying medical conditions that put them at risk; the wound having a high risk of contamination (because of location e.g. perianal wounds; or large areas of exposure); the wound being seen as at 'high risk' of infection (no other details given); patients medical history making them 'susceptible' or 'high risk' (eg diabetes); immune-suppressed or vascular compromised individuals; previous history of high risk wounds or amputation; and particular wound types (burns and scalds).
 - Four respondents said that they would consider the use of AWDs in people with peripheral vascular disease/poor peripheral circulation/arterial and venous insufficiency.
 - Four respondents said that they would use AWDs on the advice of specialist colleagues/other professionals/tissue viability nurses/from existing care plans.
 - Four respondents listed certain wound types that they might use AWDs for (eg pressure sores, leg ulcers, diabetic patients with active foot disease, large/deep wounds).

- Three respondents said that they might use AWDs in patients intolerant to oral antibiotics/unable to swallow antibiotics.
- Two respondents said that they might consider AWDs in patients recently treated with systemic antibiotics, as AWDs may avoid further treatment with antibiotics.

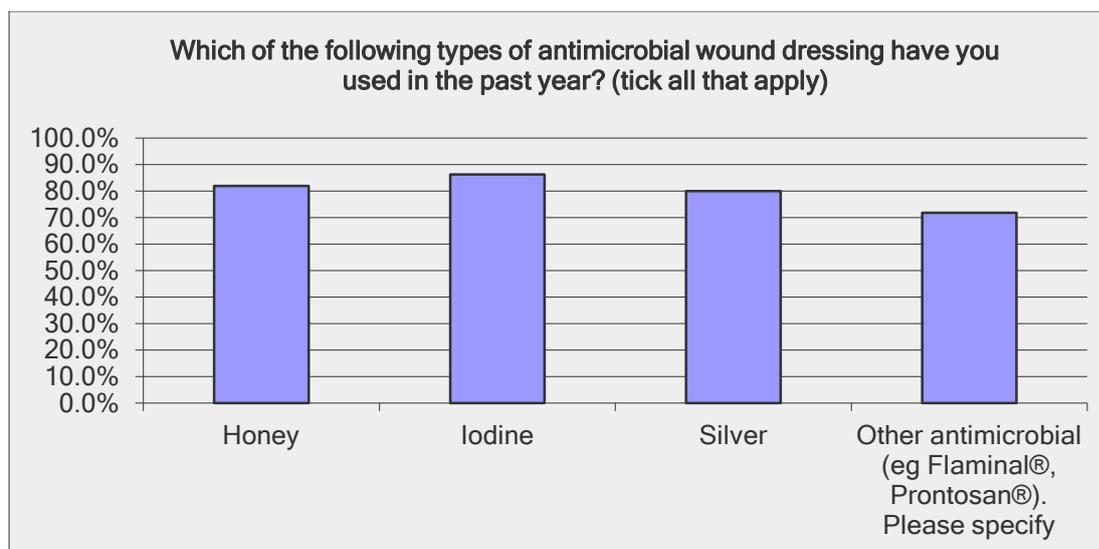
In chronic wounds that you are managing with antimicrobial wound dressings, what wound characteristics would prompt you to stop using the antimicrobial wound dressing?

256 out of 263 respondents answered this question. Most listed more than one wound characteristic. Most respondents (185/256; 72%) stated that the wound characteristics that would prompt them to stop using an AWD would be:

- an improvement in the wound (eg granulating tissue; wound healing; reduction in size) ; and/or
 - an improvement or resolution in the symptoms of infection
- 128/256 (50%) said that an improvement of the symptoms of infection listed in the previous question, or complete resolution of infection, would prompt them to stop using an AWD.
 - 115/256 (45%) said that an improvement in the wound would prompt them to stop using an AWD. 'Improvements' included: healthy epithelial tissue; granulating tissue; decreasing size; healing wound bed; clean wound bed; and healthier surrounding tissue.
 - 65/256 (25%) said that they would stop using an AWD if the wound had not changed.
 - 54/256 (21%) respondents said that they would stop using AWDs if the patients had an allergic reaction / sensitivity / skin irritation / or patient discomfort.
 - 34/256 (13%) said that if a wound deteriorated, they would stop using an AWD.
 - 12/256 (5%) said that a negative wound swab would prompt them to stop using an AWD.
 - Other prompts to stop using an AWD were: spreading infection / antibiotics commenced (five); overgranulation (three); advice from colleagues (two); presence of a biofilm (one); changes in appearance (one).
 - 51/256 (20%) included a time component in their answer.
 - 30 out of 51 respondents said that they would review a wound after 2 weeks: Some said they would stop using the AWD at 2 weeks; some said they would stop using the AWD if there was improvement in the wound at 2 weeks; and some said they would stop using the AWD if there was no improvement/deterioration of the wound at 2 weeks.
 - 14 did not specify a time but said they would follow guidelines for length of usage/manufacturer's instructions, or said they would just use AWDs for a 'short time'.
 - The remaining seven respondents referred to different time periods: 1 week (one); 1 to 2 weeks (two); 2 to 3 weeks (two); and 6 weeks (two).

Which of the following types of antimicrobial wound dressing have you used in the past year? (tick all that apply): 255 out of 263 respondents answered this question. The majority of respondents had used AWDs in the past year (figure 5).

Figure 5: Which of the following types of antimicrobial wound dressing have you used in the past year?

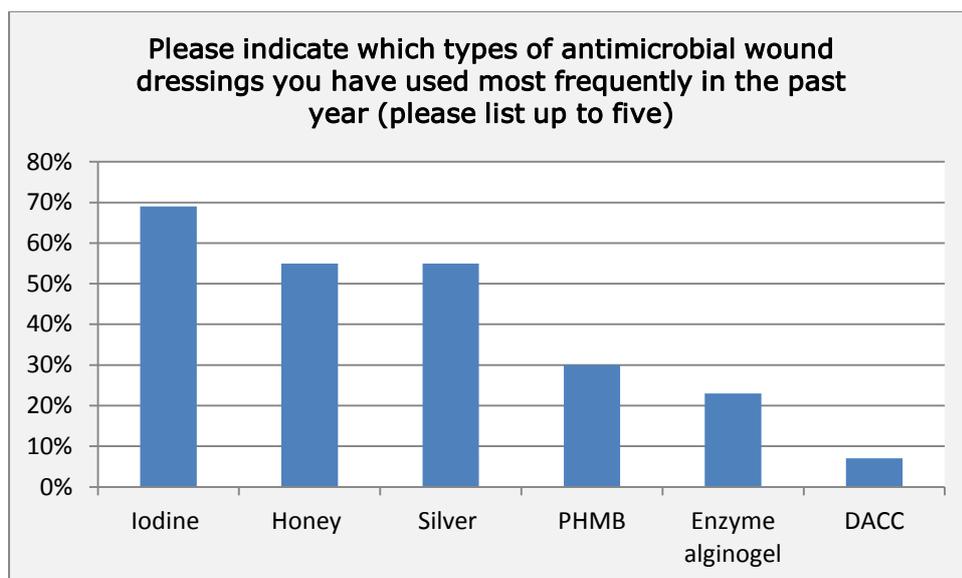


- The 'other' AWDs reported included Prontosan® (69 respondents); Flaminal® Forte/ Flaminal® Hydro (46 respondents); Cutimed® Sorbact® (24 respondents); FLAMAZINE™ cream (13 respondents); PHMB in Covidien dressings (5 respondents); and Metronidazole (2 respondents).
- The following dressings/creams/ointments were also listed by one respondent each as an 'other' AWD: AQUACEL® EXTRA™; Octenelin®; URGO®; ActivHeal®; BACTIGRAS®; TCP™; Oxyzyme™; electrolysed water/sterile water; Proflavine; Whitehead's varnish; CliniSorb®; terra-cortril® ointment; Bactroban ointment; Savlon®; and eosin.

Please indicate which types of antimicrobial wound dressings you have used most frequently in the past year? (please list up to five): 253 out of 263 respondents answered this question. The main results are as follows:

- Out of 253 respondents: 174 (69%) said that iodine dressings were one of the AWDs that they had use most frequently in the past year; 139 (55%) said honey dressings; 138 (55%) said silver dressings; 75 (30%) said PHMB dressings; 58 (23%) said enzyme alginogels; and 18 (7%) said DACC dressings (figure 6).

Figure 6: Please indicate which type of antimicrobial wound dressings you have used most frequently in the past year?



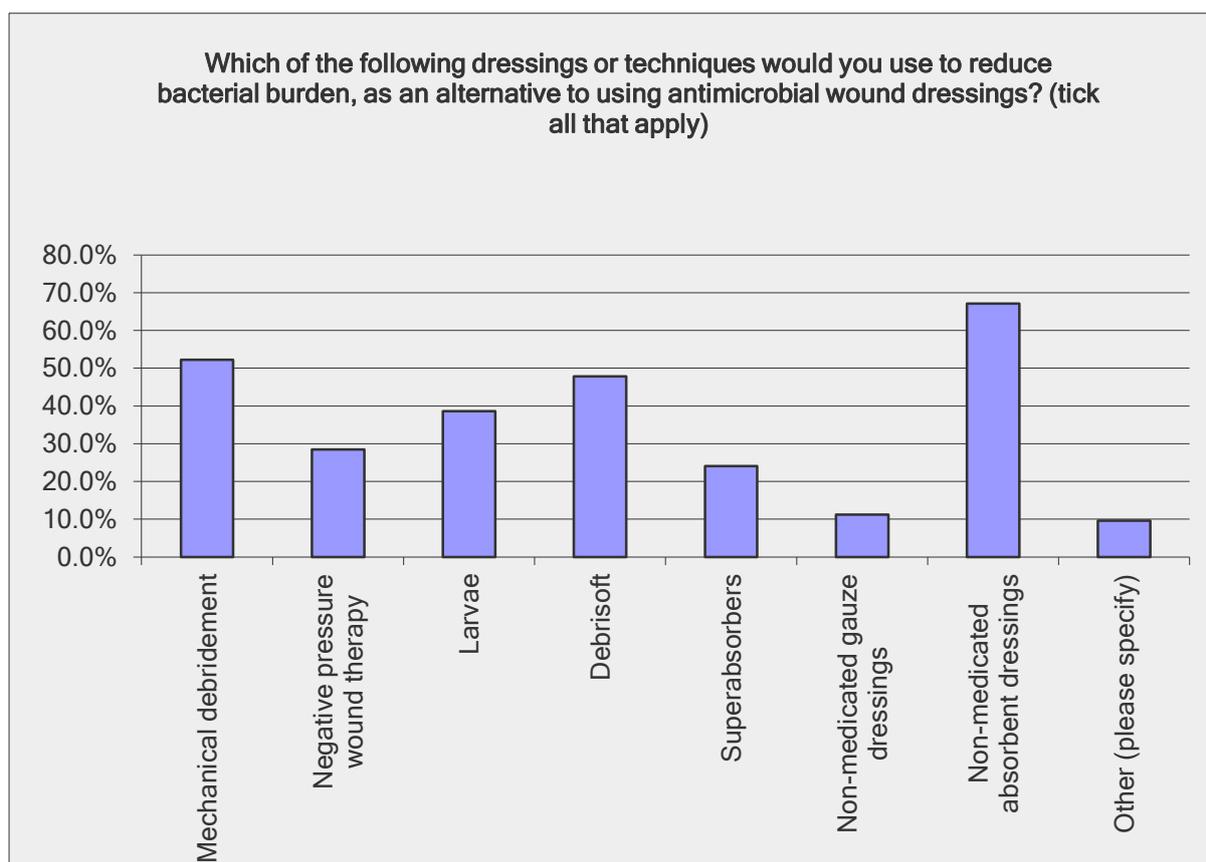
- Of the 174 that said that iodine dressings:
 - 89 said 'iodine' without specifying a type or brand;
 - 59 said they used Inadine[®] (a povidone iodine dressing); and
 - 40 said they used IODOSORB[®] or IODOFLEX[®] (cadexomer iodine dressings).
- Of the 139 that said honey dressings:
 - 102 said 'honey' without specifying a type or brand;
 - 36 said that they used Activon[®] (including Actilite[®] or Algivon[®]);
 - 13 said that they used MEDIHONEY[®]; and
 - two said they used L-Mesitran[®]
- Of the 138 that said silver dressings:
 - 67 said 'silver' without specifying a type or brand;
 - 29 said that they used AQUACEL[®] Ag;
 - 26 said that they used Silvercel[®];
 - 17 said they used FLAMAZINE[™];
 - nine said they used ACTICOAT[®];
 - eight said they used ACTISORB[®] silver;
 - Other silver dressings mentioned were Promogran[™] Prisma (four); Mepilex[®] Ag (four); ALLEVYN[®] Ag (two); Melgisorb[®] Ag (two); Urgotul[®] SSD (one); Kaltostat[®] silver (one); and Algosteril[®] Ag (one).
- Of the 75 that said PHMB dressings, most (69) said that they used Prontosan[®]. Two respondents said they used Kendall[™] AMD antimicrobial foam dressing, and one said Suprasorb X + PHMB[®]. The remaining three did not specify a type or brand.
- The only enzyme alginogel that respondents mentioned was Flaminal[®].
- Of the 18 (7%) that said that DACC-containing dressings were one of the AWDs that they had used most frequently in the past year, two did not specify a type or brand, with the remaining 16 saying that they used Cutimed[®] Sorbact[®].

- Dressings/creams/ointments listed by respondents as 'other' AWDs were: AQUACEL®/AQUACEL® EXTRA™ (three); negative pressure wound dressings (two); electrolysed water (two); UrgoClean® (two): Mepore® (one); ALLEVYN® (one); Mepilex® (one); Proflavine (one); Whitehead's varnish (one); Fucidine H (one); Metrogel® (one); salt soaks (one); BACTIGRAS® (one); 'hydrogel forte' (one) and CliniSorb® (one).
- Five out of 253 respondents said that they did not use AWDs (but this was because of their job role, rather than an opposition to their use).

Which of the following dressings or techniques would you use to reduce bacterial burden, as an alternative to using antimicrobial wound dressings? (tick all that apply).

249 out of 263 respondents answered this question. The most frequently selected options were non-medicated absorbent dressings (67%), mechanical debridement (52%) and Debrisoft® (48%) (figure 7).

Figure 7: Which of the following dressings or techniques would you use to reduce bacterial burden, as an alternative to using antimicrobial wound dressings?



- 'Other' techniques suggested for reducing bacterial burden were: surgical/sharp debridement (two); irrigation (two); VersaJet (two); antimicrobial emollients (two).

Please list any decision aids, prescribing algorithms, checklists or guidelines available to you to guide your decision making on the use of antimicrobial wound dressings.

199 people answered this question. Many respondents listed more than one decision aid/prescribing algorithm/guideline. The most common answer was that local guidelines and/or formularies were used (mentioned by 132 of the 199 respondents). The Ropper ladder (<http://www.ljf.scot.nhs.uk/EducationAndTraining/LothianJointFormularySupportMaterial/wound%20support/Ropper%20Ladder%20Mar%202013.pdf>) was also mentioned by 48 respondents.

The other answers given were:

- Experience/clinical judgement (17 respondents)
- National guidelines e.g. SIGN guidelines (16 respondents)
- TIME (15 respondents)
- Wound assessment charts (15 respondents)
- Colleagues (11 respondents)
- Websites/staff intranet (nine respondents)
- None (eight respondents)
- Wounds UK Best Practice Statement/algorithm (four respondents)
- Wound care continuum (http://www.woundsinternational.com/pdf/content_8777.pdf) (four respondents)
- Texas wound chart (<http://www.nhslothian.scot.nhs.uk/Services/A-Z/DiabetesService/InformationHealthProfessionals/DiabetesHandbookForPrimaryCare/Appendix%20%20Texas%20wound%20chart.pdf>) (three respondents)
- LearnPro (three respondents)
- BNF (three respondents)
- TV resource folder (three respondents)
- Wound care photos (two respondents)
- EWMA consensus (two respondents)

The following answers were given by one respondent each:

- Wound matrix
- Diabetic foot ulcer algorithms
- Reference materials
- Swab results
- Clinical evidence
- Purpose of dressing
- Guide to usage of wound care products
- Electronic e-clinic
- Leaflets inside dressing packs
- Diabetic foot protocol
- Wound product evaluation form
- Product reps
- Community wound assessment tool/Pressure ulcer assessment tool

- Protocol for selection of silver dressings
- Podiatry competency framework for integrated diabetic footcare
- QIS TV wound assessment and action guide
- Turner's criteria
- Full history from patient/inspection and assessment of wound
- Wound classification and dressing guide
- Wound management/TV guidelines
- Wound bed preparation
- TV guidelines on use of dressings
- Wound classification and product selection guide
- Wound care education sessions
- Scottish adapted pressure grading tool
- Wound chart care plan
- Burns wound management as per cobis
- Made easy documents
- European pressure ulcer chart
- Global wound academy
- Wound assessment pathways

Once you have established that an antimicrobial wound dressing is required, and in the absence of any contraindications, do you have a preference for certain types (for example, silver, honey, iodine etc) in the following wounds? Please list brand names if you can.

198 people answered all or part of this question. The results are summarised in figure 8. Detailed results for each wound type are given below:

- *Pressure ulcers*: 150 respondents gave an answer to this part of the question. Honey dressings were the most commonly cited AWDs for pressure ulcers (58/150; 39%); followed by iodine (41/150; 27%) and then silver (39/150; 26%).
- *Venous ulcers*: 148 respondents gave an answer to this part of the question. Iodine dressings were the most commonly cited AWDs for venous ulcers (48/148; 32%); followed by silver and iodine (39/148 for both; 26%).
- *Arterial leg ulcers*: 128 respondents gave an answer to this part of the question. Silver dressings were the most commonly cited AWDs for arterial leg ulcers (40/128; 31%); followed by honey (30/128; 23%) and then iodine (28/148; 19%).
- *Foot ulcers in people with diabetes with optimum blood flow*: 158 respondents gave an answer to this part of the question. Silver dressings were the most commonly cited AWDs for this wound type (58/158; 37%); followed by iodine (57/158; 36%) and then honey (47/158; 30%)
- *Foot ulcers in people with diabetes with poor blood flow*: 155 respondents gave an answer to this part of the question. Iodine dressings were the most commonly cited AWDs for this wound type (59/155; 38%); followed by silver (54/155; 35%) and honey and other dressing types (25 responses out of 155 each; 16%).

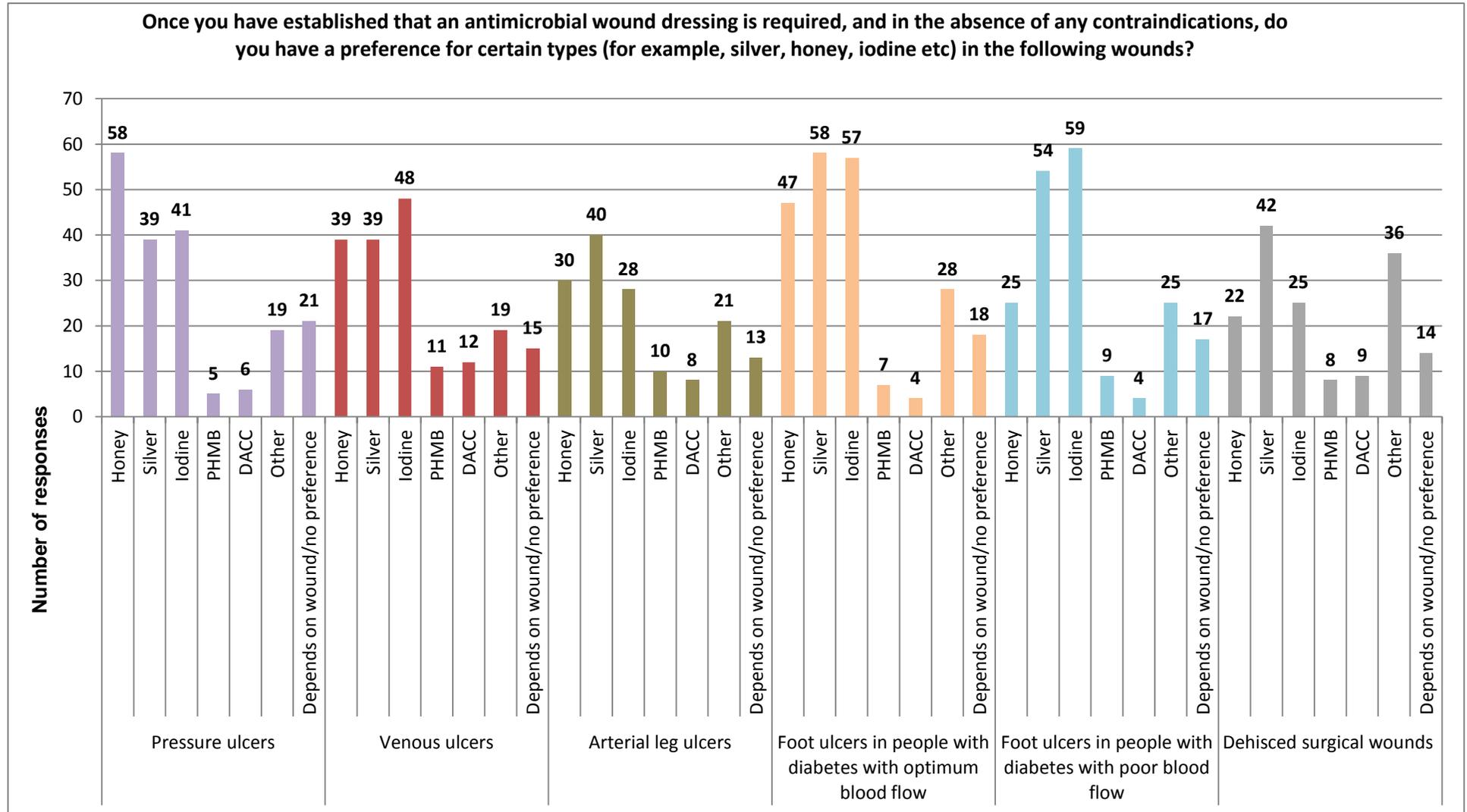
- *Dehisced surgical wounds*: 132 respondents gave an answer to this part of the question. Silver dressings were the most commonly cited AWDs for dehisced surgical wounds (42/132; 32%); followed by 'other' AWDs (36/132; 27%) and iodine (25/132; 19%).

Respondents were asked to list their preferred brands. The preferred brands for each dressing type are detailed below:

- Honey dressings: the brand cited most frequently was Activon® (listed 87 times in total for this question); followed by MEDIHONEY® (listed 40 times); and then Melladerm® (listed four times)¹.
- Silver dressings: the brand cited most frequently was AQUACEL® Ag (listed 89 times in total for this question); followed by Silvercel® (listed 77 times); and then ACTICOAT®; (listed 23 times). Other brands mentioned were FLAMAZINE™ (listed nine times); Promogran™ Prisma (listed eight times); ACTISORB® silver (listed six times); Mepilex® Ag and 'Alginate Ag' (both listed three times); and Melgisorb® Ag, ALLEVYN® Ag and Calgitrol® Ag paste (listed one time each)¹.
- Iodine dressings: the brand cited most frequently was Inadine® (listed 109 times); followed by IODOSORB®/IODOFLEX® (listed 80 times)¹.
- Other dressings: The brand cited most frequently was Flaminal® (listed 72 times); followed by Prontosan® (listed 48 times); Cutimed® Sorbact® (listed 43 times) and AQUACEL® (listed 29 times). Other brands listed were: ActiFormCool® (seven times); Kaltostat® (four times); Mesorb® and larvae (both listed three times each); Kendall™ AMD foam/gauze, ALLEVYN® and Tegaderm™ (listed two times each); and Granuflex®, Sorbsan SA, Coban™ 2 layer, Mepilex® Border, Icthopaste®, URGOClean®, 'Vidine', Biatain® alginate, Whiteshead's varnish and Actiheal® (all listed once each)¹.

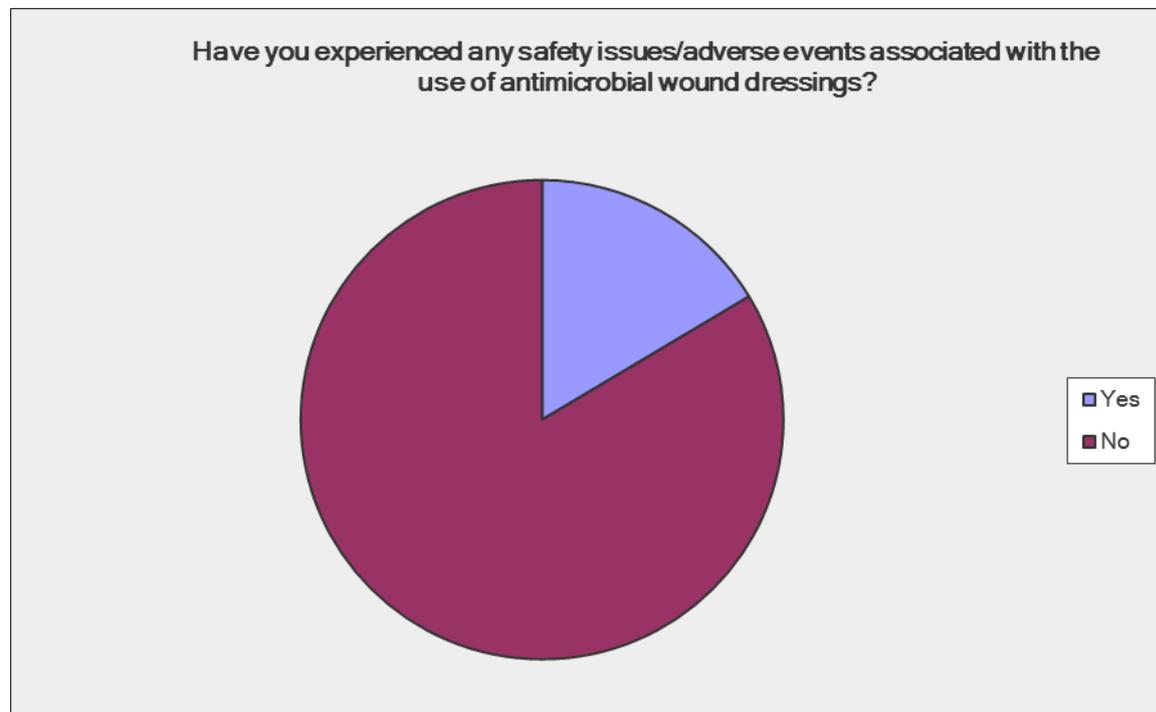
¹ NB The same brand may have been listed more than once by the same respondent for each different wound type.

Figure 8: Once you have established that an AWD is required, do you have a preference for certain types?



Have you experienced any safety issues/adverse events associated with the use of antimicrobial wound dressings?

Figure 9: Have you experienced any safety issues/adverse events associated with the use of antimicrobial wound dressings?



250 respondents answered this question. Most said that they had not experienced any adverse events/safety issues (84%).

The adverse events reported by respondents for different AWDs are detailed below:

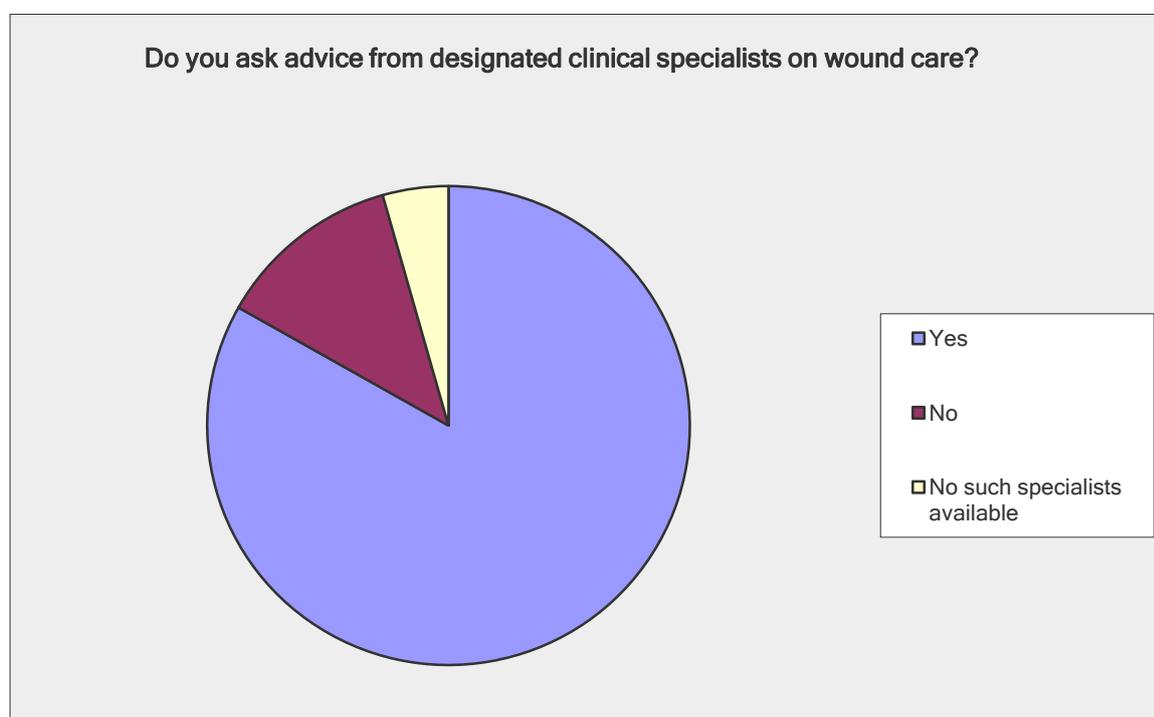
- **Honey dressings:** 11 respondents listed pain/discomfort for honey dressings. Other adverse events reported were: contact allergy (two respondents); increased wound maceration (two respondents); difficult to wash off (one respondent); and increased blood sugars in people with diabetes (one respondent).
- **Silver dressings:** Eight respondents listed localised reactions/inflammation associated with the use of silver. Other adverse events reported were: '...chronic pressure ulcers on one patient improved with discontinuation of silver...' (one respondent); silver toxicity after long term use (one respondent); 'a patient having flamazine applied when diagnosed with kidney failure' (one respondent); discolouration (one respondent); 'generally arterial wound pt report intolerance to silver' (one respondent); 'neutropaenia in a burns patient referred to us who had prolonged use of topical silver sulphadiazine' (one respondent); pain (one respondent); and 'inappropriate use of silver dressings in palliative patients who were about to receive radiotherapy...' (one respondent).
- **Iodine dressings:** five respondents mentioned monitoring thyroid function with use of iodine. Other adverse events reported were: contact sensitivity (three respondents); allergy (two respondents); pain (one respondent); and 'too drying' (IODOSORB®; one respondent).

- **Other dressings:** Flaminal® was mentioned by two respondents: 'significant (but allergic) reaction to flaminal hydro'; and 'One patient could not tolerate Flaminal Forte but could tolerate Flaminal Hydro due to reduced levels of alginate present'
- **General adverse events:** Some respondents listed adverse events, but did not apply them to a dressing type:
 - Allergy/intolerance (five respondents)
 - Pain (three respondents)
 - Damage to surrounding skin (two respondents)
 - Increased inflammatory process (one respondent)
 - Adherence to wound bed (one respondent)

Do you ask advice from designated clinical specialists on wound care?

250 respondents answered this question, and most answered 'yes' (83%) (see figure 10).

Figure 10: Do you ask advice from designated clinical specialists on wound care?



177 respondents gave further details in the comments box, with 110 saying that they would ask advice from tissue viability nurses. The next most common answer was podiatry/specialist podiatrists (mentioned by 24 respondents). The remaining answers were:

- I am the specialist (17 respondents)
- Colleagues generally (14 respondents)
- Vascular team/vascular nurse (13 respondents)
- Dermatology/dermatology nurse (12 respondents)
- District nurse (seven respondents)
- Diabetes foot care team/diabetes foot clinic (seven respondents)
- Wound product representatives (five respondents)

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- Leg ulcer nurses (three respondents)
- 'Link' nurses (three respondents)
- Surgeons (two respondents)
- Clinical nurse specialist (two respondents)
- Patient's consultant (one respondent)
- Infection control nurse (one respondent)
- Treatment room nurse (one respondent)
- Acute diabetic team (one respondent)
- Bacteriologists (one respondent)
- Cardiology (one respondent)
- Expert forums (one respondent)

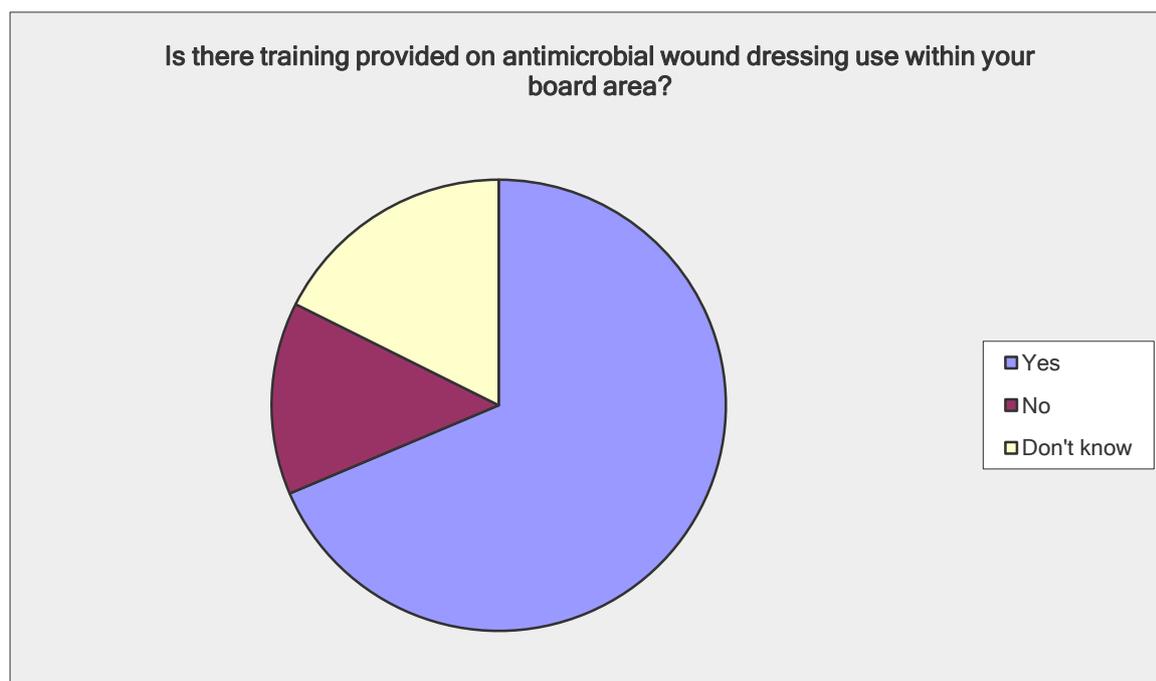
A minority of respondents gave negative comments about the specialist advice (or lack of) that was available to them:

- 'Usually not helpful at all as they seem to follow a tickbox'
- 'Yes but issues with Tissue Viability 'assessing' wounds be telephone therefore no confidence in service some of the time'
- 'No longer have tissue viability nurse in this area'
- 'Used to when we had a specialist nurse...'
- 'Occasionally have a Tissue Viability input...now poorly resourced and over stretched with little experience...had much better service in past'

Is there training provided on antimicrobial wound dressing use within your board area?

261 out of 263 respondents answered this question. Most said that training was provided in their board area (69%) (see figure 11).

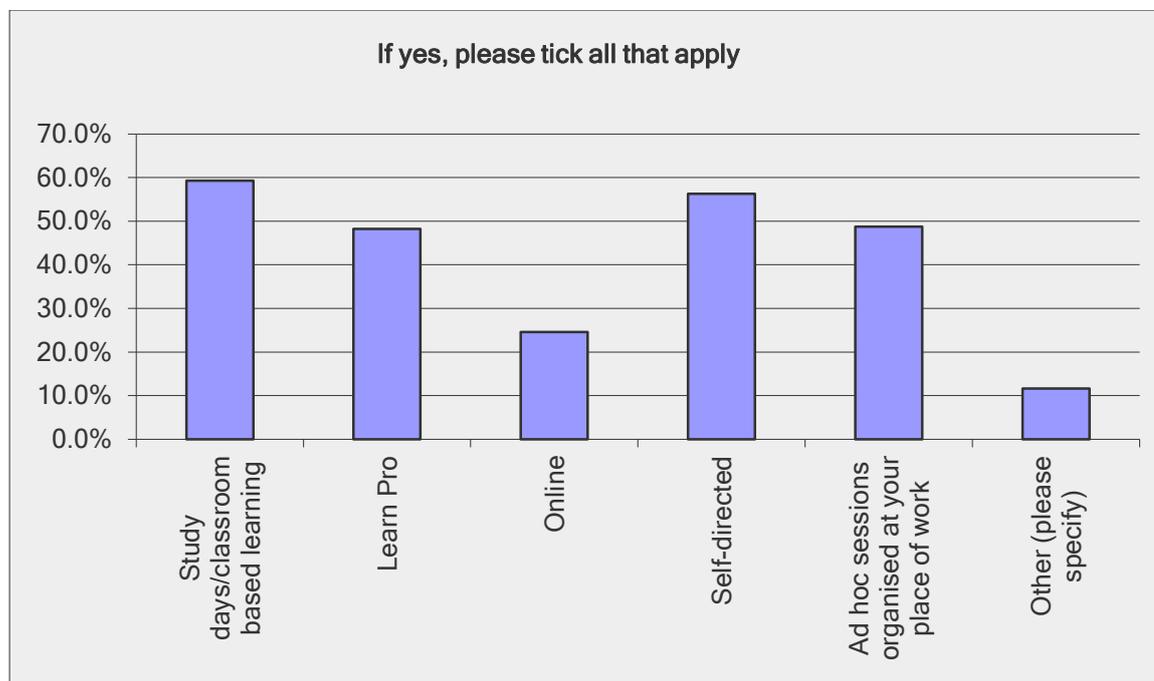
Figure 8: Is there training provided on antimicrobial wound dressing use within your board area?



If yes, please tick all that apply

199 out of 263 respondents answered this question (see figure 12).

Figure 9: If yes, please tick all that apply



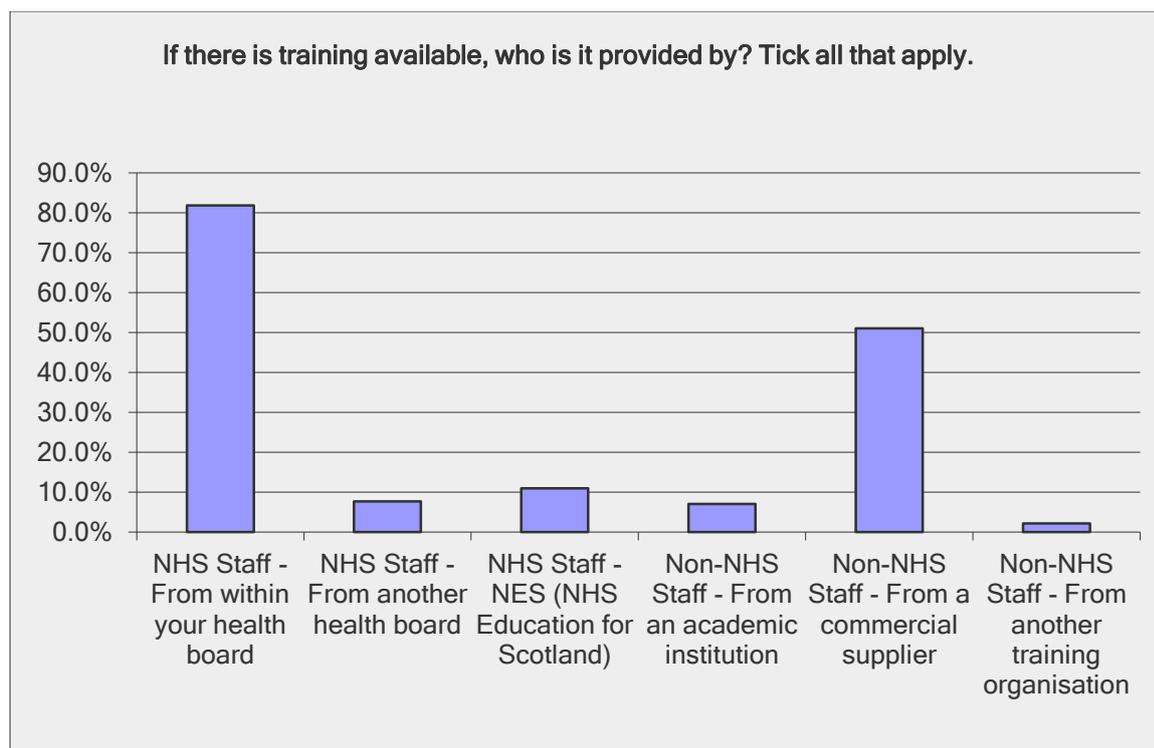
48 respondents provided additional comments to this question:

- 15 said that training had come from company representatives or manufacturer sponsored events.
- Other answers included:
 - Tissue viability led education sessions/study days (four respondents)
 - Training associated with wound formulary (three respondents)
 - Clinical support (three respondents)
 - 'reps are discouraged' (one respondent)
 - Locality forums in place (one respondent)
 - Skin vitality training (one respondent)
 - Forms part of rolling programme of study events (one respondent)
 - 'lunch and learn meetings' (one respondent)
 - 'x4 yearly wound management meetings' (one respondent)
 - 'practice nurse magazine' (one respondent)
 - 'Useful LearnPro module, but there were some problems with the marking and certification of this' (one respondent)
 - NES (one respondent)
 - Conferences (one respondent)

If there is training available, who is it provided by? Tick all that apply.

182 out of 263 respondents answered this question. The results suggest that most training comes from NHS staff from within their health board (selected by 82% of 182 respondents); followed by commercial suppliers (selected by 51% of 182 respondents) (see figure 13).

Figure 10: If there is training available, who is it provided by?



Have you attended or completed any training in the past year on antimicrobial wound dressings? This includes training on wound care more generally, where the use of antimicrobial wound dressings was covered.

262 out of 263 respondents answered this question. 54% answered 'yes' and 46% answered 'no'.

Are there any factors preventing you attending or completing training?

250 out of 263 respondents answered this question. 41% answered 'yes' and 59% answered 'no'.

125 of these respondents provided additional comments. The majority (85/125; 68%) said that lack of time/clinical pressures/staffing issues were stopping them from attending training. Other reasons given were:

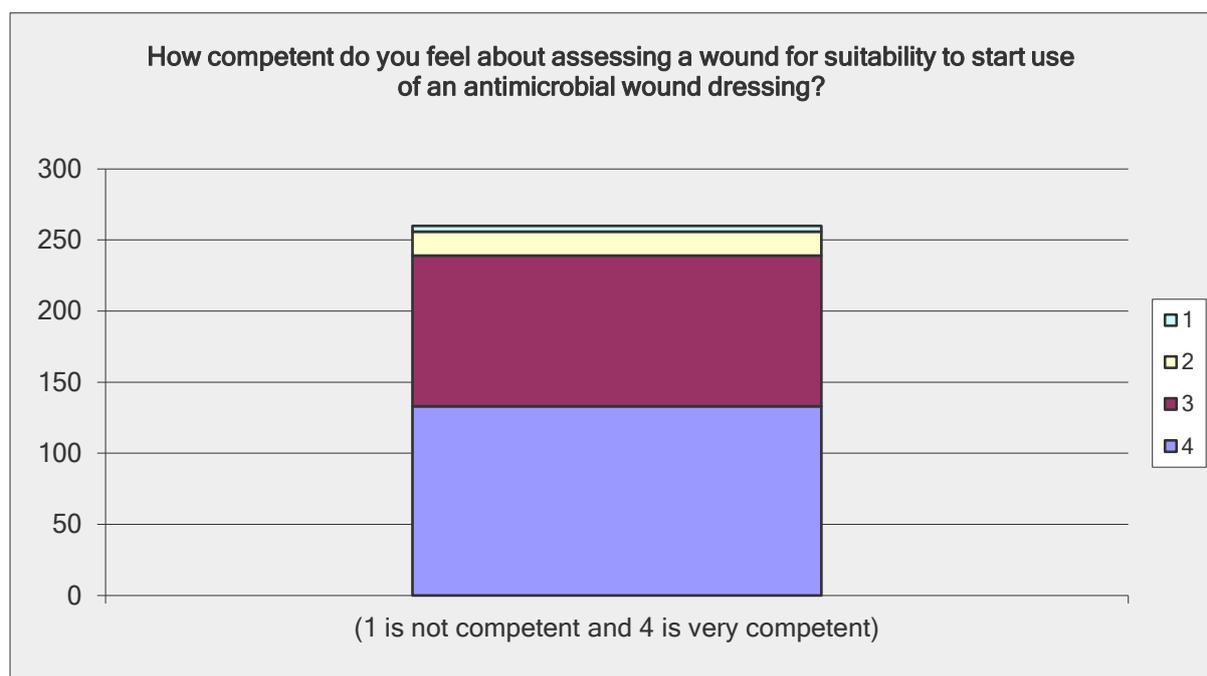
- 20 respondents said that they were not aware of any training sessions.
- 13 respondents said that financial constraints prevented them from attending training.
- Six respondents said that they had not felt that they needed any training.
- Six respondents said that the location of the training had not been suitable (two lived on an island).
- Five respondents said that their departments had banned training from company representatives; or said they would not attend due to concern that the training was biased.
- Four respondents said that they had a limited number of days per year to dedicate to training, and other topic areas had taken priority.

- Three respondents said that the date/time of the trainings had not been suitable, or that the notice required to attend was insufficient to arrange suitable cover.
- One respondent felt that they did not use AWDs enough to justify training.

How competent do you feel about assessing a wound for suitability to start use of an antimicrobial wound dressing?

260 out of 263 respondents answered this question. The vast majority (92%) answered '3' or '4', suggesting that they feel competent about assessing a wound for suitability to start use of an AWD (figure 14).

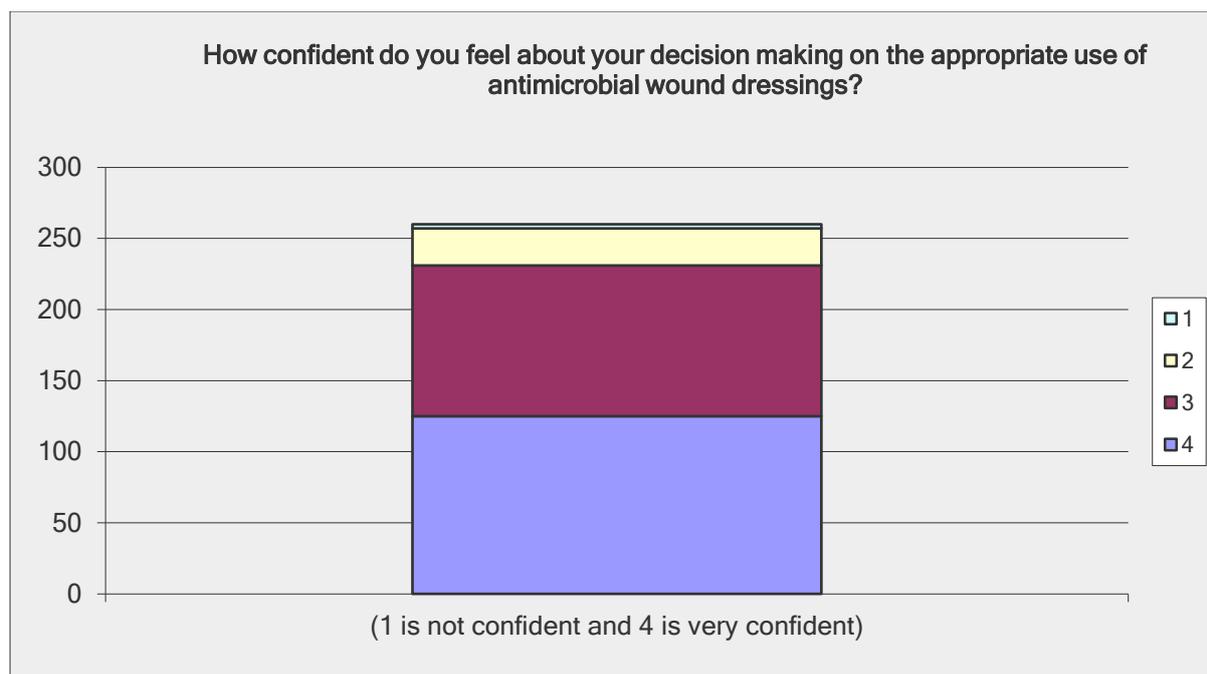
Figure 11: How competent do you feel about assessing a wound for suitability to start use of an AWD?



How confident do you feel about your decision making on the appropriate use of antimicrobial wound dressings?

260 out of 263 of the respondents answered this question. The vast majority (89%) answered '3' or '4' suggesting that they feel confident about their decision making on the appropriate use of AWDs (figure 15).

Figure 12: How confident do you feel about your decision making on the appropriate use of AWDs?



Have you anything else you would like to tell us about antimicrobial wound dressings?

74 respondents answered this question. A proper thematic analysis was not done. However, a preliminary analysis highlighted a number of common themes:

Theme 1: It is not a one-size fits all situation

- ‘This concerns more the body part the dressing is being applied to than the type of dressing; when a foot is being dressed it is important to consider the mechanics of the foot and its interaction with footwear, the movement of the product with mobilising’ [podiatrist]
- ‘...I assess wound on an individual basis...What works on one type of wound may not suit the patients needs!’ [treatment room nurse]
- ‘...it is the presenting clinical picture as well as the co-morbidities the patient has as well as the treatment objectives that form part of the decision making process for antimicrobial selection, not the wound type specifically’ [tissue viability nurse]
- ‘...wound care should be individual and choice of dressing relate to individual circumstances...’ [clinical nurse specialist, wound care]
- ‘i do think that each wound is different and the question of what type of antimicrobial for a specific wound type -ie arterial, venous etc is very hard to say one antimicrobial only to this type. i have yet to see one type of wound that does not have other factors for consideration!’ [clinical nurse specialist, dermatology]
- ‘not always able to use due to where the wound is and the patient’s condition’ [acute care nurse]
- ‘Every patient is an individual and many other factors are involved e.g. nutritional state.’ [district nurse]
- ‘We need a selection as wounds can vary greatly. Some have high levels of exudate and so require absorbency along with the topical antimicrobial, some have minimal levels of

exudate. Some tissue needs debriding so honey would be helpful as it combines the debriding with the antimicrobial activity. Some require purely a reduction in the bacterial burden and so a non-absorbent silver containing dressing would be appropriate, rather than a silver releasing dressing...' [nurse lecturer]

- 'my decision is based upon an individual holistic assessment of the patient concerned not wound type.' [tissue viability nurse]
- 'All dressings have a cost implication and a holistic wound assessment is required for the best treatment.' [community staff nurse]

Theme 2: AWDs are useful, if they are used correctly

- 'Very useful dressings for the correct wound' [tissue viability nurse]
- 'They are a useful adjunct to our armoury when used appropriately...They should be used appropriately and sparingly following formal wound assessment' [district nurse]
- 'I think it is very important to remember that antimicrobial dressings are used to reduce and manage bacterial burden and not to heal wounds. They should be used during that time period that a wound is not healing normally due to bacterial burden and then stopped when the wound returns to healing. The challenge with chronic wounds is often the underlying co-morbidities which can influence and slow down healing, this can mean that over a long period of time a patient may require to start and stop antimicrobial dressings several times to manage the bacterial load as it changes. I have had some patients who everytime we stopped using an antimicrobial the wound deteriorates so we had to continue for long periods of time.

Also some antimicrobial products, e.g. manuka honey, are not used just for their antimicrobial properties, they also debride the slough or necrotic tissue, and stimulate the new fibroblasts in the wound to grow, stimulating wound healing without affecting the new cells. In this situation it can be used until a wound heals as it stimulates the healing process which is often slow in patients with co-morbidities.' [tissue viability nurse]

- 'Need to use them appropriately, I have seen expensive dressings being applied to dry eschars. Also too often "silver" dressings are lumped together, especially around discussions about cost and limiting formularies to one silver dressing only, but the silver is the antimicrobial element of the dressing only and the different silver dressings are used for different types of wounds and different stages of the wound
Due to the high risk patients we treat and their delayed wound healing we tend to use antimicrobial dressings on most wounds' [podiatrist]
- 'the use of honey widely has been of great benefit to many patients however with vascular wound there is definite drawing which can be uncomfortable for the patient. Silver is particularly useful where a wound has suddenly become burdened and seems to act very quickly.
Prontosan gel has been great in painful vascular wounds.' [podiatrist]
- 'We are the 'frontline'. Despite any evidence to the contrary we are the clinicians who see results on the odd occasion silver etc is used. I do use clinical judgment and only prescribe when all else has failed.' [district nurse]
- 'I don't use a lot of them i think there is an over use but there are cases where they are needed...' [clinical nurse specialist, dermatology]

- 'When used appropriately, anti-microbial wound dressings form an essential element of holistic wound management.' [lead staff nurse]
- 'In my experience they are excellent and work very well' [practice nurse]
- 'Used appropriately these are very effective methods of treatment of localised wound infection...' [district nurse]
- 'I feel that silver dressings when used appropriately can be very useful in diabetic foot ulcers. It is very unfortunate that there is very little evidence for their use therefore there use is restricted.' [podiatrist]
- 'they are very good used appropriately' [practice nurse]
- 'do not use to heal a wound. use to remove some of the barriers to wound healing such as too much bacteria' [tissue viability nurse]

Theme 3: AWDs might negate the use of antibiotics

- 'They are a useful adjunct to our armoury when used appropriately often negating the need for oral antibiotics...' [district nurse]
- 'Topical antimicrobials can sometimes prevent using systemic antimicrobials' [tissue viability nurse]
- 'I also think that we have to be aware that in the current climate with the push to reduce antibiotic use that we will actually come to a point where if something like an antimicrobial dressing can prevent someone requiring antibiotics then we will need to use the dressings more rather than less. When they start looking at the cheaper cost of an antimicrobial wound dressing to prevent someone using an expensive antibiotic especially when antibiotics are going to be more scarce I think we will see an increase in use of dressings over the next 10 years.' [tissue viability nurse]
- 'I appreciate that used incorrectly they are an expensive and not completely proved resource but I believe that without these on formularies we risk not being able to treat wounds effectively and an increase in use of antibiotics when the drive is on to reduce these' [district nurse]
- 'I feel that the use of antimicrobial wound dressings are needed to aid in healing and prevent the use of oral antibiotics' [practice nurse]
- 'they play an important part in healing wounds and can prevent deterioration reducing the need for antibiotic therapy. They also can enhance antibiotic therapy' [district nurse]
- 'I also think that as pressure to reduce oral antibiotic use continues, there may be a correlated rise in use of topical antimicrobials' [clinical nurse specialist, community vascular]
- 'They are a necessity in managing complex wounds and the reduction of antibiotic use' [paediatric tissue viability nurse]

Theme 4: What is available on the formulary is not adequate/dressings not available

- 'The current honey dressing on our formulary is not as effective as other honey dressings available so feels somewhat of a false economy.' [district nurse]
- 'We are no longer allowed to order Mepilex Ag or aquacel ag, both of which we had great results with' [podiatrist]
- 'choice of dressing is dependent on what is available in that particular clinic' [podiatrist]

- 'Only that it requires formal assessment and a willingness to look for alternatives and seek advice from wherever is a hand.....I usually look on line and check what is being used in other areas then I look at what I have available and go from there. Ordering can be a lengthy process in remote areas.' [district nurse]
- 'although i appreciate antimicrobial dressings can be overused I feel often the use is frowned upon and dressing choice from formularly is very limited as a result' [podiatrist]
- 'I would like to have the ability to choose a silver dressing if I think it appropriate without having to justify it in paper work and send it off. We should be making decisions in the best interests of our patients' [practice nurse]
- 'we only have access to inodine outwith day time hours so can only use this and ask day staff to asses in am' [district nurse]
- 'I would like on formulary an absorbant dressing which covers large areas with an antimicrobial action. Especially lower limbs, infected covering an area knee to ankle' [district nurse]
- 'Not allowed to use silver dressings in NHS Lothian unless can justify or prescribed from acute sector' [treatment room nurse]
- 'we are VERY limited due to formula and find it frustrating when speak to tissue viability nurses and experts ie dermatology and they go off formula. Always had good results with iodine but can't use routinely filling out forms all the time to go off formula not helpful' [practice nurse]
- 'REALLY DISAPPOINTED THAT SILVER DRESSINGS WERE TAKEN OFF THE FORMULARY IN IOTHIAN. DECISION MAKING SHOULD BE DONE BASED ON CLINICAL NEED. HAVING TO COMPLETE DOCUMENTATION EVERY TIME A PATIENT HAS BEEN ASSESSED AS REQUIRING AN ANTIMICROBIAL THAT IS NOT ON THE FORMULARY TAKES UP TIME THAT COULD BE SPENT MORE EFFECTIVELY' [district nurse]
- 'I feel we had more autonomy previously on the wider selection of wound dressings' [district nurse]
- 'It would be good to have access to all appropriate antimicrobials / dressings and not only be limited to the ones on the wound formulary e.g. Prontosan' [podiatrist]
- 'HAD PREVIOUSLY HAD VERY GOOD RESULTS WITH ACTICOAT ABSORBANT BUT UNFORTUNATELY THIS IS NO LONGER AVAILABLE ON WOUND FORMULARY.' [district nurse]

Theme 5: AWDs are of minimal benefit / AWDs are overused

- 'Usually of minimal benefit in infected wounds' [doctor, general surgery]
- 'There is a fantastic amount of money wasted on wound dressings, particularly in the community, with no scientific evidence to back the use of most dressings' [doctor, surgery]
- 'Although I have commented on which ones I use I try and avoid their use and prefer products such as purilon/intrasite gel or alginate dressings to clean wound beds. The patients I have used iodine and silver on have long standing problem. Also more recently a fungating breast wound was treated with charcoal/silver and metronidazole gel.' [practice nurse]
- 'They are overused and expensive and bring very little to the party in chronic wound management but there is the odd occasion that I would use them.' [district nurse]

- 'I still believe they are over used within our health board area in wounds that are maybe chronic but are not infected...' [podiatrist]
- 'I would not support antibiotic impregnated wound dressings, and I would refuse their use in my hospital. I would also question the use of heavy metals and antiseptics except for electrolysed water. Honey, phage dressings and larvae require more evidence of clinical benefit.' [consultant microbiologist]
- 'There is a need to reduce inappropriate use of antimicrobials; however, there is a place for them when used correctly...' [clinical nurse specialist, community vascular]
- '...It is the inappropriate use particularly by non prescribers which is cause for concern' [district nurse]
- 'I feel that my own knowledge is good and I try to keep up to date, however this is not the case for a lot of staff.' [acute care nurse]
- 'Very aware of overuse and inappropriate use in patients returning, or referred to our service. Antimicrobials are reserved for instances listed above where normal sequence of wound repair/remodelling is interrupted.' [acute care nurse]
- 'Antimicrobial dressings likely have some appropriate indications but available evidence is insufficient to recommend routine use of any of these modalities for treatment or prophylaxis.
I feel as competent as I can be given the lack of good evidence.
In treating diabetic foot ulcers it's not what you put on the wound but what you take off: debridement, offloading and use of oral or IV antibiotics. Antimicrobial wound dressings appear in my experience to have some good effect on some patient's wounds but I probably use them out of fear of not using 'something antiseptic' rather than using them out of confidence that they will really work. Frankly I think many are overused and all the other reasons for non-healing are not thought about enough.' [podiatrist]
- 'I think that silver is most commonly misused.' [police custody health care]
- 'i feel that assessment is key and that often antimicrobials are overused and based on poor assessment from staff.' [nurse prescribing co-ordinator]
- 'Concerned regarding over use of these products both in primary and secondary care' [district nurse]

Theme 6: Industry influences use of AWDs

- 'The pressures from industry can have an effect on dressings and their uses , we promote Lothian Joint formulary 1st and second choice , we are also locally getting feedback from practitioners when such wound products are being used' [clinical nurse manager]
- '...Also as far as I am aware there is no studies or evidence to say that using silver dressings has any benefit in wound care, most of the push for silver dressings seems to come from the suppliers and their reps. Many of these dressings are not evidence based but seemed to be produced as dressing companies compete with one another then promoted as gospel with anecdotal evidence from some other clinic which you are supposed to be impressed by.' [podiatrist]

Theme 7: AWDs are sometimes used prophylactically

- 'When dealing with high risk diabetic wounds which can easily become infected with the risk of amputation, (especially if that person has had a previous amputation), there is always the thought at the back of your mind that its safer to use antimicrobials to prevent infection as the possible consequences will be disastrous...' [podiatrist]
- '...There are some situations where they are required prophylactically such as patients with immunosuppression or vascular problems to prevent infection. These patients have a much higher chance of morbidity if they develop a wound infection so prevention is essential...' [tissue viability nurse].
- '...I sometimes feel they are used prophylactically and this needs to be addressed.' [podiatrist]
- 'Burn wounds rarely become "chronic" although some may take longer than others to heal. Keeping the wound free from heavy bacterial load promotes the healing process. The wound requires the support of antimicrobials as many of our patients lead chaotic lifestyles and that extra wound protection goes a long way to prevent huge infections - something that burns are prone to and the potential to make the patient very sick' [acute care nurse]

Theme 8: Personal preferences

- 'Inadine is a favourite of mine and has been for over 20 years! Over the years, lots of new wound dressings have made an appearance but always seem to come full circle back to Iodine!' [podiatrist]
- 'Have found cutimed sorbact useful in chronic wounds, try to prescribe carefully and take into account cost of dressings and alternatives that could be used.' [district nurse]
- 'Whiteshead Varnish has consistently helped in difficult intra and extraoral wounds' [doctor, Maxillofacial, Head & Neck Surgery]
- 'personally I love using honey in practice but I'm not entirely sure whether there is a suitable or better alternative that i should be trying?' [practice nurse]

Other

- 'We have very few wounds in our surgery, As our elderly population is very small - We mainly get wounds healed with compression' [practice nurse]
- 'Having made a decision to use antimicrobial dressing, taking into account the specifics of the wound ie. wet or dry; position; frequency of dressing - I would commence use of the most inexpensive dressing suitable progressing to more expensive dressings if assessment of wound indicated no improvement.
I would assess each wound individually for suitable dressing whether it be diabetic ulcer; surgical etc.' [district nurse]
- 'I would normally only use antimicrobial dressings when there is a clinical need ie when there is localised infection and when a patient is taking antibiotics for skin infection. the silver dressing would only be applied for the duration of the antibiotics and for one week if localised infection evident. The reason I have continued to use silvecell on this particular patient, is due to the presence of wet infected necrosis, and the underlying diagnosis of arterial disease.' [district nurse]
- 'As I deal with diabetic foot wounds antimicrobial dressings are probably more readily used due to the complexity of these wounds, however if they are having no benefit I would

change my dressing regime and not continue to use a particular dressing. These wounds are reviewed once or twice weekly so you can quite quickly assess if there has been a positive effect.' [podiatrist]

- 'I see a lot of drug-injecting wounds which are less straight-forward. There also seems to be old, superficially conflicting advice available about treatment of infected wounds in this health board. Also auditing use of antimicrobials in this health board: we are required to submit forms that are overly complex and I doubt whether anything happens with these that is useful: that's my personal view though only!' [practice nurse]
- 'Have found medical staff tend to want to use systemic antibiotics based on wound swab results although no other evidence of systemic infection' [acute care nurse]
- 'I think this questionnaire is looking to reduce expenditure rather than improving clinical outcomes. I think the issue we have is no real ability to monitor and record wound care outcome in a unambiguous way. Clinical photography is limited, as well as wound measuring devices.' [acute care nurse]
- 'I know the research is weak and I also know we have to work as a partnership to develop a working collaborative of knowledge to improve the structured manner in which we use this type of product effectively at the right time and not be complacent where over use of this product with no clinical need is not acceptable. However we also want to improve outcome measures and to do this we cannot jeopardise high risk patient care. I'd be happy to be involved in any joint working partnerships.' [tissue viability nurse]
- '...The problem is identifying whether or not an antimicrobial product is required in the first place. Staff need access to more information that would help them decide. Then a clear guide on what products will do what - e.g. debride and topical antimicrobial; protect and reduce bioburden; release antimicrobial into the wound bed etc.' [nurse lecturer]

Where no published evidence is available, we intend to produce consensus based recommendations on the use of antimicrobial wound dressings. What would be the most useful question that we could address using this method to support your decision making on the use of antimicrobial wound dressings?

107 people answered this question. A proper thematic analysis was not done. However, a preliminary analysis highlighted a number of common themes:

Theme 1: What are the clinical indications justify the use of an AWD/How long should they be used for?

- 'Description of the type/presentation of wounds that would benefit from the use of antimicrobial dressings, how long to use for before re assessing.'
- 'What is most suitable for specific organisms (and how long should you use it for- we know that oral antimicrobials are used for a specific period of time usually 1 week), I think it would be useful to have a time span for antimicrobial dressings'
- 'What clinical signs and symptoms of wound infection require the use of a topical antimicrobial as part of the treatment plan including what the treatment objectives are and when to commence and stop treatment.'
- '...Is 2 weeks the optimum treatment length?...'
- 'Is wound exudate and odour increasing, consider antimicrobial dressing.'

- 'advise staff to utilise 2 week challenge and if no improvement stop or change antimicrobial'
- 'Given the ongoing problems with antibiotic resistance when is it appropriate to use an antimicrobial dressing rather than prescribing an antibiotic'
- 'When do you stop using an antimicrobial dressing?'
- 'To ensure it is not used long term unless under the supervision or recommendation of specialist, to revert back to hydrocolloid dressings such as Aquacel after 2 weeks as wound should have improved, if not to refer to stage 3 of ropper ladder and swab wound and oral antibiotics if suitable, then stage 4 if still no improvement. The key is regular assessments of wound and systemic signs of patient'
- 'clinical indications'
- 'Length of time to use antimicrobials for.'
- 'When should it be decided to go off formulary for an anti-microbial dressing?'
- 'time frame for antimicrobials'
- 'when to change product'
- 'Is there clinical evidence (clinical presentation) to consider commencing the use of antimicrobial wound dressings?'
- '1. What are the risks to the patient using silver based products long term.
2. Is there evidence to suggest that the patient can become tolerant of the silver.'
- 'Clearer guidance on the "two week challenge" and what pathway of management should be taken if wound continues to show signs of clinical infection following two weeks antimicrobial use'
- 'Will using an anti microbial dressing reduce the time of healing of this wound for this particular patient?'
- 'That training is required to assess response of all antimicrobial dressings and not 'one size fits all' and also to reinforce the legal consequences as well as patient harm of these dressings used inappropriately whilst also recognising the need for antimicrobial dressings to be utilised and not ostracised!'
- 'Is the surrounding tissue inflamed?'
- 'Has vascular status been assessed to confirm the right level of expected signs and symptoms of infection will occur to ensure appropriate commencement of antimicrobial wound dressings?'
- 'Could the use of an antimicrobial dressing prevent the use of antibiotic'
- 'When to use a antimicrobial dressing'
- 'I think that this would be beneficial to practice.
The most useful area to address would be use of antimicrobials when there is a suspected bioburden in chronic wounds which is preventing wound healing rather than waiting for clinical signs of cellulitis and infection.'

Theme 2: Which AWD should I use?

- 'what is the most effective antimicrobial wound dressing in terms of reducing bacterial burden and getting the wound healed'
- 'Preference of dressings for wound type, have it linked to particular identifiable traits eg on a continuum. So that there was slightly less guess work in making decisions.'

- 'Which antimicrobial agents e.g. honey, DACC, silver etc. show a reduction in the signs of wound infection in the clinical setting with positive patient outcomes and experience?'
- 'What type of silver is most effective? Should we be using silver donating dressings or those that retain silver in dressing? ... Are there bacteria which do not respond to certain antimicrobials?'
- 'Indications for using specific dressings.'
- 'which type of antimicrobials best for differing kinds of wound'
- 'Effectiveness of each type of antimicrobial against infected wounds - however we know little evidence for this exists.'
- 'characteristics and actions of dressings'
- 'Which one will heal this type of wound the quickest'
- 'Which antimicrobial dressing to use and when? is there a preferred one or does it depend on locality, cost and availability?'
- 'The Ropper Ladder seems to be the most efficient way of using our learning time and is a particularly useful guide. I would advocate adding to this rather than re inventing another wheel to act as a guide.' [This could also go under algorithm theme. It has been put under this theme as the Ropper ladder guides when to use an AWD, so an addition would be which AWD.]
- 'What is the most cost effective dressing which is likely to produce the desired wound condition.'
- 'Type of product to use for specific presenting symptoms'
- 'Is the dressing the most effective rather than the least expensive'
- 'the effectiveness of silver dressings'
- 'on surgically closed wounds that hydration antimicrobials are not used, as the moisture levels are enough to dissolve soluble sutures, which will dehisce the wound further'
- 'Which dressings/antimicrobial ointments for which wound?'
- 'What type of infected wounds works best with what type of antimicrobial dressing: specifics'
- 'Indications for the use of silver dressings they seem to have fallen from favour (probably related to cost)'
- 'Which antimicrobial is shown to be the most effective and why, particularly on patients with peripheral arterial disease and ischemic feet?'
- 'How do different antimicrobial products work?'
- 'what is most cost effective'
- 'Which is the cheapest most effective antimicrobial wound dressing?'
- 'Which if any of the antimicrobials confers best results on wounds'
- 'How effective antimicrobial dressings are and which are the most effective to use in a safe and appropriate way.'
- 'what is the most effective AWD'
- 'which antimicrobial wound dressing works the best?'

Theme 3: Simple algorithms/decision aids

Some respondents mentioned that algorithms and decision aids would be helpful – but did not specify whether this was to help identify *whether* an AWD should be used, or *which* AWD to use.

- ‘require an algorithm where decision making is clear and followed by everyone involved in the care of the patient’
- ‘a simple flo chart would be beneficial, a quick check list as an aid memoire’
- ‘An algorithm of what to do from easy to complicated wounds would be useful particularly for newly qualified nurses that live in remote areas would be helpful. Have a look at South West Regional Wound Care Toolkit.
The problem of remote and rural nursing is accessing education and dare I say it 'reps'more VC education would be helpful.’
- ‘Straightforward guidelines and cost effective dressing choices’
- ‘Algorithm maybe? As with all prescribing it should be an experienced person who is doing the prescribing, this involves thorough assessment of the wound by sight and swab result.’
- ‘Is the wound infected?
If borderline - what to use...
If yes - what to use...
A decision algorithm.’

Theme 4: When should an AWD not be used?/Do I really need to use an AWD?/Do AWDs work?

- ‘Is an antimicrobial dressing really needed?’
- ‘Why does the clinician think they need an antimicrobial? Often there is no articulated reasoning...’
- ‘Do I really need to use topical antimicrobials/ what are my alternatives?’
- ‘IS IT APPROPRIATE’
- When is this dressing NOT appropriate?
- ‘do you think the patient would suffer unnecessarily if antimicrobials were not used.’
- ‘contraindications’
- ‘What are the alternatives for antimicrobial dressings?’
- ‘Do antimicrobials wound dressings reduce bacterial load in vivo and reduce use of antibiotics’
- ‘Does the outcome merit the use of antimicrobial dressings? If you find that there is no difference in healing rates with no antimicrobial dressings being used in Chronic wounds this would be interesting reading and as long as the patient's care wasn't compromised we'd all have to change our practice.’
- ‘Are we frightened NOT to use antimicrobials on many of our patients?’
- ‘does the use of antimicrobial dressings help to reduce smell, high exudate levels, reduce dressing changes, reduce embarrassment to the patient ie from smell and leakage onto clothes.’

Theme 5: We need more evidence/making recommendations is not possible

- ‘surely impossible to advise if no scientific research to back up recommendations?’
- ‘If no published evidence to support their use then why are we using them?’
- ‘Could not base decision on one sentence’

- 'Why would you use this dressing - what is the rationale without evidence?'
- 'More informed. evidence is very contradicting.'

Theme 6: Prophylactic use

- 'Prophylactic use of antimicrobials is always an area of disagreement in diabetic foot ulceration.'

Theme 7: Is the dressing on the formulary?

- 'Make sure it is available on wound formulary or it cannot be used.'
- 'most important question would be is it on our formulary, otherwise D/N colleagues unable to prescribe without making a very strong case for it'
- 'IS MY DRESSING OF CHOICE ON THE LOTHIAN WOUND DRESSING FORMULARY?'
- 'Is my dressing of choice available on the wound formulary?'

Other

- 'How patient friendly is the dressing?'
- 'IS IT AN APPROPRIATE TREATMENT REGIMINE TO BE INCLUDED IN AMBULANCE SERVICE "SEE & TREAT" PROTOCOLS?'
- 'has an oral antimicrobial ever been used or considered'
- 'More updated types off dressing and sizes a swell as best suited to skin breakdown needs for to help reach and treat 100per cent healing off skin breakdown on damaged peer dermis'
- 'decision is not based in interest of commercial outlets. natural products considered too-
NON ANIMAL TESTING'
- 'Others experience of products.'
- 'w3h'
- 'Does it improve the wound'
- 'why is there inconsistency within specialist hospital vascular/dermatology dressings relating to wound management which we are requested to follow'
- 'multiplication rate of bacteria, how quickly a wound can go from colonised to infected, use of antimicrobial dressings in colonised wounds in patients more susceptible to infection means fewer dressing changes as can leave longer knowing that the bacterial burden is being addressed'
- 'how to work in opportunity to use professional judgement in decision making rather than being held strictly to protocols and guidelines.'
- 'Asking nurse their experience of what antimicrobial dressings have they actually used to improve wounds.'
- 'Any allergies'
- 'I am concerned that business and industry might be involved or interested in this survey and I would request that any such representation on antimicrobial dressing guidelines is removed.'
- 'Point of contact seek advice from specialist nurses.'
- 'what is your rational and experience of this product for your group of patients'

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- 'Consensus may be gathered from case studies, although bias may be a negative factor. Professional recommendations.'
- 'Time to heal'
- 'Holistic wound assessment to get accurate diagnosis'
- 'If the product would debride a skin graft'
- 'How do you intend to do this when most paper focus on healing as an outcome and not reducing signs of infection. Even the health technology paper fell into this trap'
- 'If the wound has increased levels of exudate/odour and has shown little or no progress is the patient systemically well?'
- 'unsure'
- 'dont forget to include advice on necrotic fungating tumours which cause great distress to patients and relatives'
- 'well it has to be tailored to each individual needs and assessed at each routine, nurses need to use their knowledge better and not just go by what's advocated price wise'
- 'Has the registered nurse carried out and recorded a comprehensive wound assessment to back up decision for utilising AWD?'
- 'A range of antimicrobials dressing need to be available to clinicians so the most appropriate dressing can be chosen based on the patients holistic assessment , needs and goals of treatment.
Recognition and treatment of suspected wound Biofilms.'

Focus Group Discussion Guide

1. Have you heard of antimicrobial wound dressings?

Prompts:

- What do you know about antimicrobial wound dressings?
- What if I say 'silver dressings', 'iodine dressings' or 'honey dressings'?
- Were you aware that you have been treated with an antimicrobial wound dressing?
- Did you know what type of antimicrobial wound dressing you were treated with?

2. Can anyone share their experience of being treated with one of these dressings?

Prompts:

- Was your experience good or bad?
- Can you tell me what happened when your nurse used one of these dressings in your treatment?
- Why do you think your nurse used one of these dressings?
- How long did they use it for? More than 2 weeks?
- Did they tell you why they stopped using the dressing?

3. Do you think the antimicrobial wound dressing made a difference to you?

4. Did the dressing makes things better, worse or no different?

Prompts:

- Was there anything about the dressing you particularly liked?
- Was there anything about the dressing you disliked? Side-effects? Pain?
- Did treatment with the dressing make a difference to your day-to-day life?

5. What did you hope would happen when you were treated with an antimicrobial wound dressing?

Prompts:

- Did this happen?

6. Can you tell me about the discussions you had with your nurse about dressings?

Prompts:

- What did they tell you about the different dressings that they used?
- Do you feel that they gave you the right amount of information about the dressings?
- Was there anything you wanted to know that they did not tell you?
- Was there anything about your care that you would have changed?

7. What symptoms/difficulties did you most wanted addressed by the dressings?

Prompts:

- What is important to you?

AWD in chronic wounds focus group schedule

- 8. Is there anything else you would like to tell us about wound dressings more generally?**
- 9. Does anyone want to tell us anything else?**

A synthesis of qualitative research on patient experiences of chronic wounds and wound dressings.

The clinical effectiveness section of this HTA has revealed a lack of evidence for AWD use in patients with a chronic wound. Patients' perspectives in particular have not been explored, we have synthesised qualitative research on patients' perspectives on wounds and wound dressings to address this gap in the literature.

Patient experiences of chronic wounds have been examined mainly through studies of quality of life (QOL) and qualitative studies. Two reviews of QOL and qualitative studies in patients with leg ulceration^{1,2}, and one qualitative synthesis³ have established that having a leg ulcer has a detrimental impact on patient wellbeing and functioning. This synthesis of qualitative research will expand on it by capturing the experiences of patients living with multiple types of chronic wound, and enable the extraction of patients' views on wound dressings.

Aims

The aim of this synthesis is:

to explore and describe patient experiences of chronic wounds and wound dressings.

The synthesis will also be guided by the patient issues sub-questions of the full HTA:

1. *What is the burden of the wound on the daily life of patients?*
2. *What is patients' current experience of wound dressings?*
3. *What would patients like to see in the future with regards to the use of AWDs?*
4. *What information on dressings is being communicated and shared by health professionals to patients and their family/carers?*
5. *What are the views of patients and their carers on these dressings?*
6. *What factors affect access to AWDs?*

Epistemological perspective

Information on the perspectives of the researchers undertaking qualitative synthesis is considered helpful in assessing the quality of the qualitative methodology used⁴. The researchers undertaking this synthesis:

- Utilised a pragmatic, "subtle realist" approach⁵, in which it is assumed that social phenomena exist independently of people's representations of them, although they are only accessible through these representations.
- Strived for as objective and neutral an approach to qualitative analysis as possible, while acknowledging that the role of researchers and participants' personal interpretations is key in qualitative research.

Methods

This synthesis includes primary qualitative research studies which, using methods such as interviews and focus groups, explicitly asked adults about their experiences of having a chronic wound and its treatment.

There is currently a wide range of approaches available for synthesising qualitative research.⁶ Framework synthesis, based on the framework approach for the analysis of primary data,⁷ was used in this analysis. This method was selected because it provides a detailed and rigorous method for charting and summarising the data and provides an audit trail leading directly back to the data supporting any findings. It also offers flexibility in the use of a priori and emergent themes for the development of a thematic framework.⁵ It is recommended where the data available may be “thin” (lacking in rich detail) and theory development may be limited.⁸

Literature search

Electronic search

Electronic searching was carried out in two stages:

Stage one took place in April 2014. A search of key patient involvement and patient opinion resources took place to identify patient issues surrounding the use of AWDs. The search strategy used was developed by the information professionals at Healthcare Improvement Scotland and included resources such as [Patient UK Discussion Forums](#)⁹ and the [The James Lind Alliance](#)¹⁰. The bibliographic databases below were searched at this stage using the Nederlands Huisartsen Genootschap filter for identifying patient issues for guideline development, combined with terms for the UK:

- MEDLINE (Ovid)
- MEDLINE in Process (Ovid)
- EMBASE (Ovid)
- CINAHL (EBSCOHost)
- PsychInfo (EBSCOHost)

Searches used the concepts of “chronic wounds” and “dressings” (not specifically antimicrobial wound dressings). All primary literature searches were limited to 1990-2014 and English language. The date limitation was applied to reflect the time period in which AWDs became available for clinical use following advice from clinical experts from the topic group of the HTA. The limitation to English language is due a lack of resources for translation.

Stage two took place in April and July 2014. A second literature search of the primary literature was carried out. This search used a filter which was developed in-house to identify qualitative research studies. It was carried out in the same databases as the first searches that are listed above.

The search strategies used to identify patient issues and qualitative studies in MEDLINE are presented in Appendix 1. These strategies were adapted to search all other databases. A complete listing of all strategies can be obtained by contacting Healthcare Improvement Scotland.

Other sources

In addition to electronic searches, we contacted authors of multiple qualitative research studies on chronic wounds, and searched the reference lists of included studies.

Selection of the literature

Inclusion criteria

- Qualitative study design, such as studies utilising focus groups and interview methods. Studies using mixed methods were only included if the qualitative element was reported separately to the quantitative findings.
- The study sample included adults with a chronic wound (such as diabetic foot ulcer, venous leg ulcer, chronic surgical wounds and pressure ulcers) who would be likely to have had some experience of wound dressings.
- Use of qualitative methods for data analysis, such as thematic analysis or any other appropriate method that allows the analysis of text and observations and presents a narrative account of the findings.

Exclusion criteria

- The paper used quantitative methods to gather qualitative data e.g. qualitative answers from a largely quantitative questionnaire. Such data lacks the conceptual depth to contribute to a qualitative synthesis⁶.
- The paper is in a language other than English.
- Wound type is malignant ulcers, or another wound type excluded from the clinical effectiveness section of this HTA.

Selection of studies¹

The selection of studies took place in two stages

Stage one: One reviewer assessed all the identified records by title and abstract to evaluate their eligibility. This initial sift was undertaken to exclude papers that were clearly unrelated to the aim of the synthesis. Two reviewers independently assessed the eligibility of the remaining titles and abstracts. The full texts of all potentially relevant papers were obtained

¹ Qualitative synthesis can be hindered by the inclusion of too many studies since the quality of data analysis can be adversely affected¹¹. The results of a conceptual synthesis will not change if eight rather than four studies containing the same concept are included, rather they will be influenced by the context, range of concepts found in the studies, and whether there is any disagreement in the conclusions of the studies¹². Sampling for heterogeneity of included studies was therefore undertaken since contradictory studies may be most helpful in identifying the fullest range of themes¹².

and assessed further for eligibility. Disagreements between reviewers were resolved by discussion, and the involvement of a third reviewer as required.

Stage 2: A large number of studies were identified therefore, following the full quality appraisal of the papers identified in stage one, a purposive sampling strategy was utilised based on the inclusion of a range of wound types, the degree to which the study focused on wound dressings, and study quality. Therefore studies were not excluded, on the grounds of quality if they sampled patients with the under-represented wound types of diabetic foot ulcers or pressure ulcers, focused on wound dressings, or provided any information on patients' views of AWDs. See Appendix 3 for a table of included and excluded studies and appendix 4 for a table of quality assessment.

Data Extraction

A data extraction table was populated for each included study. Information extracted included first author's name; year of publication; country of study; study setting; type of wound; type of dressings used (if available); data collection and analysis approach (see Appendix 3). As part of the analytical process, the key themes identified by the authors, the findings identified under each theme and any explanatory models developed were also extracted.

In a qualitative synthesis, "informants" are the authors of individual studies rather than the participants in these studies. Therefore, the authors' interpretations, represented for example through themes and categories, represent our data¹¹. Due to difficulties often experienced in distinguishing findings from data in qualitative papers¹³, all text labelled as findings or results, or supported by data in the discussion of the study, was treated as such for the purposes of the thematic analysis. This approach is thought to increase the transparency and "auditability" of the synthesis¹².

QSR NVivo 10 software for qualitative analysis was used to manage and analyse the data thematically. The results of all included studies were entered verbatim into NVivo to undergo analysis.

Quality assessment

The inclusion criteria that studies need to use both qualitative data collection and analysis methods provided basic quality criteria for the included studies. In addition to this, quality appraisal of each study fulfilling the inclusion criteria was carried out. The selection of methods for quality appraisal was informed by the guidance laid out by the Cochrane Qualitative Research Methods Group¹⁴.

Appraisal was performed using the Critical Appraisal Skills Programme (CASP)¹⁵ quality assessment tool for qualitative studies. Two researchers independently applied the CASP tool to each eligible study. A quality level of low, moderate or high was jointly applied to each study guided by the independent CASP ratings and the Swedish council on health technology assessment's handbook for qualitative evaluation and synthesis¹⁶, at a consensus meeting. Disagreements were resolved by seeking a third reviewer's opinion as necessary. See Appendix 3 for details on the quality of the studies.

There is currently no consensus among qualitative researchers on how quality criteria should be applied and how they should be used in qualitative syntheses¹⁴. However, it does appear that poorer quality studies contribute less to the syntheses and that the synthesis therefore becomes weighted towards the findings of the better quality papers included¹¹. It has also been noted that studies considered “low quality” due to methodological flaws may still provide valuable insights arising from the data and, conversely, methodologically strong studies may suffer from poor or limited interpretation of their data, leading to limited insights into the phenomena under investigation¹⁷. A further challenge is distinguishing between poorly reported and poorly conducted studies⁸, although both are likely to limit the contribution of the paper to the review.

Due to the challenges of the use of quality in the selection and weighting of qualitative studies, we did not exclude low quality studies from this synthesis. However we did use quality as part of our purposive sampling strategy to exclude lower quality studies of people with leg ulcers because this wound type was over-represented (See Appendix 2 and 3).

Data synthesis

Framework analysis⁷ was used to allow the identification of common and variable patterns of themes within and across different studies. This approach has been widely utilised in the synthesis of qualitative health data and is one of the approaches to qualitative synthesis recommended by the Cochrane Qualitative Review Methods Group⁸. This approach has several overlapping stages of analysis:

- *Familiarisation* - Two researchers (NF & SHM) read all of the included studies, with reference to the review questions.
- *Identifying a thematic framework* - In this stage, a researcher (NF) examined all the themes/findings from these papers to identify the initial themes for the thematic framework. The second researcher (SHM) independently reviewed the identified themes and agreement was reached on amendments. The seven overarching themes identified arose consistently across multiple studies' findings or were identified by one or more study as a key theme. They were: physical impact, psychological impact, restrictions to lifestyle, dressings, the chronic wound journey, the patient and the healthcare system, and coping.
- *Indexing* – A researcher (NF) systematically applied the thematic framework to the results and discussion section of all studies. Frequently, text was identified as supporting more than one theme, for example a quote describing how pain impaired mobility would be placed in the thematic categories ‘physical impact’ and ‘restrictions to lifestyle’. A second reviewer (SHM) applied the thematic framework to a sub-set of six papers, the highest quality two identified for each wound type.
- *Charting and interpretation* - a matrix of findings for each theme by study was created by one researcher (NF). In each cell of the chart a summary of the study's contributions to the theme was made, with a reference that can be directly linked to the original text. A second researcher (SHM) carried out the same process for a sub-set of six studies and the results were contrasted to enrich and validate the analysis. This stage involved a refinement of the sub-themes, comparisons of any differences in wound type and contrasts between dressing types when possible. Given the largely descriptive nature of the research aim and the studies included in the

synthesis, an extensive interpretation and theory development stage was not undertaken.

Results

4512 studies were identified through electronic database searching and 17 potentially relevant studies were identified through reference list searching and contact with the study authors. Of these studies, 29 were selected for full text screening and 20 were subsequently included in the synthesis. See Appendix 2 for a figure illustrating the screening process.

Description of studies

20 studies were included in the synthesis¹⁸⁻³⁷. One study was published in two parts^{19, 38}, part 1 contains the methodology and part 2 contains the findings of the analysis. For the purposes of the synthesis only part 2¹⁹ was included in the framework analysis, while part 1³⁸ was used for data extraction. Only two of these papers focused on wound dressings specifically; one was focused on patient experiences during dressing changes²² and the other on the adherence and compression bandaging³¹. Two papers focused on the chronic wound patient's experience of pain^{29, 32}. One paper was part of a broader research project into the quality of life of patients with pressure ulcers²⁴. All the other studies had a broad focus on patient experiences of chronic wounds^{18-21, 23, 25-28, 30, 33-37}.

The studies were published between 1995 and 2013. A number of countries were represented: 11 were based in the UK^{18, 19, 21, 23, 24, 26, 31, 32, 35-37}, 4 in the USA^{20, 29, 30, 33}, 2 in Norway^{25, 34}, 1 in Sweden²², 1 in Australia²⁸, and 1 study had multiple sites based in the UK and Belgium²⁷.

By far the most represented wound type was leg ulcers, for which 12 studies were included in the synthesis^{19-22, 25, 26, 28, 29, 31, 32, 36, 37}. Five studies on people with pressure ulcers were included^{23, 24, 27, 30, 35}, and two studies on people with diabetic foot ulcers were included^{18, 34}. One study's sample included different types of chronic wound; it appeared to be comprised of a mixture of the three wound types included in the other studies³³. No qualitative studies of any other wound types were identified.

Six of the included studies were rated as high quality^{21, 26-28, 30, 33}, nine as moderate quality^{18, 20, 22, 24-26, 29, 35, 36} and five as low quality^{19, 23, 31, 32, 34}. Please see Appendix 3 for more details on the quality of the included studies.

Results of the framework synthesis

Analysis of the 20 included studies identified seven themes each with a set of sub themes (Table 1). Where differences were identified in the experiences of patients of different wound

types this is highlighted in the text. A supplementary table containing the findings supporting the framework synthesis is available on request.

Table 1 themes and subthemes	
Theme	Subtheme
Theme 1: Physical impact	1.1 Pain
	1.2 Odour and exudate
	1.3 Infection
	1.4 Other physical features
Theme 2: Psychological impact	2.1 Emotional impact – Hopelessness & helplessness
	2.2 Loss of independence and identity change
	2.3 Being on guard
Theme 3: Restrictions to lifestyle	3.1 Impaired mobility and restrictions on social life
	3.2 Work and financial restrictions
Theme 4: Dressings	4.1 Dressing changes
	4.2 Purpose of dressings
	4.3 AWDs
Theme 5: The chronic wound journey	5.1 Onset and cause of the ulcer
	5.2 Co-morbidity
	5.3 Length of time to healing & recurrence
	5.4 Knowledge of wound care
Theme 6: The patient and the healthcare system	6.1 Healing verses well-being
	6.2 Positive aspects of interacting with healthcare professionals
	6.3 Negative aspects of interacting with healthcare professionals
Theme 7: Coping	7.1 Acceptance and hope of healing
	7.2 Staying positive and minimisation of illness
	7.3 Care from family and friends

Synthesised themes

Theme 1: Physical impact

1.1 Pain

[It's] the worst thing that I have ever gone through in my life. And believe me, I've had surgery, multiple surgeries, I've never had nothing hurt like this. Never. It feels like someone's sticking a hot poker in you. They're sticking pins in you...And it never stops hurting. The damn thing never stops hurting. I had one day that my leg didn't hurt. [Krasner, p.162²⁹]

Pain was a theme in all of the studies and its detrimental impact on patients' quality of life and functioning was discussed in detail by the studies¹⁸⁻³⁷.

The pain experienced by many of those with a chronic wound can be severe and unbearable at times, having a major impact on the patient's well-being^{18, 21, 26-30, 32, 33, 35-37}. A feature of the pain from a chronic wound is patients' descriptions of it as "ever present"²⁷; some experience the pain constantly and others intermittently. However, even those who gain relief from the pain temporarily or through the healing of the wound are anxious about its return^{18, 21, 23, 27-30, 32, 36, 37}.

The studies indicated that pain was a major feature of chronic wounds, however, experiences of pain seemed more variable for those with a pressure ulcer^{23, 30, 35}. Two studies suggested that, for some patients with a pressure ulcer, the underlying condition is so severe that the pressure ulcer was only a minor additional problem and that the experience pain in the affected area may also be reduced^{30, 35}. Despite this, the studies indicated that patients with a pressure ulcer frequently experience pain from the wound, even if it extends into the subcutaneous tissue and deep fascia, regardless of the position of the ulcer^{23, 27, 35}.

The studies indicated that ineffective pain management for chronic wounds is common and analgesia is often inadequate or ineffective^{18, 21, 24, 27, 29, 35-37}. Multiple studies suggested that it is common for patients to feel that healthcare professionals (HCPs) do not understand or acknowledge their level of pain^{18, 21-24, 27, 35, 36}.

'I just kept telling it was too painful...but she insisted it was the right treatment...After she left I took it all off' [Douglas, p.357²¹]

Studies of people with leg or diabetic ulcers suggested that if patient reports of pain or discomfort caused by treatment are ignored by HCPs then non-adherence is likely, even if the patients knows that this may affect healing^{19-21, 25, 34}. However, reluctance in patients to take analgesia, due to being on multiple medications for co-morbidities, and concerns regarding addiction, reduced efficacy, and stigma were also identified in multiple studies^{18, 20, 28, 30, 32, 34, 37}.

A strong finding across many studies was the link between the uncontrolled pain from the chronic wound and sleeplessness^{18, 21, 23, 28, 29, 32-34, 36, 37}. Sleep deprivation can lead to fatigue and contribute to impairment in patients' functioning^{18, 21, 32-34, 37}.

1.2 Odour and exudate

'Oh, and when you first have them, I wondered what the smell was—it's terrible the smell, it all comes out, a lot of rubbish. When you went anywhere, you didn't get too close to people, because I can smell it, terrible.' Ellen [Green et al 2013, p.62³⁷]

Although odour was named as a theme in a relatively small number of papers^{21, 28, 33, 36, 37}, many studies identified it as a common and highly distressing feature of these wounds, which can cause horror and dismay for patients^{20, 21, 26-28, 33, 35-37}. Fear of others detecting the odour from the wound, and the associated shame and embarrassment, prevents many people from engaging in social activities^{21, 26-28, 33, 36, 37}.

Studies identified exudate as another common feature of chronic wounds, which can be very distressing for the patient and difficult to manage adequately with dressings^{21, 23, 28, 33, 35-37}.

Exudate presented problems for patients both inside and outside the home, but was particularly concerning for patients in a social settings due to fears of embarrassment if they were unable to contain it:^{21, 28, 33, 36, 37}

"I couldn't wear a shoe because the bandage was so big. So I wore the kind you buy for broken bones. That's probably when I stopped going out. The wound would drain a lot. The nurses would put layers and layers of stuff on it, and it would be sopping with drainage. It was a mess." Betty [Neil et al, p.31³³]

Odour and exudate were not identified as themes in the two studies of patients with a diabetic foot ulcer^{18, 34}. However this may be a feature of the limited number of studies identified for people with diabetic foot ulcers rather than a difference in the experience of these patients.

1.3 Infection

Overwhelmingly, however, the greatest issue was the unpredictability of recurrent infections. The participants all expressed a fear of infection and this was particularly prominent during the dressing change process as it was perceived to be the most infectious. [Mudge et al, p.24³²]

Infection was not one of the most prominent themes. However, several studies mentioned that patients frequently experience repeated and unpredictable infections^{28, 29, 32-35}, and one study indicated that patients' fear of infection was a major issue, particularly during dressing changes³².

These infections can delay healing, lead to additional health difficulties and increased pain/discomfort^{28, 29, 32-35}. All but one of the studies of patients with a pressure ulcer highlighted their experience of infection leading to life threatening complications, hospitalisation, and multiple additional treatments^{23, 27, 30, 35}. The worry that infection could lead to hospitalisation was also mentioned by a small number of studies of other wound types^{28, 33, 34}. Studies suggested that patients who had experienced a serious infection feared subsequent infection and its treatment burden^{23, 27, 28, 30, 33-35}.

"Oh, I don't know. You just get sick, and, uh, last year I was septic. You end up getting sick—sick through the night and you have to have all kinds of antibiotics. I've had my veins collapse on me, and they had to put central lines in, stuff like that...you gotta really worry about it." [Langemo et al, p. 232³⁰]

1.4 Other physical features

My wound would also itch a lot. It was hard to keep my hands off it. And when I would scratch it, it would feel so good so I would scratch it until it got bloody. Isn't that awful? [Neil et al, p. 32³³]

Swelling and its link with pain was mentioned by three studies of people with leg ulcers^{20, 22, 29}. Krasner²⁹ in particular discusses swelling and its interaction with other symptoms leading to restricted activity levels. Wound itchiness was highlighted by just two studies^{20, 33}. However, these studies describe itchiness as a frequent complaint that can be difficult to tolerate. Itchiness can be interpreted as a sign of healing, but can also be the first sign of recurrence of an ulcer^{20, 33}.

Theme 2: Psychological Impact

2.1 Emotional impact – helplessness and hopelessness

Some were striving to maintain their 'normal' functioning, whereas others suffered from anxiety and depression, with one respondent disclosing that he had had suicidal thoughts. 'It's just depressing really, if you think about it. I am on antidepressants. I just have to put up with it— it's either that or kill myself.' Steve [Green et al, p.62³⁷]

The psychological, and social, impact of the chronic wound was a common theme in the studies. Studies highlighted that depression, anxiety, poor self-image, and fear of others' reactions to the wound are common psychological consequences^{18, 19, 23, 27, 29, 30, 35, 37}. The extent of the psychological impact of the wound varied, with some patients reporting severe depression and even suicidal thoughts^{29, 37}.

A variety of factors that may contribute to the adverse psychological impact were identified in the studies. For some patients, the onset of the wound can lead to an extreme role reversal from an independent person to one dependent on care from others^{18, 20, 21, 27, 33, 37}. The unpredictable and severe pain that some people experience can lead to a sense of powerlessness and frustration^{18, 19, 21, 23, 30, 34}. This can combine with the persistence and recurrence of the wounds to precipitate feelings of helplessness/loss of control, hopelessness/depression and low self-esteem^{18, 19, 21, 23, 26, 30, 34}. Factors explored under other themes, including the physical symptoms of the chronic wound, decreased mobility, fear of further bodily trauma and pain, social isolation, and dependence on others are also likely to contribute to feelings of hopelessness and helplessness in patients with a chronic wound.

2.2 Loss of independence and identity change

Venous ulcers represent both the literal breakdown of the skin and the figurative breakdown of the embodied self. Venous ulcers cause chronic illness that profoundly changes the meaning of life when compared with its meaning as perceived by a healthy person. [Krasner, p.165²⁹]

The onset and persistence of a chronic wound can lead to alterations in body image and personal identity, which many studies linked to lowered self worth^{20-22, 26, 27, 30-34, 36}. The loss of the ability to perform previous roles in life, such as caring for others, which can precipitate depression, can also have a major impact on personal identity^{20-22, 26, 27, 30-34, 36}.

Chronic wound patients are dependent on others for treatment, they frequently suffer greatly reduced mobility, and patients with a pressure ulcer in particular may require assistance to reposition themselves¹⁸⁻³⁷. This dependence on others can be very distressing, prompting an attempt to retain as much control and independence over daily living and self-care as possible^{18, 20, 21, 23, 25, 27, 30, 32-34}.

'What I'm least satisfied with is that I've got no control myself, and that's what I'm most afraid of, to be declared incapable of looking after myself' [Haram et al, p.199²⁵]

For patients with a pressure ulcer, the nature of the underlying condition led to a substantial variation in reported levels of dependence on others³⁵. Many of those with chronic pre-existent conditions, such as spinal cord injury, had learnt to cope and adapt to living with their pre-existent conditions and the onset of a pressure ulcer caused them to lose this independence²⁴. While it may not be possible to separate the impact of the chronic wound from the underlying health conditions, or impact of aging, for all these patient groups, all studies described additional restrictions resulting from the onset of the wound¹⁸⁻³⁷.

Body image can be greatly impaired by the chronic wound studies reported some patients seeing themselves as “dirty” or “disgusting”, leading to feelings of shame and embarrassment and avoidance of others^{20, 21, 23, 26, 28, 30, 31, 33, 36, 37}. The patient’s loss of the ability to dress as they used to because of the bulkiness of dressings, or the location of wound(s), can also threaten self image^{23, 31, 36, 37}. Several studies suggested that women especially may find this and symptoms, such as wound odour, particularly detrimental to self image because of their threat to traditional notions of femininity and attractiveness^{23, 28, 31}.

Studies described some patients’ failure to acknowledge the wound as part of the self^{18, 20, 24, 29, 30, 33, 35}.

‘My butt ain’t my butt anymore. It ain’t the butt I was born with. I have muscle from all other parts of my body holding it together’ down there’. It ain’t a ‘pretty sight.’ [Langemo et al, p. 230³⁰]

One study suggests that this is explained by the experience of the wound as a violation of the body leading the patient to objectify bodily experiences by hiding the wound from others and seeing the wound as separate to the self²⁰. Indeed, two studies discussed patients who did not want to see the wound, or any images of it, even when it was present for a long period^{33, 35}. This refusal to acknowledge the wound as part of the self may, in some way, protect the patient from its negative impact on body image and self esteem. However, patients reacted to the bodily presence of the wound in different ways and two studies described patients for whom the wound had become a fundamental part of their self image: they were no longer able to envision their life, or their body, without it^{26, 33}.

The theme of body image was less prominent in studies of patients with diabetic foot ulcers^{18, 34}, however, the small number of these papers within the synthesis makes it difficult to draw any firm conclusions.

2.3 Being on guard

Others stayed at home in order to limit their contact with others or to avoid further injury. For whatever reason, normal daily life was interrupted for many as a result of ulceration. ‘I’m frightened in the supermarket. I am frightened when I’m out, when I have been at the supermarket cause some people, they do push their trolleys everywhere. So it means that you’re on your guard all the time.’ Margaret [Green et al, p.64³⁷]

Studies described patients’ experiences of being “on your guard”, that is living in a state of hyper vigilance to pain and bodily trauma. The studies indicated that people with leg ulcers believed that new ulcers may develop because of any trauma to the body, like a knock to a vulnerable area^{21, 26, 31, 36}. This belief combined with fear of pain from any, even minor,

trauma to the wound or body can lead patients with leg and foot ulcers to avoid places or activities associated with any such risk, limiting their social life^{18, 19, 21, 28, 31, 32, 36, 37}. Such fears may be partially due to aging and co-morbidities but are clearly amplified by the presence of the wound.

Studies also described patients' awareness of the risk of their condition worsening, leading to a fear of amputation or other unpleasant complications^{20, 28, 30, 33, 34, 37}. Two studies of people with leg ulcers indicated that many patients did not understand the difference between arterial and venous leg ulcers and were therefore unnecessarily fearful of amputation from their lower risk venous disease^{20, 26}. One study describes a leg ulcer patient's attempts to protect their limbs from the threat of amputation²⁸:

'It was getting no better so they put me into hospital and he [the surgeon] says, 'Well I'll have an exploratory'. I said, 'Alright', so when the anaesthetist came he said...'I see you're having your leg off'. I said, 'No I'm just having an exploratory'...he said, 'Well I'll ring the doctor up'. . . he said, 'Yes you're going to have an exploratory, but on the bottom it says, if necessary amputation'. [Hyde et al, p.194²⁸]

This patient awoke to find that the leg had been amputated and then described having to argue with her surgeon to prevent her other leg being amputated. This patient attempted "to maintain the integrity of her body regardless of the consequences"²⁸ and had to be vigilant in order to do so. For this patient, amputation was a catastrophic outcome. However, some studies describe patients' willingness to have a limb amputated to eliminate symptoms and reduce treatment burden^{18, 20, 33}.

Theme 3: Restrictions to lifestyle

3.1 Impaired mobility and restrictions on social life

Leg ulcer patients describe limitations to their mobility and activity that are at times profound. When asked what area of her life had been affected by ulcer disease, one woman responded, "What area of my life? My whole life. I cannot do anything I want to do. I cannot go any place. [after a pause, and with sadness] I kind of got used to it." [Chase et al, p.75²⁰]

The impact of the chronic wound on mobility and social life was one of the most widely discussed themes in the studies. Many of the studies highlighted severe restrictions on mobility, which has a profound effect on lifestyle, reducing the ability to get out of the home and socialise with others^{18, 20, 21, 26-28, 30, 31, 33-35, 37}. The impairment in mobility (resulting from the wound) is mostly a result of pain^{18, 23, 26, 27, 29, 32-36}, but is also impacted on by poorly controlled exudate and odour^{20, 21, 26-28, 31, 33, 35, 37}, bulky dressings^{19, 20, 23, 31-33, 37}, and difficulties with footwear^{18, 34}. The psychological impact of the wound, and fear of further physical trauma, can also greatly restrict the patients social life^{18, 19, 23, 26-28, 30, 31, 33-35, 37}. Some studies suggest that social withdrawal may form a cycle with feelings of powerlessness, low self worth, fatigue and depression adversely affecting social life and wellbeing^{18, 26, 30, 34}.

He also felt unable to perform any household maintenance or previously enjoyed social activities, especially as there were steep steps outside his house: "...I'm not in the mood, I just can't be bothered. I'm sick of being in but I don't want to do anything else". [Bradbury et al, p.30¹⁸]

HCP prescribed limits on movement frequently led to isolation, boredom and limitations in daily activities, patients often believed that it was better for them to be more active and did not always adhere strictly to such limits^{21, 24, 27, 30, 33-35}. The negative impact of prescribed immobility and restrictive pressure relieving equipment^{30, 33} was a notable finding for patients with a pressure ulcer^{28, 31}.

Many studies highlighted patients' shame and embarrassment when others noticed symptoms, in particular odour/exudate, or visible dressings. This led them to limit social activity unless they were confident of being able to hide these signs of illness^{20, 21, 26-28, 31, 33, 35, 37}. Dressings are frequently ineffective at containing symptoms, leading patients to withdraw from social contact^{19, 23, 24, 33}.

Studies described variation in the level of social isolation experienced by people with a leg ulcer, suggesting that some patients do manage to maintain a relatively active social life^{19, 20, 22, 32}. Several studies suggested that they do not necessarily suffer higher levels of loneliness than their 'healthy' peers without leg ulcers^{19, 32}. It is not possible to completely separate the impact of aging and co-morbidities on the patient's limited mobility and restricted social life, and these factors are likely to underlie some of the variation in levels of social isolation described in the studies.

Theme 3.3 Work and financial restrictions

Although most participants were retired, they all vividly recalled their experiences of coping with exudate at work: 'Used to try all sorts but in the end wore wellington boots at work... anything to hide the leakage.' [Douglas, p.358²¹]

A number of studies highlighted patients inability to work because of the symptoms of the wound or their struggle to find ways to cope with symptoms at work^{20, 24, 29, 33, 34}. However, difficulties at work are not mentioned by the majority of studies. This is likely to reflect the older age and co-morbidities of the samples, which may have already had a major impact on a patient's ability to work. Studies suggest that patients who do continue to work may find it difficult to manage exudate and odour; they described adapting clothing and taking other measures to hide these symptoms^{21, 28, 33}. Patients were especially worried about the shame or embarrassment that would result from others noticing the wounds symptoms in a working environment.

There was very limited discussion of financial restrictions in the studies. Only one UK study of people with pressure ulcers²⁴ and one U.S. based study of people with leg ulcers²⁰ mentioned the financial implications of receiving treatment for a chronic wound. The U.S. study highlighted the difficulties experienced by disadvantaged groups, such as people experiencing homelessness, in accessing healthcare and buying dressings²⁰. Gorecki et al²⁴ noted the costs incurred by people with a pressure ulcer (e.g. buying topical lotions, dressings, pressure-relieving cushions and replacing stained bedding), and the difficulties involved in managing financial obligations during a hospital admission.

Theme 4: Dressings

4.1 Dressing changes

“The participants complained that they did not receive enough pain medication or other assistance during the painful process of changing the bandages. As one said: That is exactly what I thought, but they don’t listen to me. I thought about that, when it ached and also about that gauze bandage. Can’t they hear what I say? Why don’t they listen?” [Ebbeskog et al, p.1228²²]

Dressing changes can take place frequently and take up a considerable amount of the patient’s time, impacting on their social life^{19, 24-27, 31, 35, 37}. By far the most frequent issue about dressing changes raised by the studies was the pain experienced during the procedure, which can persist for some time after dressing change is completed^{18, 20-22, 26-29, 31, 32, 35}. However, the level of pain experienced by patients during dressing changes is variable^{18, 20}. Factors that influenced the experience of pain during dressing changes included: tenderness of the wound and the application of pressure to it, the technique of the HCP, adverse reactions to the dressing, the adhesiveness of the dressing material and problems with the application of the dressing^{18, 20-22, 26-29, 31, 32, 35}. Two studies explicitly highlighted patients’ difficulties in dealing with the anticipation of pain from cleansing and dressing changes^{22, 32}. One study discusses this in some depth, stating that:

“The regularity of dressing changes ensures that the anticipation of pain is never far from the patient’s mind and as such largely dictates how they lead their day-to-day life.” [Mudge et al, p.26³²]

This study also acknowledges patients’ positive experiences at dressing changes, particularly the opportunity to monitor the wound’s progress, relieve compression (if it is in place) and have the area washed, but notes that these are always balanced by anxiety regarding pain³². Just one study of people with pressure ulcers described a person who experienced dressing changes as comforting and who actually looked forward to them³⁵.

Mudge et al³² highlight some methods used by patients to cope with dressing changes and the pain associated with them. These included: distraction during the procedure (for example thinking about a treat for after the change), having some element of involvement in the dressing change procedure, and having some control over the environment (such as having changes done at home). Some patients also took pain relieving medication prior to the dressing change and found this essential to bearing the process.

Theme 4.2 Purpose of dressings

“One woman, a retired teacher, described the way she used to cope at work when the ulcer suppuration leaked through the bandages. ‘Oh,terrible [the seepage]. All the time and that’s why I used to have to rush home of an afternoon and change the bandages . . . because they’d be soaking wet.’” [Hyde et al, p.193²⁸]

Studies indicated that patients want dressings that will aid healing^{19, 22, 24, 35}. However, patients also want dressings that are comfortable and effectively contain symptoms^{21, 23, 25, 26, 28, 33, 35, 36}. Studies of people with a leg ulcer indicated that certain types of dressings, such as compression bandaging, can cause considerable discomfort and even pain^{19, 21, 22, 31, 32, 36}.

Restrictions from bulky and uncomfortable dressings^{19, 20, 23, 31-33, 37}, such as compressions bandaging, can be so severe that patients may be willing to trade off potential healing for freedom from bandaging¹⁹. One study describes a patient's decision to ask HCPs to "take my leg off" because of dressing's inability to contain exudate and the restrictions on her social life that this caused, this patient:

"...voiced tremendous relief at not having to sleep in the recliner, not having to go to whirlpool therapy and endure debridement three times a week, and foremost, being able to go out and resume her social life. She said she had lost a year with her friends and church because she had not been able to go out with her thick, wet bandage." [Neil et al, p.36³³]

Figure 1, below has been developed during the synthesis process to illustrate the factors highlighted as important in dressing acceptability by the authors of the studies. The qualities or wound dressings are represented non-hierarchically because the synthesis suggests that the various qualities of wound dressings will be more or less important to different patients and at different times. Healing seems to be of paramount importance to patients who expect a full recovery, while for others who have had a long history of chronicity and/or recurrence other factors may gain in importance, therefore the value attached to each will differ for each individual. For example, a patient who already has severely impaired mobility at the onset of the chronic wound (more common in those with pressure ulcers), may not experience a further reduction in mobility because of a bulky dressing and therefore this aspect of dressings will be of little importance.

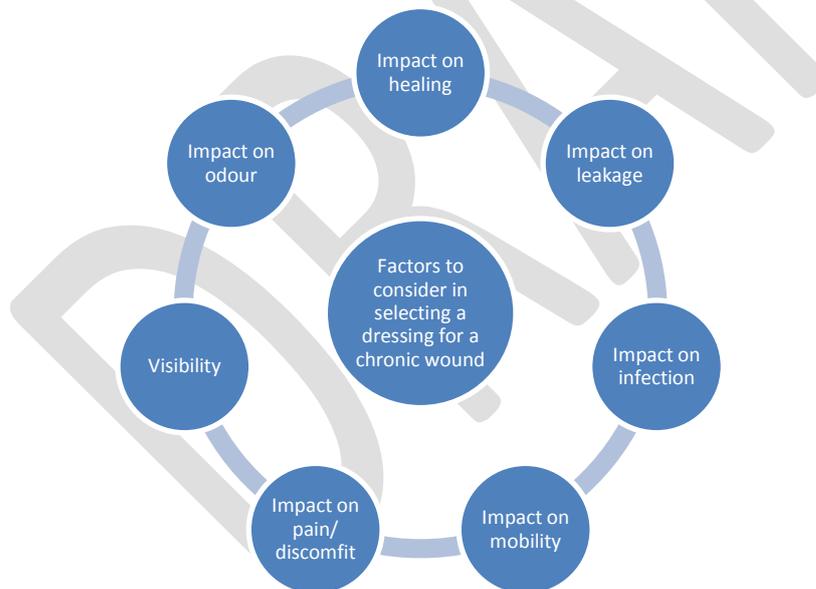


Figure 1: Factors to consider in selecting a dressing for a chronic wound

Another restriction mentioned by several studies of people with a leg ulcer, is a dressing's impact on patient's ability to bathe and adequately maintain their personal hygiene^{20, 36, 37}. In order to keep the dressing dry and fulfil other treatment restrictions, patients went for longer periods of time without bathing or washing the affected area than they felt comfortable with^{20, 36, 37}.

A small number of studies identified concerns from patients that "nothing gets a chance to work"²¹ because of the many types of dressing available and the frequent changes of dressing type by HCPs^{22, 24, 37}. When a dressing has appeared to be effective in wound

healing, patients may develop great faith in it^{31, 37} and this can make them reluctant to try a new dressing³¹. Conversely, a small number of studies directly raised patients' concerns about HCPs' persistence with dressings they viewed as ineffective, both in terms of healing and symptom containment^{22, 24, 35}. Although it is only raised in one study, patients may view the persistence with non-preferred dressings as motivated by attempts to minimise costs to the healthcare provider²².

Theme 4.3 Antimicrobial Wound Dressings (AWDs)

'You name it, all the different patches with stuff in and creams and the patches come out with the silver in and we went through every one of them. Errr... I've gone through loads of different stuff—they've put, I've had trials of different stuffs put on and some worked and some hasn't.' Steve [Green et al, p.64³⁷]

No studies focusing on AWDs were identified in the literature search, and no study contained a named theme focused on AWDs. However, several studies indicated that patients perceived the healing properties of topical antibiotic creams and AWDs positively^{19, 20, 24, 29}. In two studies, patients mentioned having tried many different products, including different types of AWDs^{25, 37}, and indicated that some appeared to have been effective while others had not³⁷. In this study³⁷, the patient seemed to believe that trial and error was used in the selection of these products, by the HCP, until one "worked" and the wound improved.

An adverse reaction to the use of an AWD is mentioned in just one study, and was linked by the patient to care from primary care instead of specialist HCPs:

"This ulcer on this leg was caused by bandages from the doctor (GP) really. Well, not from the doctor, from the nurse, because it wasn't done tidy...you go to your local surgery and they bandage and say, oh yeah, put iodine on it or Inadine sometimes, and that's it. And when I went to •••• (specialist wound clinic) a couple of months ago my leg was disgusting. It was all from the Inadine pads apparently because it had burnt me." [Mudge et al, p.1168³¹]

While AWDs were mentioned more often in studies of leg ulcers than in any other type of wound, no conclusions can be reached from this since none of the studies had intended to examine patients' perceptions of their use, and this is likely to be a reflection of the larger number of studies on leg ulcers identified in the literature search.

Theme 5: The chronic wound journey

5.1 Onset and cause of the wound

This group of patients was not able to describe what causes leg ulcers. Patients frequently look for a reason for the ulcer. "Could that break and that fracture have something to do with this?" Another man wondered if a knee problem caused the leg ulcer. [Chase et al, p.76²⁰]

Studies of all wound types mentioned patients' attempts to self-manage the wound for some time before seeking input from professionals. This tended to be based on a failure to realise the severity of the wound and help seeking was only prompted by deterioration^{20, 24, 33-35, 37}.

Many studies highlighted patients' lack of understanding of the underlying cause of their chronic wound, leaving them to seek out an understandable rationale^{19-21, 24-26, 30, 31, 33, 34, 36, 37}. People with a leg ulcer seemed to frequently attribute the cause to a knock of some kind without an understanding of the underlying disease or why healing was so slow^{21, 26, 31, 36}. Several studies of people with leg ulcers, also mentioned patients' explanations of their condition as rooted in a family history of leg ulcers apparently leading to a sense of resignation or acceptance of the condition and the likelihood of recurrence^{21, 26, 36, 37}.

Studies of patients with a pressure ulcer discussed patients' attribution of blame for its onset, with some patients placing the blame in HCPs (such as injury from a hoist)^{24, 30, 35}, or factors to do with their pre-existent medical conditions (such as reduced sensation and immobility)^{24, 35}, while others blamed failures in their own self-care (such as failure to check skin, ignorance and poor hygiene)^{24, 30, 35}.

5.2 Co-morbidity

The participants in our study all had comorbidities, the most common being significant arthritis, which already served to restrict their lives. For this reason, age, their life experiences and health to date possibly further mediated the impact of restriction. [Hopkins et al, p.351²⁷]

The impact of co-morbidities on the lifestyles of people with leg or foot ulcers was highlighted in several studies^{18, 19, 33, 34, 37}. Some patients had suffered considerable difficulties with mobility and other impairments prior to the onset of the chronic wound^{18, 19, 33}. In the case of patients with diabetic foot ulcers, the overall impact of diabetes on the patient's physical well-being was acknowledged³⁴. However, several studies indicated that, regardless of the patient's level of functioning prior to the onset of the ulcer, its onset prevented them from functioning at what they considered to be their maximum capacity^{18, 36, 37}.

Pressure ulcers are commonly a consequence of a condition that limits mobility and the studies of patients with pressure ulcers reveal the major impact of co-morbidities on the patient's experience^{27, 35}. For some patients with a pressure ulcer with chronic underlying conditions (e.g. multiple sclerosis), studies reported that the wound represented a serious threat to their independence since they had learned to function and live within the restrictions of their existing condition^{24, 35}. For some patients with a pressure ulcer with an acute condition (such as a major accident), the wound was described as "*just another irritation*" given the burden of their overall condition^{24, 35}. However, one study is clear that the pressure ulcer has a "*marked impact*" on the patient regardless of the nature of the underlying condition²⁷ and others highlight delays to recovery/rehabilitation^{24, 27, 35}.

For all the chronic wound types, but particularly pressure ulcers, the impact of co-morbidities and underlying conditions are difficult to separate from the experience of the chronic wound itself^{18, 19, 27, 30, 34, 35}. This is further compounded by the impact of aging since many of these patients are older adults. Aging may be a factor in mobility restrictions and other impairments discussed in this synthesis, and is likely to affect the patient's ability to accept these impairments^{19, 27, 36}.

5.3 length of time to healing and recurrence

Another man living with the condition for years said, "It's like a forever healing process, not getting better, not getting worse." [Chase et al, p.74²⁰]

Recurrence, and living with the possibility of recurrence, is described as a major feature of the experience of having a leg ulcer^{19-21, 26, 28, 37}. While it is not as prominent in the studies of people with diabetic or pressure ulcers, it is also a feature of the experience of the patients in these studies^{18, 24, 34, 35}. For patients with a chronic wound, the unpredictable nature of healing and recurrence, and the emotions associated with this, is part of living with the condition. Studies describe patients experiencing guilt, frustration, disappointment, worry and sadness because of the persistence of the chronic wound^{18, 20-23, 26, 27, 30, 33, 35, 37}, and the fear of never regaining previous levels of functioning and independence.

5.4 knowledge of wound care

Many respondents who had experienced a PU demonstrated knowledge and understanding related to prevention and care of a PU, while others revealed a significant lack of knowledge in these areas. [Langemo et al, p.231³⁰]

Studies described patients' lack of understanding about the rationale behind treatments, such as compression bandaging, and a lack of clarity around expectations of healing^{19-21, 24, 25, 30, 31, 34-36}. Patients can be frustrated by HCPs' failure to keep them well informed, which may exacerbate feelings of helplessness and hopelessness experienced by many^{18, 21, 22, 24, 26, 30, 31, 34, 35}. Studies suggested that patients who have HCPs who do keep them informed about the wound and treatment rationale, and feel involved in the decision making process, are more likely to be adherent to treatments^{21, 24, 29, 36}.

Some studies described patients becoming an expert in wound care, treatment and prevention, enabling the prediction of the progression and onset of a wound^{19, 22, 25, 26, 28-30, 37}. Patients who have become such experts can work in partnership with HCPs, even alerting them to the need for prophylactic treatment of infection and managing their own pain treatments^{22, 28, 37}:

The women cited in the present study, at this stage, had doctors who responded to their requests for prophylactic or prompt treatment with antibiotics. It is important for visiting nurses to be aware of this potential for self-expertise among clients with long-term conditions, because it is likely that earlier in the clients' lives their medical practitioners were not necessarily so responsive. [Hyde et al, p.196²⁸]

Studies also describe variation in patients' desires to be actively involved in wound care and management. Some patients are described as motivated and seeking involvement in decisions about wound care and prevention^{24, 25}, while others minimise their involvement with the wound and its treatment^{20, 22, 25, 36}.

Theme 6: The patient and the healthcare system

Theme 6.1 Healing verses well-being

...nurses may have viewed complete wound healing as the only desirable treatment outcome, whereas for many participants, alleviation of the distressing symptoms experienced was more important than complete wound closure. While aware of the benefits of compression therapy, they were willing to trade off potential healing against relief of

unpleasant side effects of treatment. [Brown, p.988¹⁹]

Multiple studies suggest that HCPs tend to be focused on achieving complete wound closure as the sole outcome of treatment^{18-20, 23, 27, 36, 37}. This can lead to a lack of acknowledgement of the chronic nature of the wound, the likelihood of recurrence and a failure to focus sufficiently on symptom alleviation, comfort and other quality of life issues^{18-20, 23, 27, 36, 37}. To redress this balance, these studies suggest a focus on the holistic treatment of the patient, identifying the priorities for each individual^{18, 19, 23, 29, 30} and giving “as much importance to comfort and symptom control as to speed of healing”³⁶.

Patients wished to live as “normal” a lifestyle as possible and therefore treatments that can interfere with this, such as compression bandaging and pressure relieving equipment, were challenging^{19, 27, 36}. They may experience a tension between following treatment plans in order to achieve healing and the restrictions that treatment can place on their lives, influencing adherence^{19, 27, 36}. This may be compounded by the apparent ineffectiveness of treatments if the wound continues to persist or recur. As Brown¹⁹ noted; even if the patient is aware of the rationale behind a treatment, the need for maximising wellbeing within the restrictions of their health may lead to a willingness to forego the healing potential of a treatment if it causes significant discomfort. Many factors will affect the extent to which the patient is focused on well-being or healing and this is discussed more under theme 7.1.

Theme 6.2 Positive aspects of interacting with healthcare professionals

“The therapeutic relationship with the district nurse was linked to the importance of feeling known, feeling heard and appreciated as people. The visits are marked by enjoyment, a 'laugh and a joke'. They move beyond the task in hand to friendship...It appears that by showing interest in the participant as an individual this promoted confidence and hope for the future....where these interactions are absent, the patients' needs will be left unfulfilled or frustrated.” [Hopkins et al, p.562²⁶]

The relationship between patients and HCPs was a prominent theme across studies. It was plain from multiple studies that patients value a strong therapeutic and personal relationship with a consistent HCP^{18-20, 22, 24-26, 32, 34, 36, 37}. Studies described a good relationship with a HCP to be one of trust and confidence in which: the patient felt listened to and respected, was informed about treatment, and could ask questions^{18, 19, 22, 24-26, 34, 36, 37}.

Studies, mainly of people with a leg ulcer, suggested that by forming a trusting and collaborative relationship with the patient, in which the patient feels that they have some control over treatment, the HCP is able to instil hope for the future and a feeling of increased control over their own lives in the patient^{21, 22, 26, 30, 36, 37}. One study highlights that patients spoke highly of their nurses and maintained faith in their abilities in spite of the “the failure to heal their ulcers”¹⁹, suggesting that the positive impact of the relationship may be achieved even in the absence of healing.

6.3 Negative aspects of interacting with healthcare professionals

The word ‘they’ was used to refer to staff who changed the dressings in a perfunctory manner: “There are many who have come and gone during all these the years of treatment. You could say they didn’t show the same consideration... You get the feeling that they do

not know what they are doing...It's just a matter of routine for them. They change the bandage, and then you can go home." [Ebbeskog et al, p.1226²²]

A common criticism of HCPs was their failure to empathise with the patient's condition, to truly attempt to understand from their perspective^{18, 21, 22, 24, 25, 27, 28, 30, 33-36}. This lack of empathy was perceived by patients in many different ways, including the failure of some HCPs to communicate with them about the wound, or to acknowledge their pain level and the discomfort and lifestyle implications caused by some treatments^{18, 21, 22, 26, 30, 31, 34, 35}. Two studies of patients with pressure ulcers even described some patients' perceptions that they were not respected by HCPs^{24, 30}.

Studies also mentioned patients' concerns about HCPs' levels of competence and knowledge of wound care^{18, 21, 22, 24, 25, 27, 31}. Conflicting advice and treatment from HCPs, and the perception that HCPs did not spend sufficient time or attention on the care of their wound, contributed to these concerns^{18, 21, 22, 24, 25, 27, 31, 35}. Perceptions of HCP competency were also linked to HCPs being identified as "rough handed"¹⁸, patients reporting some HCPs taking insufficient care during treatment resulting in increased pain and even injury^{18, 22, 24, 25, 28, 31}. Two studies of people with leg ulcers discussed patients' preferences for care from specialist services (e.g. wound clinics or district nurses) because they did not believe that HCPs in primary care had the required skills to effectively dress and treat their wound^{22, 31}.

A lack of staff continuity, or the use of agency staff, was identified as a difficulty for patients by some studies^{19, 24, 26, 37}. The preference for continuity of care was due to feeling uncomfortable in raising concerns with unknown HCPs, inconsistencies in care, and a lack of information and insight into wound progression^{19, 24, 26, 37}.

Some studies reported patients' feelings of disempowerment in their relationships with HCPs^{22, 24, 25, 28, 30}. This was related to a lack of involvement in decision making about treatment and loss of independence^{28, 30}. A small number of studies reported patients' fears of the consequences of questioning HCPs, or non-compliance with treatment^{19, 37} leading them to "put up" with things that they did not agree with or that caused pain^{24, 25}. The studies of people with diabetic foot ulcers did not discuss patients' experiences of disempowerment.

Theme 7: coping

7.1 Acceptance and hope of healing

"All of the participants revealed various ways of coping with leg ulceration. The main feature was that of pure acceptance of their situation, using such phrases as 'the way it is' and 'you get used to it'". [Hopkins et al, p.558²⁶]

A coping strategy mentioned by multiple studies is that of acceptance by patients of the long-term nature of their difficulties^{18, 20, 21, 24, 26, 27, 36}. Some studies link patients' acceptance of their situations with a fatalistic stance on healing, while others discuss the difficulty of separating acceptance as a coping strategy from the patient having "given up" on healing^{20, 27, 33, 34, 36}. The patients who had accepted the chronic nature of their wound, or/and underlying health conditions, appeared to be more satisfied with their lives and were able to focus on improving their lifestyles within these limitations^{20, 26-28, 30, 31, 36}.

One study of people with a leg ulcer suggests that HCPs should help patients to acknowledge the uncertainty inherent in living with a condition in which recurrence is a possibility, even if healing is achieved, or they risk delaying the patients acceptance of lifestyle accommodations that may allow them to lead a more fulfilling life²⁰. However, many studies also acknowledge that hope of healing is important, and is generally retained even in patients that have experienced multiple recurrences and believe that full healing is unlikely^{21, 25, 26, 28, 33, 34, 37}. Two studies emphasised that acceptance of their situations, and even a “cheerful” appearance, does not indicate that the patient does not desire complete healing, just that they are finding ways to accept and cope with the persistence of the chronic wound^{19, 36}:

Despite these serious limitations, others fought to maintain their functioning; attempting to engage as they had before their current episode of ulceration and a theme of hope, especially for healing, was evident for all. [Green et al, p.65³⁷]

Some studies suggested that patients only adhered to treatments that they believed would heal the wound. This means that adherence may well tail off if treatments prove ineffective for long periods of time^{24, 25, 33}. A positive relationship with HCPs, in which the patient feels cared for and is kept well informed about the progression of the wound, can inspire the required hope of healing and therefore may help to maintain adherence^{21, 22, 26, 36}.

Theme 7.2 Staying positive and minimisation of illness

“Most informants tried to be positive about the experience, often negating the symptoms as ‘not bad at all’, or describing themselves as lucky ‘Oh, sort of on and on, it’s one of those horrible pains, that keeps on, especially at night sometimes I am very lucky at the moment because I am not so bad’” [Walshe, p.1098³⁶]

Studies highlighted patients’ needs to stay positive in their outlook, giving into negative thinking was considered counter-productive and would prevent them from “carrying on”²⁶ or gaining maximum control and functioning in their lives²¹ in spite of their health difficulties^{18, 21, 24, 26, 29, 30, 37}. It appears that pain may present the biggest obstacle to maintaining a positive attitude^{18, 36}. Maintaining any activities that are still possible from before the onset of the chronic wound and taking up new activities that are possible within its restrictions enables the patient to stay active and feel more in control of life, having a positive effect on mood and functioning^{18, 20, 21, 24, 26, 29, 30, 33, 37}.

Studies of people with leg or pressure ulcers mentioned patients’ use of comparison with other people whom they considered worse off than themselves or times when they had been more ill. These helped them to stay positive about their own condition^{19, 24, 26, 27, 30, 36}. However, some studies acknowledged that, while staying positive was adaptive, some patients were minimising the impact of the chronic wound in order to make their genuine concerns “more tolerable”²⁶ or to “put on a brave face”¹⁹ for others^{27, 30, 32, 37}. The studies of patients with pressure ulcers in particular mentioned both patients’ tendencies to downplay the enormity of the impact or seriousness of the wound,^{27, 30, 35} and even to deny “that the pressure ulcer was a part of them”²⁴ at all.

7.3 Care from family and friends²

“Sam” was also distressed by his limited mobility. He had severe pain in his right foot when he walked and was supposed to be on bedrest with his foot elevated. His wife Judy said: He went from being a tractor trailer driver and (having) a grass-cutting business to not being able to do anything. He’s always been very active, and it’s frustrating now. He hasn’t been able to do anything but lay around. He has to stay completely off his feet. We haven’t been able to do anything not even go to dinner.” [Neil et al, p.34³³]

For patients, support from carers can be instrumental in coping with wounds as it provided practical and emotional support^{18, 24, 27, 34, 35}. The restrictions on the patient caused by symptoms such as pain and impaired mobility also restrict the activities and psychological functioning of the patient’s family/carers, potentially having a profound effect on their lives^{20, 21, 23, 24, 27, 30, 33}. This can leave the patient feeling guilty and they may view themselves as a burden on their family and friends^{18, 20, 27, 34, 35}.

It was not unusual for carers to have a role in changing the dressings of a family member^{18, 23, 24}, which some found stressful^{23, 24}. Their role in applying dressings leads to the family being less dependent on HCP input, freeing up a considerable amount of time spent waiting for input from HCPs²⁴. Carers can become expert in changing dressings and this can lead them to become critical of HCPs’ methods²⁴. In one study of people with a leg ulcer all carers, conflicting advice given by different HCPs was found to be frustrating²¹. It also suggested that carers did not feel listened to or understood by HCPs. They longed for support and recognition from HCPs, and felt these needs were not being met²¹.

Discussion

Previous research on the experiences and perspectives of people with a chronic wound have revealed the extent of the detrimental impact of such a wound on well-being and the ability to live a “normal” life^{1, 2}. Our search to identify literature that examines patients’ perspectives on AWDs and provides information on patient issues revealed a lack of research focused on AWDs specifically, therefore a broader qualitative synthesis of patient perspectives on chronic wounds and wound dressings was undertaken.

We identified seven major themes associated with patients’ experience of chronic wounds and wound dressings from this synthesis of qualitative studies: physical impact; psychological impact; restrictions to lifestyle; dressings; the chronic wound journey; the patient and the healthcare system; and coping.

This synthesis included different wound types, in order of the prevalence of identified studies. They were: leg ulcers, pressure ulcers and diabetic foot ulcers. It was notable that patients’ experiences were often similar across the three wound types. However, patients with a pressure ulcer did differ to patients with the other two wound types, and differences have been highlighted where identified. Due to the small number of studies on people with diabetic foot ulcers identified, it is uncertain to what extent their experiences differ from the other two groups.

The results of this synthesis are consistent with the results of previous reviews of QOL and qualitative research in people with a leg ulcer,¹⁻³ which strengthens its validity. This

² The synthesis did not seek out studies on carers of people with a chronic wound and the below reflects only the views of the patients themselves, and a small number of carers whose views were collected unplanned in the primary studies.

synthesis has also added to previous work by including studies on other chronic wound types, and specifically extracting findings on wound dressings.

Limitations of this synthesis

The literature search failed to identify any qualitative research focused on AWDs, and only a limited number of studies focused on wound dressings. The synthesis is also reliant on what researchers chose to report from within their primary data and it is therefore possible that information that was available on dressings and AWDs was not reported in the primary studies included. Authors of more than one qualitative study in the area were contacted to identify relevant literature. Therefore we found it necessary to conduct our own primary research.

The scope of the synthesis was wide, in terms of including studies of multiple chronic wound types and exploring the patient burden of having a chronic wound, and was therefore focused on the commonality between the different wound types. The primary studies identified were overwhelmingly skewed towards leg ulcer patients, while all studies of other eligible wound types were included, the findings may therefore reflect leg ulcer patients experiences more extensively than diabetic foot or pressure ulcer patients.

The extent to which findings from qualitative research can be transferred to different contexts and cultures is debatable^{5, 16}, therefore it should not be assumed that all findings from this synthesis will apply across different socio-cultural settings. However, the authors of the framework method of synthesis suggest that findings from qualitative research and synthesis can have a degree of transferability given due attention is paid to the validity and reliability of the research or synthesis process⁵ and qualitative synthesis is being used increasingly in HTA and health services research^{11, 39}.

It is difficult to set clear boundaries around themes because of the strong inter-relationship between them. To avoid repetition, subthemes have been placed within the theme that they appeared to be most strongly associated with, but aspects of these themes could appear in others.

Conclusions

The persistence, recurrence and symptoms of a chronic wound can have severe physical, psychological and social consequences. Treatment should be focussed on healing and symptom containment, and should be holistic in its awareness of the impact of treatment burden on lifestyle.

Dressings:

- There was a perception that “trial and error” was the basis of dressing selection and that this process would continue until something worked to heal the wound. Patients may then develop a strong faith in a particular dressing type. Conversely, they may also become dissatisfied with HCPs’ persistence with a dressing that is “ineffective” or causes discomfort.
- Patients want dressings that minimise the impact of pain, odour and exudate on their lives, while also helping with wound healing. Bulky, restrictive, or uncomfortable dressings can cause considerable restrictions to patients’ lives.
- Treatment burden was considerable for these patients. In particular, dressing changes could be painful and time consuming. Patients were particularly fearful of infection during dressing changes. Time spent waiting for HCPs to carry them out can impact on patients’ ability to undertake social activities; this appeared to be a particular issue for people with a leg ulcer who frequently had dressing changes at home.
- Pain, fear of further injury, and mobility difficulties combined with fear of others noticing exudate or odour from the wound and bulky or visible dressings/special clothing, can limit the patient’s ability to socialise or get out of the home.
- Studies described patients’ concerns about HCPs’ competences; these were related to “rough hands” causing pain or injury during dressing changes, persistent use of dressings disliked or considered ineffective by the patient, a lack of specialist knowledge, inadequate information sharing and the nature of the therapeutic relationship.

Physical impact, psychological impact, and restrictions to lifestyle:

- The impact of pain suffered by chronic wound patients was a major theme in the synthesis. Patients’ reports of pain are not always acknowledged by HCPs, and it seemed that pain frequently remains uncontrolled. The reported experiences of pain were more variable in the studies of people with a pressure ulcer, but could still be considerable. Sleep difficulties were reported across the wound types and were strongly linked with uncontrolled pain during the night.
- The chronic wound can have a damaging psychological impact. The symptoms and restrictions caused by the wound and any co-morbidities can have an impact on identity and bring about feeling of hopelessness, helplessness and low self-esteem. Giving patients more control and independence back, for example through collaboration or increasing activity level, can have a positive effect on psychological well-being.
- The physical impact of odour, exudate and unrelieved pain combines with the potential psychological impact of depression, fear of further trauma and low self esteem to restrict mobility, independence, social contact and the ability to work.

The chronic wound journey, the patient and the healthcare system:

- Holistic and empathic patient focused care is very important for these patients' well-being and satisfaction. Patients may maintain their appreciation for HCPs whom they perceive as caring and trying to heal their wound, even if wound healing is slow.
- Collaborative relationships with HCPs were appreciated by patients. Some become an expert in wound care and patients with long-term wound(s) develop knowledge of the signs of recurrence or infection. A small number of studies described successful collaboration with patients, including identification of the need for prophylactic treatment of wound infection.
- All studies indicated that patient's desire wound healing. However, the restrictions of treatment can cause a tension between healing the wound and maximising quality of life within its restrictions. This tension appears to worsen the slower the healing process is or if recurrence is likely. These patients' goals of living as "normal" a life as possible may come into conflict with HCPs goals, particularly if they focus exclusively on wound healing.

Coping:

- Acceptance of the long-term nature of the wound, and the risk of recurrence, is positive in enabling the patient to identify how to live best within its restrictions. This aspect of coping will become more important for those with particularly long-term/recurrent wounds. Coping was also aided by staying active and maintaining a positive outlook, this appeared to be facilitated by acceptance. However, maintaining hope of healing was also important for coping.
- Support from family and friends can be very helpful for coping with lifestyle restrictions. However, patients may feel that they are a burden on their family members because the onset of the chronic wound places multiple restrictions on their families' lives as well as their own.

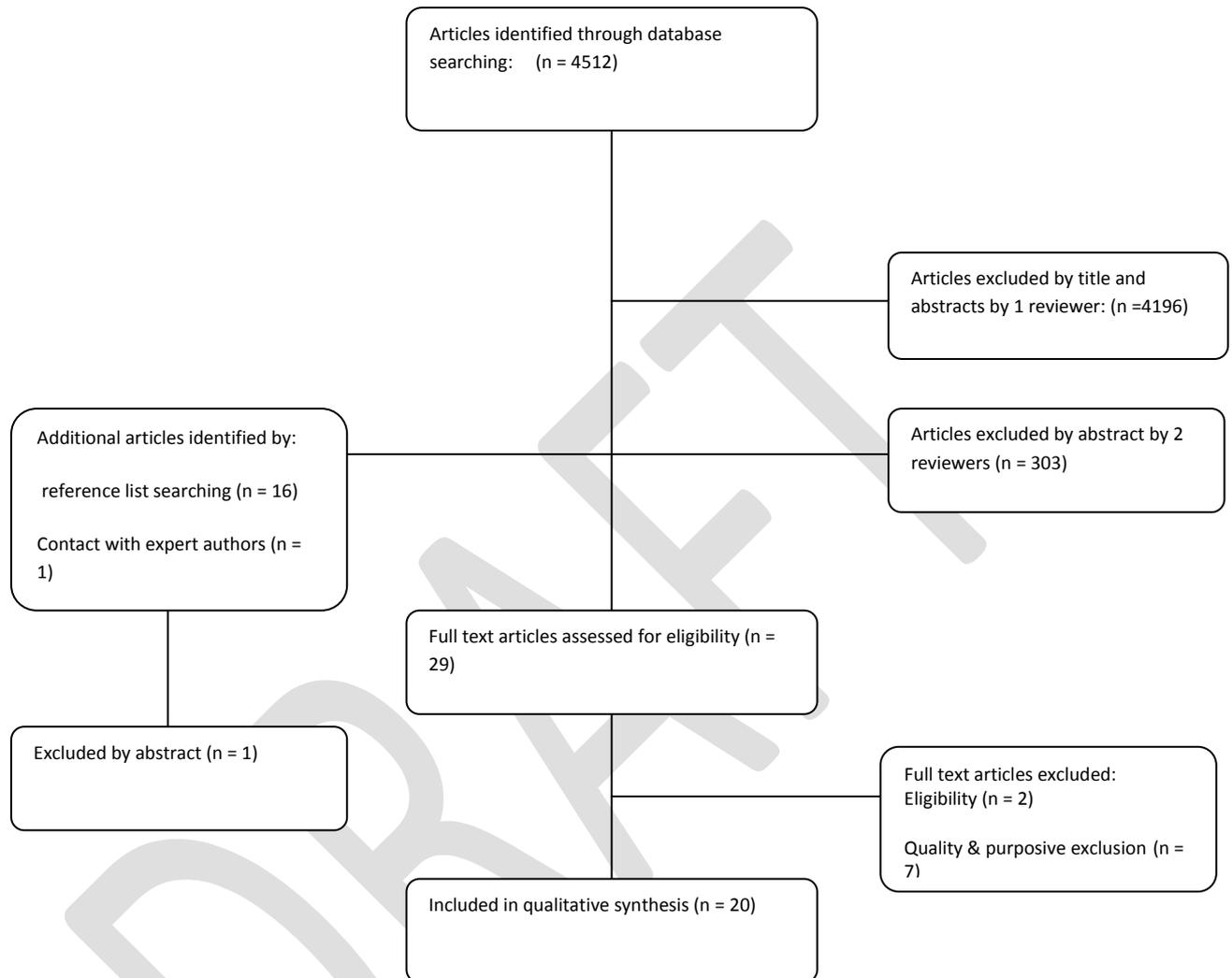
Appendix 1: Qualitative research filter

49. exp Interviews as Topic/
50. exp Attitude to Health/
51. exp Observation/
52. qualitative research/
53. Narration/
54. exp Nursing Research/
55. exp Tape Recording/
56. experience*.ti,ab.
57. interview*.ti,ab.
58. qualitative*.ti,ab.
59. theme*.ti,ab.
60. analytic memo.ti,ab.
61. anecdote*.ti,ab.
62. audiotape*.ti,ab.
63. axial coding.ti,ab.
64. (conceptual adj2 (categor* or framework*)).ti,ab.
65. (concurrent adj2 (analys* or data)).ti,ab.
66. confirmability.ti,ab.
67. content analys*.ti,ab.
68. (comparative adj2 (analys* or method*)).ti,ab.
69. convenience sampl*.ti,ab.
70. data saturation.ti,ab.
71. dependability.ti,ab.
72. ((descriptive or document) adj2 analys*).ti,ab.

73. emergent theor*.ti,ab.
74. ((semistructured or semi-structured or unstructured or informal or in-depth or indepth or face-to-face or structured or guid*) adj3 (discussion* or questionnaire*)).ti,ab.
75. (ethnograph* or ethnological or ethnomethodol* or ethnonursing research).ti,ab.
76. exploratory design.ti,ab.
77. (field notes or fieldwork or field work or key informant*).ti,ab.
78. focus group*.ti,ab.
79. grounded theor*.ti,ab.
80. hermeneutic.ti,ab.
81. (inductive adj2 (analys* or grounded or reasoning)).ti,ab.
82. informational redundancy.ti,ab.
83. (iterative adj2 approach*).ti,ab.
84. interpretive.ti,ab.
85. life histor*.ti,ab.
86. maximum variation sampl*.ti,ab.
87. (meta-ethnography or metaethnography).ti,ab.
88. (narrative* or narration or metanarrative* or meta-narrative*).ti,ab.
89. naturalistic.ti,ab.
90. observation*.ti,ab.
91. (open-ended or open coding).ti,ab.
92. phenomen*.ti,ab.
93. ((purposeful or purposive or probability) adj2 sampl*).ti,ab.
94. saturation.ti,ab.
95. selective coding.ti,ab.

96. (semistructured or semi-structured).ti,ab.
97. snowball sampling.ti,ab.
98. symbolic interactionism.ti,ab.
99. (tape record* or taped discussion*).ti,ab.
100. thematic.ti,ab.
101. (theoretical adj2 (grounding or sampl* or model* or saturation)).ti,ab.
102. transcendental phenomenology.ti,ab.
103. (transcrib* or transcript*).ti,ab.
104. triangulation.ti,ab.
105. verbatim.ti,ab.
106. (video tape* or videotap*).ti,ab.
107. or/49-106

Appendix 2: PRISMA flow chart of articles



Appendix 3: Summary of included and excluded studies

First author & year	Wound type	Participants	Method data collection	Method data analysis	Setting	Quality rating	Reason excluded
Bradbury (2011) ¹⁸	Diabetic foot ulcer	Gender: 2 male, 1 female. Age range: 71-86. Mean age: 76.	Semi-structured interviews	Thematic content analysis	UK, Wales. All recruited from one specialist diabetic foot clinic.	Moderate	Included
Brown (2005) ¹⁹	Chronic venous leg ulcer	n=8. No details of the sample are given.	Semi-structured interviews	Phenomenological thematic analysis	UK, England. District Nursing Service.	Low	Included
Charles (1995) ⁴⁰	leg ulcer (type n/k)	Gender: 3 male 1 female. Age range: 43-62, Mean age : 56.	Semi-structured interviews	Phenomenological thematic analysis	UK, England. Setting details not given.	Low	Excluded – Lower quality leg ulcer study
Chase (1997) ²⁰	leg ulcer (type n/k)	n=7 for semi-structured interviews n=37 for participant observation. No details of the sample are given.	7 semi-structured interviews, 37 participant observation, 12 activity logs	Phenomenological analysis	USA. An ambulatory surgical clinic population in, an urban teaching hospital.	Moderate	Included
Douglas (2001) ²¹	leg ulcer (type n/k)	Gender: 2 male, 6 female. Age range: 65-94.	Semi-structured interviews	Grounded theory based approach	UK, England. All participants interviewed in own home.	High	Included
Ebbeskog (2001) ⁴¹	Venous leg ulcer	Gender: 4 male, 12 female. Age range: 74-89. Mean age: 79.4.	Unstructured research interviews	Phenomenological-hermeneutical approach	Sweden, Stockholm. Interviewed in homes and in clinic.	Moderate	Excluded - Ebbeskog 2005 is a re-analysis of the same data focused on dressings.
Ebbeskog (2005) ²²	Venous leg ulcer	Gender: 4 male, 12 female. Age range: 74-89.	Unstructured research interviews	Interpretative phenomenological analysis	Sweden, Stockholm. Interviewed in	Moderate	Included

		Mean age: 79.4.			homes or in clinic.		
Flaherty (2005) ⁴²	leg ulcer (type n/k)	Gender: 5 male, 5 female. Age range: 52-91.	Semi-structured interviews	A form of thematic analysis	UK, England. London based Healed ulcer clinic.	Low	Excluded – Lower quality leg ulcer study
Fox (2002) ²³	Pressure ulcer	Gender: 4 male, 1 female. Age range 30-64. Mean age: 49.	Semi-structured interviews	14 stage method described by Burnard (1991). A form of thematic analysis.	UK, England. University Hospital Lewisham, London.	Low	Included
Gorecki (2012) ²⁴	Pressure ulcer	Gender: 18 male, 12 female. Age range: 22-94 Mean age: 62.2 years.	Semi-structured interviews	Framework analysis	UK. Recruited from 7 community and hospital services around England and Northern Ireland.	Moderate	Included
Green (2013) ³⁷	Venous leg ulcer	Gender: 4 male, 5 female. Age range 39-99yrs. Median age: 76	Unstructured interviews	Thematic analysis	UK, West Midlands.	Moderate	Included
Haram (2003) ²⁵	Leg ulcer (mixed)	Gender: 4 male, 5 female. Age range: 60-96 (not available for 1 participant)	"open ended interviews" that used a structured 30 question schedule	Martinsen's (1989) theoretical framework	Norway. All participants interviewed in own home.	Moderate	Included
Hopkins (2006) ²⁷	Pressure ulcer	Gender: 3 male, 5 female. Age range: 67-101 Mean age: 77	Unstructured interviews	Interpretative phenomenological analysis	Four centres in two European countries, 3 in the UK and 1 in Belgium.	High	Included
Hopkins (2004) ²⁶	venous leg ulcer	Gender: 4 male, 1 female. Age range: 47-48. Median age 75.	Unstructured interviews & diaries	Interpretative phenomenological analysis	UK, England. Tower Hamlets Primary Care Trust, London.	High	Included
Hyde (1999) ²⁸	leg ulcer (type n/k)	Gender: 12 female, 0 male.	In depth semi-structured	phenomenological analysis	Australia, Sydney. Sydney	High	Included

		Age range: 70-93.	interview and a brief follow up interview.		nursing home service.		
Hyland (1994) ⁴³	leg ulcer (type n/k)	n=22. No details of the sample are given.	Focus groups	Thematic analysis (not described)	UK, England. Focus groups held in a hotel.	Low	Excluded – Lower quality leg ulcer study
Krasner (1998) ²⁹	Venous leg ulcer	Gender: 7 male and 7 females. Age range 30-86. Mean age: not reported but states that "the majority were over 50".	Semi-structured interviews	Phenomenological analysis	USA. Baltimore, Maryland.	Medium	include
Krasner (1998) ⁴⁴	Venous leg ulcer	Gender: 7 male and 7 females. Age range 30-86. Mean age: not reported but states that "the majority were over 50". Duration of ulcer: 2 months to 7 years.	Semi-structured interviews	Phenomenological analysis	USA. Baltimore, Maryland.	Low	Exclude – Lower quality leg ulcer study
Langemo (2000) ³⁰	Pressure ulcer	Gender: 7 male, 1 female. Age range: 27-52. Mean age: 35.75.	Unstructured interviews	Phenomenological method of analysis	USA. Interviews conducted in private setting chosen by participants.	High	include
Mudge (2006) ³¹	venous leg ulcer	Gender: 4 female, 2 male. Age range: 64 to 86.	Single focus group	Content analysis	UK, Wales.	Low	include
Mudge (2008) ³²	leg ulcer and diabetic foot ulcer	Gender: 10 male, 13 female. Age range: not given	Focus groups	Content analysis	3 European countries. UK, France, & Canada.	Moderate	Exclude – UK data already in analysis. No new themes arising from this paper.
Mudge (2008) ⁴⁵	Chronic venous ulceration	n=6. No details of the sample are given.	Focus groups	Content analysis	UK.	Low	include
Neil (2000) ³³	Chronic wounds of	Gender: 4 male, 6 female.	Semi-structured	Phenomenological analysis	USA, Carolina.	High	include

	mixed type	Age range: not given. Mean age: not given.	interview				
Ribu (2004) ³⁴	Diabetic foot or leg ulcer	Gender: 4 male, 3 female. Age range 21-83	In depth interviews	Thematic and meaning analysis	Norway. Recruited from one large municipality by home care nurses.	Low	include
Rich (2003) ⁴⁶	Venous leg ulcer	Gender: 3 male, 5 female. Age range 55-89 Mean Age: 77.	Semi-structured interviews	Thematic analysis (not described)	UK, England. Nottingham.	Low	Exclude – Lower quality leg ulcer study
Spilsbury (2007) ³⁵	Pressure ulcer	Gender: 5 male, 18 female. Age range: 33-92 Median age: 78.	Semi-structured interviews	Thematic analysis	UK. NHS setting.	Moderate	include
Walshe (1995) ³⁶	Venous leg ulcer	Gender: 1 male, 12 female. Age range: not given. Sample older adults. 50% over 85 yrs	Unstructured interviews	Phenomenological thematic analysis	UK, England.	Moderate	include

Appendix 4: Quality assessment included and excluded studies

First author & year	Research design appropriate	Recruitment strategy appropriate	Data collected appropriately	Relationship between researcher & participant considered	Ethical issues taken into consideration	Data analysis sufficiently rigorous	Statement of findings clear	Value of research	Summary rating	Exclusions
Bradbury (2011) ¹⁸	Yes.	Can't tell.	Yes.	No.	Yes.	Can't tell.	Yes.	Acknowledges limited transferability due to small sample. However valuable insight into patient experiences in an under-researched area. Discusses implication for healthcare and future research.	Moderate quality. Small sample. No discussion of impact of researchers on the research, descriptive findings. Description of analysis lacking in detail.	Included
Brown (2005) ¹⁹	Yes.	No.	Yes.	Yes.	Yes.	No.	No.	A valuable review of the literature in this area and discussion of theories of social isolation and loneliness. However a limited presentation and probably analysis of the actual data of this study limits the strengths of its conclusions.	Low quality. Possible bias in sample selection. Solo researcher from same district nursing service as recruitment. No reporting of demographics of sample. Heavy on discussion of theories and literature context - limited in presentation and apparently analysis of own data.	Included
Charles (1995) ⁴⁰	Yes.	Can't tell.	Can't tell.	No.	Yes.	No.	Can't tell.	Discussion of implications for practice.	Low quality. Although reporting may be an issue. No description of recruitment of small sample. Solo researcher with no validation, except for respondent validation of transcripts. However good description of analysis method. Outline of findings is marred by the way it is laid out with quotes	Excluded – Lower quality leg ulcer study

									separated from findings, however it appears that themes are well grounded in the data. More description of the data and less application of theories might have been more useful.	
Chase (1997) ²⁰	Yes.	Can't tell.	Yes.	Can't tell.	No.	Yes.	Yes.	Discusses implication for practice and provides an insight into the experience of a leg ulcer from the patient's perspective. Some ethical reporting failures.	Moderate quality. Some quality criteria are unclear from the paper however it does seem to give a real insight into the experience of the patients. Has used multiple methods to gather diverse qualitative data.	Included
Douglas (2001) ²¹	Yes.	Yes.	Yes.	No.	Yes.	Yes.	Yes.	Discussion of implications for practice and areas of further research.	High quality. Clear and explicit methodology and findings. Although relatively small sample, all from NHS Trust area so may have limited transferability and no explicit discussion of any measures to counteract bias in solo researcher.	Included
Ebbeskog (2001) ⁴¹	Yes.	Yes.	Yes.	No.	Yes.	Can't tell	No.	Discusses how findings should influence care of people with leg ulcers and places in context of other literature.	Moderate quality. No discussion of impact of researchers on the research, descriptive findings. While a good description of analysis is given, the presentation of findings is not well supported by quotes. However there is great deal of thought on theory and context with other research. Not easy to extract specific findings.	Excluded - Ebbeskog 2005 is a re-analysis of the same data focused on dressings.
Ebbeskog (2005) ²²	Yes.	Yes.	Yes.	No.	Yes.	Can't tell.	Yes.	Discusses how findings should influence care of people with leg ulcers and places in context of other	Moderate quality. No discussion of impact of researchers on the research, and no description of any involvement of second	Included

								literature. Also considers possible areas of future research.	researcher. Clear description of findings and supported by description of paradigm cases, however no consideration of any atypical cases within the sample.	
Flaherty (2005) ⁴²	Yes.	Can't tell.	Can't tell.	No.	Yes.	No.	No.	Author does discuss implications and place in context of other research.	Low quality. Many flaws.	Excluded – Lower quality leg ulcer study
Fox (2002) ²³	Yes.	No.	Yes.	Yes.	No.	No.	Can't tell.	Discusses implications of findings and places in research context. Reservations about level of bias since use of own caseload and solo researcher.	Low quality. A small sample and a solo researcher. However appears like a rigorous analysis and findings made explicit and supported by quotes. Findings may sound more like the voice of the researcher than the participant.	Included
Gorecki (2012) ²⁴	Yes.	Yes.	Yes.	No.	Yes.	Yes.	Can't tell.	Research is part of an ongoing National Institute for health research project looking at factors that contribute to HRQOL.	Moderate quality. A large and well recruited purposive sample. However limited consideration of impact of researchers own bias and background on research. Measures such as multiple coders used to counteract this.	Included
Green (2013) ³⁷	Yes.	Yes.	Yes.	Can't tell.	Yes.	Yes.	Yes.	Discusses future research and implications.	Moderate quality. Borders on high key problem is depth of analysis and whether considered potential bias in researchers.	Included
Haram (2003) ²⁵	Yes.	Can't tell.	Yes.	Can't tell	No.	Yes.	Yes.	Discussion of practice implications and degree of transferability.	Moderate quality. Exploratory. No discussion of saturation. Used bracketing but no discussion of second researcher or respondent validation. Did not describe recruitment and selection process. Sound analysis.	Included
Hopkins	Yes.	Can't tell.	Yes.	Yes.	Yes.	Yes.	Yes.	Research	High quality. A fairly small	Included

(2006) ²⁷								implications discussed e.g. Need for awareness of pain during treatment.	sample but well described.	
Hopkins (2004) ²⁶	Yes.	Yes.	Yes.	Yes.	Yes.	Yes.	Yes.	Research implications well discussed.	High quality. A relatively small sample and use of solo researcher may limit transferability, credibility but methodology well described.	Included
Hyde (1999) ²⁸	Yes.	Yes.	Yes.	Yes.	Yes.	Yes.	Yes.	Research implications discussed	High quality. Insufficient detail on recruitment, otherwise of high quality.	Included
Hyland (1994) ⁴³	Yes.	Can't tell.	Can't tell.	No.	No.	No.	No.	Valuable as part of a programme to design a QOL questionnaire	Low quality. Limited description of a preliminary element of the overall research project.	Excluded – Lower quality leg ulcer study
Krasner (1998) ²⁹	Yes.	Yes.	No.	No.	Yes.	Yes.	Yes.	Focus on pain useful particularly at time of study. Discusses implications for practice.	Moderate quality. Concerns re possibility of bias in recruitment and lack of detail on how data gathered. However findings seem largely well supported by data presented.	include
Krasner (1998) ⁴⁴	Yes.	Yes.	No.	No.	Yes.	Can't tell.	No.	Research focus on QOL and patient experiences particularly useful at time of publication.	Low quality. Unclear how recruited and analysis has been done. Risk of bias in selection and analysis is quite high. Not enough data presented to root analysis in patient views.	Exclude – Lower quality leg ulcer study
Langemo (2000) ³⁰	Yes.	Yes.	Yes.	Yes.	Yes.	Yes.	Yes.	Valuable in discussing the lived experience of participants, and highlighting issues for nursing practice. Researchers discuss implications for practice	High quality. Although relatively small sample, all from same medical centre, so consideration of how transferable the all findings are to any other groups is necessary.	include
Mudge (2006) ³¹	Yes.	Can't tell.	Yes.	No.	No.	Can't tell.	Yes.	Research implications discussed.	Low quality. A small sample selected in an unclear way from an existent manufacturer	include

									funded trial. Analysis is not well described. A good discussion of findings in their research context but themes identified very broad.	
Mudge (2008) ⁴⁵	Yes.	Can't tell.	Yes.	No.	Yes.	Can't tell.	Yes.	Discusses implications for patient management.	Moderate quality. Lacking in description of researchers impact on research or measure to counteract any researcher bias. Limited description of process of analysis. However findings appear well grounded in the data.	Exclude – UK data already in analysis. No new themes arising from this paper.
Mudge (2008) ³²	Can't tell.	Can't tell.	Can't tell	No.	No.	Can't tell.	Yes.	Valuable insight into pain and focus on dressing change. Implications for professionals highlighted.	Low quality. However this may be a reporting issue, conclusions appear sound and unbiased.	include
Neil (2000) ³³	Yes.	Yes.	Yes.	Yes.	Yes.	Yes.	Yes.	Valuable insight into experience of having a chronic wound. Implications for practice discussed.	High quality. Well described rigorous methodology. Relatively small sample with no description of refusals etc could lead to bias. However researcher discusses degree of transferability of findings.	include
Ribu (2004) ³⁴	Yes.	Can't tell.	Yes.	No.	Yes.	Can't tell.	Yes.	Valuable in discussing the lived experience of participants, and highlighting issues for professional practice.	Low quality. No discussion of impact of researcher on the research, no described involvement of second researcher. No discussion of whether saturation was achieved. Otherwise methodologically sound.	include
Rich (2003) ⁴⁶	Yes.	No.	No.	No.	Yes.	Can't tell.	No.	Some consideration of implications for practice and some suggestions for further research	Low quality. Edging towards moderate. Highly descriptive. Unclear how analysed, sampled in a way that did not fulfil aim.	Exclude – Lower quality leg ulcer study
Spilsbury (2007) ³⁵	Yes.	Yes.	Yes.	Can't tell.	Yes.	No.	No.	Researchers draw attention to the research	Moderate quality. Well sampled. No discussion of impact of researchers on	include

								implications.	the research, limited breakdown of findings. Description of analysis lacking in detail.	
Walshe (1995) ³⁶	Yes.	Yes.	Yes.	No.	Yes.	No.	Can't tell.	Valuable in discussing the lived experience of participants, and highlighting issues for nursing practice.	Moderate quality. Study reveals lived experience of participants, and identifies a set of key themes, but does have some methodological flaws.	include

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CLINICAL EFFECTIVENESS: FULL WRITE UP

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1.0 Methodology: Clinical Effectiveness Section

1.1 Objectives

The main research question for the clinical effectiveness section was:

What is the clinical effectiveness of different antimicrobial dressings, compared to other dressings and techniques, for treating localised wound infection in chronic wounds?

Although the primary outcome related to wound infection, the population eligible for inclusion was not limited to those defined as having a chronic wound with localised infection. This is because studies on some relevant secondary outcomes (for example, wound healing) would have been missed if the population was limited to those defined as having infected chronic wounds. Full details of what studies were eligible for inclusion are given in section 1.4.

1.2 Sources of Evidence

The following bibliographic databases were searched to identify systematic reviews and primary studies:

- MEDLINE (Ovid)
- MEDLINE in Process (Ovid)
- EMBASE (Ovid)
- CINAHL (EBSCOHost)
- Web of Science (ISI)
- Cochrane Central Register of Controlled Trials – CENTRAL (Cochrane Library)

In addition, various websites were searched for relevant systematic reviews. These included the Cochrane Database of Systematic Reviews, HTA organisation websites and the websites of clinical guideline developers.

Manufacturers of AWD were also invited to submit evidence, from which good quality systematic reviews and RCTs were included.

1.3 Literature Search

Website and database searches, to identify systematic reviews relating to AWDs, were undertaken in January 2014. All searches combined the concepts of “chronic wounds” and “antimicrobial wound dressings”, and aimed to be as comprehensive as possible using all relevant subject terms and keywords. Searches for systematic reviews were limited to 1990-2014, and used the SIGN systematic review filter.

Searches for RCTs were run in July and August 2014. This involved database searches for selected wound and AWD combinations (table 1). Searches were limited to RCTs published after the included systematic reviews. The Cochrane RCT filter, or an adaptation of it, was used in all primary literature searches. All searches were restricted to English language.

Table 1: summary of primary literature searches

Search	Date	Limits/Filters
Venous/arterial ulcers + iodine	July 2014	RCTs, 2009-2014
Venous/arterial ulcers + honey	July 2014	RCTs, 1990-2014
Venous/arterial ulcers + silver	July 2014	RCTs, 1990-2014
Diabetic ulcers + iodine	July 2014	RCTs, 2009-2014
Diabetic ulcers + silver	July 2014	RCTs, 2005-2014
Diabetic ulcers + honey	July 2014	RCTs, 1990-2014
Pressure ulcers + iodine	July 2014	RCTs, 2013-2014
Pressure ulcers + silver	July 2014	RCTs, 2013-2014
Pressure ulcers + honey	July 2014	RCTs, 2013-2014
All ulcers + chlorhexidine, DACC, enzyme alginogels, PHMB	August 2014	RCTs, 1990-2014
Surgical wounds + chlorhexidine, DACC, enzyme alginogels, PHMB	August 2014	RCTs, 1990-2014

Relevant literature was also identified using ZETOC (the British Library table of contents service). Alerts were set up using keywords appearing in the title of articles and scanned for relevance.

An update search was conducted in January 2015 to identify any recently published systematic reviews or RCTs.

A list of sources searched and a copy of all the search strategies used in MEDLINE are available in Appendix 1. The MEDLINE strategies were adapted to search all other databases. A complete listing of all search strategies can be obtained by contacting Healthcare Improvement Scotland.

1.4 Study Selection

Literature was selected using the PICOS (Population, Intervention, Comparison, Outcome, Study design) framework.

For the systematic reviews search results, two health services researchers independently screened all titles and abstracts against the inclusion criteria detailed below. The full text of papers thought to be potentially relevant was obtained where possible. These full reports were again independently assessed against the inclusion criteria by two health services researchers. Any disagreement in selections was resolved by consensus. All exclusions were recorded, with reasons, in a table.

For the RCTs not already identified by the systematic reviews, two health services researcher screened the articles for relevance.

The PICOS criteria are detailed as follows:

1.4.1 Population

Adults (aged ≥ 18) with chronic wounds, treated in any care setting. The chronic wounds eligible for inclusion are:

- foot ulcers in people with diabetes
- pressure ulcers
- venous and/or arterial ulcers (including ulcers of lymphovenous origin)
- dehisced surgical wounds and wounds healing by secondary intention

Any definition of these four wounds that were used in the included literature was accepted.

In studies which included mixed wound types – the data relating to the wounds of interest were extracted if possible. If the data was not presented separately for the different wound types, the study was not eligible for inclusion. Authors were not contacted to try and get the data by wound type.

Although the primary outcome of this HTA related to wound infection, the population eligible for inclusion was not limited to those defined as having a chronic wound with localised infection. Studies reporting on the secondary outcomes of this HTA (eg time to healing) might have been missed if the population was limited to those defined as having infected chronic wounds.

We excluded studies on patients with acute wounds or abscesses (including burns). For clarification, an acute wound is an injury to the skin that occurs suddenly rather than over time. It heals at a predictable and expected rate according to the normal wound healing process.

1.4.2 Intervention

Wound dressings, produced by any manufacturer, containing any of the following antimicrobial agents:

- Iodine (cadexomer iodine or povidone-iodine)
- Honey
- Silver (either impregnated or topical in the form of silver sulfadiazine)
- 'Other': this category consists of all other antimicrobials listed in A5.3 of BNF68 that clinical experts told us were of interest, namely polihexanide (PHMB), enzyme (eg glucose oxidase and lactoperoxidase) alginogels, octenidine, chlorhexadine and dialkylcarbamoly chloride (DACC).

In addition, studies were eligible for inclusion if the intervention involved an antimicrobial being in contact with a wound for a period of time. This would include dressings that are impregnated with the antimicrobials of interest; and also topical application of antimicrobials underneath a non-impregnated dressing (e.g. povidone iodine ointment or honey being applied to a wound, and then held in place using a dry dressing).

There are some topical agents not listed in section A5.3 of BNF 68 that were still eligible for inclusion (provided they contain one of the antimicrobials listed above) eg silver sulfadiazine creams and povidone-iodine powder.

1.4.3 Comparison

- Dressings that do not contain any antimicrobial agent.
- Any study identified in the literature that compared one type of AWD to another was eligible for inclusion.
- Any other comparisons reported in the literature, including other wound management products/techniques that propose to reduce bioburden (Debrisoft® and debridement).

1.4.4 Outcomes

The primary outcomes of interest were: resolution of localised wound infection, improvement in signs and symptoms of wound infection, and reduction of bioburden.

All studies that reported on wound infection were eligible for inclusion. There is no one clearly defined way to diagnose wound infection, or to measure the extent of microbial contamination, which makes them challenging to use as outcome measures. Therefore, the way in which infection is measured (e.g. by clinical signs and symptoms, or by bacteriological swabs) differs in the literature. All methods for measuring infection, or definitions used by the authors, were eligible for inclusion.

Secondary outcomes were: all wound healing outcomes (for example wound size and depth, time to healing, rate of healing, proportion of wounds healed), use of systemic antibiotics, health-related quality of life (using any measure), adverse events, ease of use, and patient acceptability and comfort.

Outcomes relating to the prevention of wound infection, in apparently uninfected wounds, were not extracted from the studies.

1.4.5 Study types

We included published systematic reviews, with or without meta-analyses. Reviews of all study types were included. In addition, guidelines based on a systematic review were eligible for inclusion, provided that sufficient details of the review were provided.

To be eligible for inclusion, the reviews had to evaluate the use of AWDs in the treatment of the wounds of relevance. Where reviews had a broader, or different, scope to this HTA, only the data of relevance was extracted.

RCTs were included if they were not already identified by the systematic reviews (either they were published after the systematic review, or did not meet the eligibility criteria for the systematic reviews). However, meta-analyses were not updated if new RCTs were identified. The full texts of RCTs already included in the systematic reviews were only obtained if it was possible that they included some outcomes of relevance to the HTA (notably, treatment of wound infection) that were not extracted by the systematic reviews; or if there was some doubt about the accuracy of the data provided by the reviews.

Systematic reviews and RCTs published in languages other than English were not included. Abstracts were not eligible for inclusion. We decided not to search for primary studies beyond RCTs, as the time and resource could be best invested in other parts of the HTA.

We excluded animal studies, in-vitro studies, discussion articles, non-systematic reviews, editorials, letters to the editor, opinion papers, or other studies that did not report on patient-related outcomes.

1.5 Quality Assessment

The quality of the systematic reviews was assessed independently by two health services researchers. The SIGN methodological checklist for systematic reviews and meta-analyses was used. Disagreement was resolved through consensus, and when necessary a third reviewer was consulted. Reviews that were rated as being of high quality (++) or acceptable

quality (+) were included. Reviews that were rated as being of unacceptable quality (-) were excluded at this point in the process. This was recorded in the table of exclusions.

The quality of the additional RCTs was assessed by two health services researchers. The SIGN methodological checklist for RCTs was used.

More details on the SIGN methodology checklists are available at:

<http://www.sign.ac.uk/methodology/checklists.html>

1.6 Data Extraction

Initially, the literature search was limited to secondary evidence. Therefore, most of the data extracted did not come straight from the primary studies. However, where the reviews were deemed to be of sufficient quality, the assumption was made that the data presented was accurate and complete. Where more than one review reported on the same study, the data was cross-checked, to ensure consistency. The full text of primary papers reported in reviews was only obtained if there was reason to suspect that the data presented in the reviews was incorrect or incomplete.

The following information was extracted from the systematic reviews:

- Study details
 - Year of publication
 - Study objectives
 - Selection criteria (main inclusions and exclusions)
- Quality (assessed using the SIGN checklist for systematic reviews/meta-analyses)
- Results
 - Number of included studies, and total number of participants
 - Main characteristics of included studies (including quality)
 - Main results (pooled results; narrative summary)

For the RCTs, the main details of the study were extracted (using the PICO framework).

Data extraction was recorded in evidence tables in word. A different evidence table was produced for each type of wound and category of antimicrobial. Data extraction was performed by one health services researcher, and then quality assured by a second.

1.7 Data Synthesis

For each of the different wound types, a narrative review of the evidence was written, separately for each category of antimicrobial.

Rather than reappraising the same primary studies included in existing synthesised reports on AWDs, the narrative review focused initially on good quality systematic reviews. Any additional RCTs not incorporated into these reviews were also included.

The narrative review was written by one health services researcher and quality-assured by a second.

1.8 Update Search

An update search was run in January 2015. The same search strategy (detailed above) was used, and was limited to systematic reviews and RCTs.

2.0 Clinical effectiveness: Results

2.1 Venous leg ulcers

Sixteen systematic reviews were identified that included studies on the use of AWDs in venous ulcers¹⁻¹⁶. The scope of the systematic reviews varied, with some evaluating a mixture of wound types, or a variety of interventions (for more details, refer to the evidence tables in Appendix 4). However, in almost all the reviews, the primary outcomes related to wound healing (such as time to complete healing and change in wound surface area). Very little data was reported on outcomes relating to the treatment of localised wound infection. Seven of the reviews included wound infection related outcomes (often as a secondary outcome)^{1, 2, 9, 11, 13-15}, with only one stating that they were considering bacterial load and wound infection as a primary outcome¹⁵. However, the data presented was limited and not sufficient to make any firm conclusions. Ulcer infection status at baseline varied across the primary studies: some excluded participants with infected (or 'critically colonised') ulcers; others included them; and some did not mention, or were not clear about, ulcer infection status.

Most of the evidence for this chapter has been taken from a high quality Cochrane review (O'Meara 2014)¹¹. Detail from the other reviews is only presented if it adds to the results of O'Meara 2014.

O'Meara (2014) included prospective RCTs evaluating systemic or topical antibiotics or topical antiseptics in the treatment of venous ulcers, in any care setting. Data relating to iodine (povidone iodine and cadexomer iodine), honey, silver and chlorhexadine were included in this review, and were extracted for this HTA.

As the methods of diagnosis of venous ulceration may vary, O'Meara 2014 accepted all definitions as used in the literature. Furthermore, RCTs were not restricted to those with a certain wound infection status (colonised or infected wounds) at baseline. The primary outcome of the review related to wound healing, in particular: time to complete wound healing; proportion of ulcers healing during follow-up; and change (or rate of change) in wound size. When reported in the RCTs, O'Meara 2014 also extracted data on several secondary outcomes, including: changes in signs and/or symptoms of clinical infection; changes in bacterial flora; and development of bacterial resistance. However, studies were only eligible for inclusion if they reported on one of the primary outcomes. All included RCTs were assessed using the Cochrane Collaboration's risk of bias tool.

A literature search for this HTA identified only one further RCT on venous ulcers that was not included in any of the systematic reviews. This compared a membranous dressing with silver ions to a hydrocolloid dressing (Kucharzewski 2013)¹⁷, and has been detailed in section 2.1.3.6.

2.1.1 Venous ulcers: Iodine

Five systematic reviews were identified that included studies on the treatment of venous leg ulcers with topical iodine or iodine impregnated dressings^{1, 3, 11, 12, 15}. One of these was rated as acceptable quality¹⁵, with the remaining four as high quality^{1, 3, 11, 12}.

In addition, two high quality guidelines based on a systematic review were identified^{18, 19}. These reported on an earlier version of the O'Meara 2014 review. Despite being based on the same evidence, the recommendations made are not consistent. One of the guidelines, produced by SIGN 2010, does not make a recommendation as 'there is insufficient consistent evidence on which to base a recommendation for either cadexomer iodine or povidone iodine'¹⁹. The other guideline, from Australia/New Zealand, makes the following B-grade recommendation:

'Cadexomer iodine could be used to promote healing in VLU when there is known increased microbial burden'¹⁸.

As the evidence reported by the guidelines is the O'Meara 2014 review, which is informing most of this section of the HTA, they have not been discussed further.

O'Meara (2014) included 11 RCTs (12 comparisons), encompassing 962 participants, that evaluated the effects of cadexomer iodine¹¹. They also included six RCTs (seven comparisons), encompassing 639 participants, evaluating povidone-iodine preparations. The four other systematic reviews identified for this HTA did not include any studies that would change the conclusions of the O'Meara 2014 review.

A literature search for this HTA did not highlight any RCTs on the use of iodine-impregnated dressings or topical agents that had not already been included in the systematic reviews.

A manufacturer submitted one manuscript of an RCT eligible for inclusion²⁰, which has been accepted for publication. It evaluated a dressing which produces iodine, but does not contain cadexomer iodine or povidone iodine. It is detailed separately in section 2.1.1.9.

The main results are summarised below:

2.1.1.1 Cadexomer iodine versus standard care

O'Meara (2014) identified seven RCTs that compared cadexomer iodine with standard care (Skog 1983; Ormiston 1985; Harcup 1986; Lindsay 1986; Steele 1986; Laudanska 1988; Holloway 1989)¹¹. All seven RCTs were assessed as having either a high or unclear risk of bias. Four RCTs were conducted in the United Kingdom, one in Sweden, one in Poland and one in the United States. One RCT was conducted in an inpatient setting, and the remaining six in community or outpatient settings. Four RCTs mentioned the use of compression as a concurrent therapy in all participants (although it was not clear whether the level applied was therapeutic), with the remaining three mentioning the use of light retention or support bandages for all participants. What the trial authors defined as 'standard care' varied between the studies, but normally consisted of ulcers being cleansed and then a non-adherent dressing being applied. One RCT limited inclusion to patients with infected ulcers at baseline, but the remaining six did not specify baseline ulcer infection status. Treatment duration ranged from 4 to 24 weeks.

Outcome – wound infection

Four of the seven RCTs reported on outcomes related to wound infection (three of these did not specify baseline ulcer status, but it appeared that those with infected ulcers would not be excluded from the trial). Two assessed infection using swabs, with both reporting differences in favour of cadexomer iodine compared to standard care: one reported statistically

significant differences for the number of participants with eradication or improvement of staphylococcal infection ($p < 0.001$), *Pseudomonas aeruginosa* infection ($p < 0.05$), and other pathogenic organisms ($p < 0.001$); and the other reported that cadexomer iodine resulted in elimination or decrease in bacterial organisms in most cases (no further details given). The other two studies reported no significant difference between cadexomer iodine and standard care on bacterial numbers (no other information presented). These results are conflicting, and are from studies assessed as low quality. Therefore, no conclusions can be drawn on the effect of cadexomer iodine, compared to standard care, on wound infection.

All seven RCTs reported on other secondary outcomes that might be related to infection, for example pain, pus and exudate. Again, the results are conflicting, and the study quality did not allow any conclusions to be drawn.

Outcome – wound healing

With regard to wound healing, O’Meara 2014 pooled the data from four RCTs for the outcome of complete healing at 4 to 12 weeks. This indicated that 35/106 (33%) ulcers healed when treated with cadexomer iodine and 16/105 (15%) healed on standard care. This gives an RR of 2.17 (95% CI 1.30 to 3.60), in favour of cadexomer iodine. Findings from the other three RCTs were also in favour of cadexomer iodine; reporting evidence of a difference in mean percentage change in ulcer area and mean rate of ulcer healing. As already noted, the included studies were rated as having a high or unclear risk of bias.

Outcome – adverse effects

For adverse effects, O’Meara 2014 pooled the results from two RCTs. This suggested a higher incidence of adverse events in those receiving cadexomer iodine (RR 4.59; 95% CI 1.40 to 15.05). Data from a third RCT provided insufficient detail for inclusion in the meta-analysis, but reported that six participants treated with cadexomer iodine experienced adverse events compared to none allocated to standard care (based on 54 people who completed the trial, with numbers in each group not reported). The adverse events reported included itching, pain, eczema, pruritus, rashes and difficulty removing cadexomer iodine from the ulcer.

Two other systematic reviews included RCTs of relevance to this section^{1, 15}, but none that had not already been included in O’Meara 2014. The main results from the systematic reviews are summarised in table 2.

Table 2: Summary of evidence: venous ulcers - Cadexomer iodine versus standard care

Reference	Quality	Main results (of relevance to this section)
O’Meara 2014 ¹¹	++	Included seven RCTs rated as having a high or unclear risk of bias. Healing outcomes were better for cadexomer iodine compared with standard care. However, the incidence of adverse events was greater in those receiving cadexomer iodine. The results relating to wound infection are conflicting, with two studies favouring cadexomer iodine, and two reporting no evidence of a difference compared with standard care.
AHRQ 2014 ¹	++	Included 2 RCTs (Ormiston 1985; Holloway 1989), which were already reported on in O’Meara 2014. Does not add to the data already presented.

Vermeulen 2010 ¹⁵	+	Included 4 RCTs (Skog 1983, Ormiston 1985, Laudanska 1988, Holloway 1989), which were already reported on in O'Meara 2014. Does not add to the data already presented.
<i>Primary evidence: A literature search identified no RCTs that had not already been included in the systematic reviews.</i>		

2.1.1.2 Cadexomer iodine versus hydrocolloid dressing/paraffin gauze dressing

A three-armed RCT by Hansson (1998; n=153) was included in four of the systematic reviews identified for this HTA (refer to table 3)^{1, 3, 11, 15}. This RCT was of low quality, with a high dropout rate, unclear blinding, and an analysis that was not intention-to-treat.

The RCT included patients with exudating or sloughy, non-infected venous ulcers. The three treatments participants were randomised to were: paraffin gauze, cadexomer iodine paste, and a hydrocolloid dressing. All participants received compression, and treatment lasted for 12 weeks, delivered in an outpatient setting.

Outcome – wound infection

This RCT limited inclusion to patients with non-infected wounds and therefore reported no outcomes relating to the treatment of localised wound infection.

Outcome – wound healing

The primary outcomes of the RCT related to wound healing. At 12 weeks, 14% (8/56) of ulcers had healed in the cadexomer iodine group compared to 10% (5/48) in the hydrocolloid group. O'Meara 2014 calculated an RR of 1.37 (95% CI 0.48 to 3.91), and so did not detect evidence of a difference between the groups¹¹. The number of ulcers healed in people treated with paraffin gauze (14%) was similar to the numbers in the cadexomer iodine group (14%): RR 1.00; 95% CI 0.39 to 2.56.

Outcome – adverse effects

Nineteen adverse events were reported in the cadexomer iodine group, compared with 33 in the hydrocolloid group and 26 in the paraffin gauze group.

Table 3: Summary of evidence: venous ulcers - Cadexomer iodine versus paraffin gauze and hydrocolloid dressings

Reference	Quality	Main results (of relevance to this section)
O'Meara 2014 ¹¹	++	Included a three-armed RCT (Hansson 1998), rated as having a high risk of bias. This reported no evidence of a difference in the number of non-infected venous ulcers healed when treated with cadexomer iodine, paraffin gauze or hydrocolloid dressings.
AHRQ 2014 ¹	++	Included the same study, and does not add to the data already presented.
Vermeulen 2010 ¹⁵	+	Included the same study, and does not add to the data already presented.
Bradley 1999 ³	++	Included the same study, and does not add to the data already presented.
<i>Primary evidence: A literature search identified no RCTs that had not already been included in the systematic reviews.</i>		

2.1.1.3 Cadexomer iodine versus dextranomer

The O'Meara 2014 review included two RCTs that compared cadexomer iodine with dextranomer (Kero 1987, Moss 1987)¹¹. Kero 1987 was rated as having an unclear risk of bias, and Moss 1987 as having a high risk of bias¹¹. The RCT by Moss 1987 was also included in a systematic review by Vermeulen 2010¹⁵ (see table 4 for summary of systematic reviews).

Both RCTs included patients having their venous leg ulcers treated in the outpatient setting. Both stated that all participants received compression therapy, but ulcer infection status was not reported at baseline.

Outcome – wound infection

Moss 1987 reported on the proportion of participants eradicating organisms during 6 weeks of treatment, but no p-values were given for between group differences. Moss 1987 also reported that complete eradication of bacteria during the 6 week trial was associated with a reduction in mean ulcer size in both treatment groups. In terms of specific isolates, this association was statistically significant for *Pseudomonas* species ($p < 0.05$).

Outcome – wound healing

Both RCTs included outcomes relating to ulcer healing (complete healing, and reduction in ulcer area). In Kero 1987, 27 participants were included. In those treated with cadexomer iodine, 50% (7/14) had complete ulcer healing at 8 weeks, compared to 38% (5/13) of those treated with dextranomer. O'Meara 2014 calculated a RR of 1.30 (95% CI 0.55 to 3.09), and so detected no evidence of a difference between the groups¹¹. Moss 1987 included 43 participants, and assessed the mean percentage change in ulcer area at 6 weeks. The authors reported a reduction of 2% in the group treated with dextranomer, compared to 3% treated with cadexomer iodine (authors stated that the difference was not statistically significant, but no p-value was given).

Outcome – adverse effects

In Kero 1987, one adverse event (pain) was reported in the group treated with dextranomer. Three adverse events (erythema, pain and stinging sensation) were reported in the group treated with cadexomer iodine.

Table 4: Summary of evidence: venous ulcers - Cadexomer iodine versus dextranomer

Reference	Quality	Main results (of relevance to this section)
O'Meara 2014 ¹¹	++	Included two RCTs, one with a high risk of bias (Moss 1987), the other with an unclear risk of bias (Kero 1987). These did not detect evidence of a difference between groups treated with cadexomer iodine or dextranomer for outcomes related to wound healing (complete healing, and reduction in wound area).
Vermeulen 2010 ¹⁵	+	Included Moss 1987, and does not add to the data already presented.
<i>Primary evidence: A literature search identified no RCTs that had not already been included in the systematic reviews.</i>		

2.1.1.4 Cadexomer iodine versus silver impregnated dressings

O'Meara 2014 included one RCT (Miller 2010; n=281) that compared cadexomer iodine to silver impregnated dressings¹¹. The study was rated as having a high risk of bias by O'Meara 2014.

Patients with venous or mixed venous/arterial aetiology leg ulcers were included, and all had signs of infection or critical colonisation at baseline. All participants received four-layer compression bandaging.

Outcome – wound infection

In terms of wound infection, the trial authors assessed bacterial growth using wound swabs during the first two weeks of treatment. The authors used the categories 'nil/scant/low' and 'moderate/high'. Similar results were presented for both the groups for: leucocytes; Gram-positive bacilli; Gram-negative bacilli; Gram-positive cocci; and Gram-negative cocci. *Staphylococcus aureus* was the most commonly isolated organism. The authors reported that when nil/scant/low bacterial growth was identified, ulcers treated with silver dressings healed faster than those treated with cadexomer iodine in relation to leucocytes ($p < 0.01$), Gram-positive bacilli ($p < 0.05$), Gram-positive cocci ($p < 0.01$), and gram-negative cocci ($p < 0.05$) within the first 2 weeks.

Outcome – wound healing

The primary outcomes of the RCT related to wound healing (time to healing, number of ulcers healed at week 12 and mean percentage daily healing rate). No evidence of a difference was reported for these. The number of ulcers healed at 12 weeks was 60% (84/141) in the cadexomer iodine group and 61% (85/140) in the silver-impregnated dressing group. A RR was calculated by O'Meara 2014 (RR 0.98; 95% CI 0.81 to 1.19)¹¹.

Outcome – adverse effects

Eight adverse events were reported in the cadexomer iodine group, compared to 13 in the silver dressings group. It was unclear if the numbers provided refer to the number of participants reporting adverse events, or the number of adverse events in the group. There was no evidence of a difference in the proportion of participants who completely or moderately agreed that the dressing was acceptable overall (91.6% in the silver group versus 88.9% in the cadexomer iodine group) (RR 0.97; 95% CI 0.89 to 1.06)¹¹.

Table 5: Summary of evidence: venous ulcers - Cadexomer iodine versus silver-impregnated dressings

Reference	Quality	Main results (of relevance to this section)
O'Meara 2014 ¹¹	++	Included one RCT, rated as having a high risk of bias, on patients with venous and mixed venous/arterial aetiology leg ulcers. No statistically significant difference between groups treated with cadexomer iodine or silver-impregnated dressings for outcomes related to wound healing, bacterial growth and patient acceptability were reported.
<i>Primary evidence: A literature search identified no RCTs that had not already been included in the systematic reviews.</i>		

2.1.1.5 Povidone-iodine versus dextranomer

For this comparison, one RCT was identified (Groenewald 1981), which was included in two systematic reviews^{11, 15}. This study was rated as having a high risk of bias by O’Meara 2014. In particular, it was not clear if the study was blinded, and the analysis was not intention-to-treat¹¹.

This RCT came from South Africa, and included 100 people with varicose stasis ulcers. All participants were outpatients, and all received compression therapy. The ulcers were colonised with bacteria at baseline, but the authors did not report if the ulcers were clinically infected.

Outcome – wound infection

With regard to outcome measures relating to wound infection, average eradication time for *Staphylococcus aureus* was reported as a secondary outcome. The time was shorter in the dextranomer group compared to the povidone iodine group, and this difference was reported as statistically significant (14.7 days versus 18.7 days; $p < 0.01$).

Outcome – wound healing

The primary outcome of the RCT was average healing time, and this was reported to be shorter in the group treated with dextranomer (4.4 weeks versus 5.3 weeks, $p < 0.05$). However, O’Meara 2014 state that it is unclear whether the time to event data were analysed appropriately using survival analysis.

Table 6: Summary of evidence: venous ulcers – Povidone-iodine versus dextranomer

Reference	Quality	Main results (of relevance to this section)
O’Meara 2014 ¹¹	++	Included one RCT (Groenewald 1981), rated as having a high risk of bias. Average healing time and average eradication time for <i>S.aureus</i> were shorter in a group treated with dextranomer, compared to a group treated with povidone iodine.
Vermeulen 2010 ¹⁵	+	Included Groenewald 1981, and does not add to the data already presented.
<i>Primary evidence: A literature search identified no RCTs that had not already been included in the systematic reviews.</i>		

2. 1.1.6 Povidone-iodine and sugar ointment versus recombinant tissue growth factor

The review by O’Meara 2014 included an RCT conducted in Japan (Ishibashi 1996), rated as having an unclear risk of bias¹¹.

This RCT compared povidone-iodine and sugar ointment to recombinant tissue growth factor. The trial included a variety of different wound types ($n=218$). Both inpatients and outpatients were included in the trial, and approximately two thirds of analysed participants had some degree of ulcer infection at baseline. Treatment was given for 4 weeks.

Outcome – wound infection

There was no mention of any outcomes relating to wound infection.

Outcome – wound healing

The data presented here pertains to those with venous leg ulcers (n=63). The use of compression therapy was not mentioned by the trial authors. The percentage of ulcers healed at 4 weeks was 16% (5/31) in the povidone-iodine and sugar ointment group and 28% (9/32) in the growth factor group. O'Meara 2014 calculated a RR, which did not highlight evidence of a difference between treatment groups (RR 0.57; 95% CI 0.22 to 1.52)¹¹.

Table 7: Summary of evidence: venous ulcers – Povidone-iodine and sugar ointment versus recombinant tissue growth factor

Reference	Quality	Main results (of relevance to this section)
O'Meara 2014 ¹¹	++	Included one RCT (Ishibashi 1996), rated as having an unclear risk of bias. No evidence of a difference was detected in percentage of venous ulcers healed when treated with povidone-iodine and sugar ointment or recombinant tissue growth factor.
<i>Primary evidence: A literature search identified no RCTs that had not already been included in the systematic reviews.</i>		

2.1.1.7 Povidone-iodine versus hydrocolloid dressing/non-adherent paraffin gauze

From the secondary literature, three RCTs (Smith 1992; Casoni 2002; Fumal 2002) and one CCT (Pierard-Franchimont 1997) were identified that compared povidone-iodine to hydrocolloid dressings in the treatment of venous ulcers. One of the RCTs also compared povidone-iodine to non-adherent paraffin gauze (Casoni 2002).

The review by O'Meara 2014 included the three RCTs, rating one as having a high risk of bias, and the other two as having an unclear risk of bias¹¹. The CCT was included in an older review by O'Meara *et al* (2000)¹². This was excluded from the more recent review by O'Meara 2014 as it is not a randomised trial. This CCT is small, and limited data is available, so it has not been discussed further in this HTA.

Outcomes – wound infection and wound healing

In the three RCTs, the outcomes related to wound healing (complete healing, time to healing and ulcer area size change), and none reported on wound infection. One trial (Smith 1992) measured ulcer pain.

Overall, the results are not reliable, and do not allow conclusions to be drawn.

Table 8: Summary of systematic reviews: venous ulcers – Povidone-iodine versus hydrocolloid dressing/non-adherent paraffin gauze

Reference	Quality	Main results (of relevance to this section)
O'Meara 2014 ¹¹	++	Included three RCTs. Overall, there was no evidence from the healing data to suggest a difference between treatment groups (estimates either indicated no difference, or were not likely to be reliable).
Vermeulen 2010 ¹⁵	+	Included an RCT already included in O'Meara 2014, and does not add to the data already presented.
O'Meara 2000 ¹²	++	Included a CCT, which does not alter the overall conclusion of insufficient evidence.
<i>Primary evidence: A literature search identified no RCTs that had not already been included</i>		

<i>in the systematic reviews.</i>

2.1.1.8 Povidone-iodine versus moist or foam dressings

O'Meara 2014 included one RCT (Kuznetsov 2009; n=30) that compared a 10% povidone-iodine dressing with different dressings applied according to ulcer status (a moist wound dressing for necrotic tissue, a foam dressing for ulcers free of necrosis or a silver-impregnated dressing for ulcer infection)¹¹. The RCT was rated as having an unclear risk of bias.

All participants received short-stretch compression bandaging.

Outcome – wound infection

The number with clinically infected wounds at baseline was not stated. Information of the number of participants with microbiological isolates at 21 days was reported, but no other details were given.

Outcome – wound healing

The primary outcome of the RCT related to wound healing. At 4 weeks, 13% (2/15) participants healed in the povidone-iodine group compared with 33% of controls (5/15). An RR estimation detected no evidence of a difference between the groups: RR 0.40 (95% CI 0.09 to 1.75).

Table 9: Summary of systematic reviews: venous ulcers – Povidone-iodine versus moist or foam dressings

Reference	Quality	Main results (of relevance to this section)
O'Meara 2014 ¹¹	++	Included one RCT with an unclear risk of bias. Did not detect evidence of a difference in healing at 4 weeks in groups treated with povidone-iodine and moist or foam dressings.
<i>Primary evidence: A literature search identified no RCTs that had not already been included in the systematic reviews.</i>		

2.1.1.9 Oxyzyme® and Iodozyme® versus standard care

A manufacturer (Crawford Healthcare Ltd.) submitted an unpublished RCT (which had been accepted for publication in Wounds Medicine at the time of writing this HTA)²⁰. This included 100 participants with venous or mixed arterio-venous ulcers randomised to treatment with Oxyzyme/iodozyme® or standard care. Standard care was defined as 'continuation with current treatment regimen including compression therapy based on formulary recommendations for the service'.

Oxyzyme®/iodozyme® contains lower levels of iodine compared to other iodine-based properties. Oxyzyme® is for use in uninfected wounds, and iodozyme® for infected wounds. The two dressings differ only in the amount of iodine they contain.

The authors described this as a 'preliminary study' with a sample size set at 100 patients (a formal sample size calculation was not done).

Patients were evaluated weekly up to 12 weeks, with a further follow-up at 24 weeks. Patients in both groups were treated with high compression therapy.

The primary outcome was time to complete healing, and no evidence of a difference was reported between the groups (HR 1.13; 95% CI 0.64 to 2.02; p=0.67). There was also no

evidence of a difference reported between the groups for health-related quality of life and pain. Overall there were 26 adverse events recorded in 18 patients. Of these 8 events were recorded in patients in the control group compared with 18 in the active group. The majority of adverse events were related to pain. Of these, only three were considered to be related with the dressing in the intervention arm, compared to none in the standard treatment arm.

The study included an analysis of cost-effectiveness, which favoured Oxyzyme®/iodozyme®. This has been detailed more in the cost-effectiveness chapter.

Given the preliminary nature of this study, the authors stated that more research is needed before firm conclusions can be made.

2.1.1.10 Update searches

An update search run in January 2015 did not highlight any systematic reviews or RCTs that add to the results presented.

2.1.2 Venous ulcers: honey

Four systematic reviews were identified that included evidence on the use of topical honey, or honey-impregnated dressings, in venous leg ulcers^{1,2,7,11}. Three of the reviews were rated as high quality^{1,7,11}, and one as acceptable quality². In addition, two high quality guidelines that were based on a systematic review were identified^{18,19}. A literature search did not identify any RCTs that had not already been included in the systematic reviews.

All outcomes

For honey-based preparations in people with venous ulcers, O'Meara 2014 identified two RCTs, encompassing 476 participants¹¹. These have been summarised as follows:

- *Gethin (2009)*: This RCT (n=108) compared manuka honey topical application with hydrogel, and was rated as having a high risk of bias. It excluded patients with clinically infected ulcers at baseline, but reported that some wounds were colonised with various micro-organisms. It included people whose ulcers were 50% or more covered in slough. Compression was used as a concurrent therapy. The main outcome of the trial was percentage reduction in slough, for which no evidence of a difference was detected at 4 weeks. The percentage change in wound size at 12 weeks was greater in the honey group (13% versus 34%; p<0.001). The number of ulcers healed at 12 weeks was also greater in the honey group (33.3% versus 44.4%). A p-value was not given, but it was stated that the difference was not statistically significant. The trial authors reported that no adverse events were considered to be attributable to either of the treatments¹¹.
- *Jull (2008)*: This RCT (n=368), conducted in New Zealand, was rated as good quality (a low risk of bias). It compared a honey-impregnated calcium alginate dressing with usual care (dressings applied according to clinician choice – included silver and iodine). Compression was used as a concurrent therapy. Baseline ulcer infection status was not reported in the RCT. No evidence of a difference was reported for three primary outcomes:
 - Ulcers completely healed at 12 weeks (50% for usual care and 56% for honey);

- Mean time to healing in days (65.3 for usual care and 63.5 for honey; $p=0.553$);
- Mean percentage change in ulcer area at 12 weeks (-65.5% for usual care and -74.1% for honey; $p=0.186$).

O’Meara 2014¹¹ pooled the results from these two RCTs for complete healing at 12 weeks, which suggested no evidence of a difference between the groups (53% of participants were healed on honey, compared to 46% on the alternative regimens; RR 1.15 95% CI 0.96 to 1.38).

O’Meara 2014 also reported that:

- the data from Gethin 2009 indicate no evidence of a difference between the groups for the proportions of participants with MRSA eradication at 4 weeks: RR 4.2 (95% CI 0.67 to 26.30);
- the data from Jull 2008 indicate that more adverse events were detected in the group receiving the honey dressing: RR 1.28 (95% CI 1.05 to 1.56). The most frequently reported local adverse event was pain. More people reported pain in the group treated with honey compared to standard care, and the between group difference was statistically significant ($p=0.001$). Other local adverse events, reported by the trial authors as not statistically significant in incidence between the groups, included bleeding, dermatitis, erythema, oedema, increased exudates, deterioration of the ulcer or peri-ulcer skin and new ulceration.

The O’Meara 2014 review concluded that the current evidence base does not support the routine use of honey-based preparations in venous leg ulcers. This is a reasonable conclusion based on the evidence and analyses presented. Both RCTs were included in another Cochrane review, and the same conclusion was drawn for honey dressings in venous ulcers⁷.

The AHRQ review¹ included the RCT by Gethin 2009, but excluded the RCT by Jull 2008 as it included mixed venous and arterial ulcers (AHRQ only included studies on chronic venous ulcers). The Bardy review² highlighted some non-randomised comparative and observational trials, but these are of insufficient quality to change the conclusions of the other systematic reviews.

Based on the same evidence presented in this HTA, the two guidelines made similar recommendations:

- ‘Honey dressings are not recommended in the routine treatment of patients with venous leg ulcers’ (SIGN 2010)¹⁹.
- ‘Honey offers no benefits over standard care in promoting healing in VLU’s’ (Australian/New Zealand guidelines 2011)¹⁸.

Table 10: Summary of evidence: venous ulcers and honey

Reference	Quality	Main results (of relevance to this section)
O’Meara 2014 ¹¹	++	Included two RCTs. One compared honey-based topical application with hydrogel (Gethin: high risk of bias), and the other compared a honey-impregnated dressing with non-honey

		dressings (Jull: low risk of bias). The results from these studies were pooled, and suggested no evidence of a difference between the groups for complete healing at 12 weeks and incidence of infection during the trial period.
AHRQ 2014 ¹	++	Included the RCT by Gethin 2009, and does not add to the data already presented.
Jull 2013 ⁷	++	Included the RCTs by Gethin 2009 and Jull 2008; and does not add to the data already presented.
Australian/New Zealand guidelines 2011 ¹⁸	++	Included the systematic review by Jull 2013, already identified for this HTA.
SIGN 2010 ¹⁹	++	Included the systematic review by Jull 2013, already identified for this HTA.
Bardy 2008 ²	+	Included two single-armed descriptive studies, and one non-randomised comparative study. Does not alter the conclusions of O'Meara 2014.
<i>Primary evidence: A literature search identified no RCTs that had not already been included in the systematic reviews.</i>		

2.1.2.1 Update searches

An update search run in January 2015 did not highlight any systematic reviews or RCTs that add to the results presented.

2.1.3 Venous ulcers: silver

The O'Meara 2014¹¹ review included 12 RCTs (13 comparisons) recruiting 1514 participants evaluating the effects of silver-based preparations in venous ulcers (Blair 1988; Wunderlich 1991; Bishop 1992; Fumal 2002; Chaloner 2004; Jorgensen 2005; Meaume 2005; Munter 2006; Lazareth 2008; Dimakakos 2009; Michaels 2009; Kerihuel 2010).

A further 11 systematic reviews were identified that included studies on the use of silver-based preparations in venous ulcers^{1, 3-6, 8-10, 12-14}. Two high quality guidelines were also identified, neither of which recommend the routine use of silver dressings in the treatment of patients with venous leg ulcers^{18, 19}. The guidelines included the same evidence base as described below, and so have not been considered further in this section.

2.1.3.1 Silver sulphadiazine cream versus non-antimicrobial dressings and topical applications

Seven systematic reviews were identified that included studies that compared silver sulphadiazine cream to non-antimicrobial dressings and topical applications^{3, 4, 6, 9, 11-13}. Three of these were rated as high quality^{3, 11, 12}, with the rest being graded as acceptable quality^{4, 6, 9, 13}. Together, these reviews included three RCTs of relevance (Fumal 2002, Bishop 1992, Blair 1988).

Outcome – wound healing

The three RCTs were all rated as having an unclear risk of bias by O’Meara 2014¹¹. One was conducted in the USA (Bishop 1992), one in the UK (Blair 1988), and one in Belgium (Fumal 2002). In all of the RCTs, the primary outcomes related to wound healing, and none reported evidence of a difference between silver sulphadiazine cream and non-antimicrobial dressings or topical applications:

- Fumal 2002: This RCT (17 participants, 34 ulcers), compared usual treatment (hydrocolloid dressing and compression) to 1% silver sulphadiazine cream underneath usual treatment. Treatment was for 6 weeks. Median time to healing (derived from Kaplan-Meier survival analysis) was 15 weeks (range seven to 23) for the silver group, and 16 weeks (range nine to 22) for the usual care group (difference not statistically significant, but p-value not reported).
- Bishop 1992: This three armed RCT (n=93) compared: 1% silver sulphadiazine cream; 0.4% tripeptide copper complex cream; and a placebo cream. All participants received a non-adherent dressing and compression. The respective numbers of participants healed per group at 4 weeks were: 6/31 (19%); 0/32 (0%); and 1/30 (3%). O’Meara 2014 reported that no evidence of a difference was detected between the groups for the comparison of silver versus placebo (RR 5.81; 95% CI 0.74 to 45.40) and silver versus tripeptide copper complex cream (RR 13.41; 95% CI 0.79 to 228.32).
- Blair 1988: This RCT (n=60) compared 1% silver sulphadiazine cream to a non-adherent dressing (all participants received four-layer compression bandaging). At 12 weeks, 19/30 (63%) of ulcers treated with silver were healed, compared to 24/30 (80%) treated with non-adherent dressings. An RR calculated by O’Meara 2014 did not suggest evidence of a difference between the groups (RR 0.79; 95% CI 0.57 to 1.10).

Outcome – wound infection

Two studies excluded patients with clinically infected wounds at baseline. In Blair 1988, baseline ulcer infection status was not explained but all ulcers were contaminated at baseline, with *Staphylococcus aureus* being the most common isolate. The trial authors stated that bacterial contamination continued throughout the trial in both groups, with only three ulcers having no bacterial growth at any stage. No other data relating to wound infection was reported in the studies.

Outcome – adverse effects

In Blair 1988, four participants in the silver group withdrew from treatment because of erythema and pruritis. Two participants in the silver group developed cellulitis compared to one treated with non-adherent dressings (unclear if they withdrew from treatment).

In Bishop 1992, the trial authors reported no statistically significant between-group differences for burning, itching, pain or oedema observed (numbers of participants and p values not provided).

Table 11: Summary evidence: venous ulcers – Silver sulphadiazine cream versus non-antimicrobial dressings and topical applications

Reference	Quality	Main results (of relevance to this section)
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O'Meara 2014 ¹¹	++	Included three RCTs, all with an unclear risk of bias. In all, the primary outcomes related to wound healing, and none reported evidence of a difference between silver sulphadiazine cream and non-antimicrobial dressings or topical applications. One trial reported that bacterial contamination continued throughout treatment with 1% silver sulphadiazine cream or non-adherent dressings.
Miller 2012 ⁹	+	Included one RCT, already described in O'Meara 2014. Does not add to the data already presented.
VA Health Care 2012 ¹³	+	Included all three RCTs, already described in O'Meara 2014. Does not add to the data already presented.
Carter 2010 ⁴	+	Included all three RCTs, already described in O'Meara 2014. Does not add to the data already presented.
Chambers 2007 ⁶	+	Included all three RCTs, already described in O'Meara 2014. Does not add to the data already presented.
O'Meara 2000 ¹²	++	Included two RCTs, already described in O'Meara 2014. Does not add to the data already presented.
Bradley 1999 ³	++	Included one RCT, already described in O'Meara 2014. Does not add to the data already presented.
<i>Primary evidence: A literature search identified no RCTs that had not already been included in the systematic reviews.</i>		

2.1.3.2 Silver-impregnated dressings compared with alternative silver-impregnated dressings

All outcomes

The O'Meara 2014¹¹ review included one RCT (Chaloner 2004), with an unclear risk of bias, which compared two different silver-impregnated dressings: a silver-impregnated polyurethane foam dressing (Avance); and a five-layer silver-impregnated dressing comprising absorbent and polyethylene net layers (Acticoat 7). All patients received compression therapy, and all patients had ulcers that were colonised with bacteria at baseline (though it was not stated if they were clinically infected). At 12 weeks, 35% (7/20) in the Avance group healed compared with 50% (10/20) in the Acticoat 7 group. O'Meara 2014 reported a RR, which did not suggest evidence of a between group difference (RR 1.43; 95% CI 0.68 to 3.00).

The RCT also reported on some secondary outcomes, although did not give much detail. They reported a greater reduction in the total number of bacteria in the Acticoat 7 group compared with Avance, but that the difference was not significant (no data or p-values). They also reported that more pathogenic bacterial groups were eliminated in the Acticoat 7 group, but again did not provide p-values.

The RCT was also included in another review⁶, but this did not add to the data already presented.

One additional RCT (from Europe; Harding 2011) was included in two other reviews^{1, 13}. It was not identified by the search conducted for the O'Meara 2014 review. It included 281 people with chronic venous ulcers. It was assessed as 'good quality' overall in one review¹³. However, the other review highlighted that the RCT was not blinded¹. It excluded patients with clinically infected ulcers, and all participants received compression therapy.

It randomised 145 participants to 4 weeks of treatment with Aquacel® Ag (an ionic silver dressing) followed by Aquacel® for another 4 weeks; and 136 participants to Urgotul® Silver (a lipidocolloid silver dressing) for 4 weeks then Urgotul® for another 4 weeks. The study did not include any outcomes related to the treatment of wound infection, as clinically infected ulcers were excluded.

The authors reported no statistically significant difference between the groups for: wound healing rate at 4 weeks (Aquacel® Ag 38.24%, SD 40.63 versus Urgotul® Silver 32.47%, SD 48.93); percentage of ulcers healed at 8 weeks (Aquacel® Ag 17% versus Urgotul® Silver 15%; $p=0.09$); withdrawals due to adverse events (Aquacel® Ag 6% versus Urgotul® Silver 9%; no p -value); and all cause mortality (Aquacel® Ag 0% versus Urgotul® Silver 1.4%; no p -value). Evidence of a difference, in favour of Aquacel® Ag, was reported for the composite outcome of healed or markedly improved ulcers (67% versus 52%; $p=0.01$).

Table 12: Summary of evidence: venous ulcers – Silver-impregnated dressings compared with alternative silver-impregnated dressings

Reference	Quality	Main results (of relevance to this section)
O'Meara 2014 ¹¹	++	Included one RCT (Chaloner 2004), with an unclear risk of bias. Compared a silver-impregnated polyurethane foam dressing (Avance); and a five-layer silver-impregnated dressing comprising absorbent and polyethylene net layers (Acticoat 7). Detected no evidence of a difference in the numbers of ulcers healed at 12 weeks. Trial authors also reported a greater reduction in bacteria in the Acticoat 7 group, but did not give sufficient detail.
AHRQ 2014 ¹	++	Included a non-inferiority RCT (Harding 2011), which was not blinded. Compared an ionic silver dressing to a lipidocolloid silver dressing. Reported no evidence of a difference for: percentage of ulcers healed at 8 weeks; withdrawals due to adverse events; and all cause mortality. A statistically significant difference, in favour of the ionic silver dressing, was reported for the composite outcome of healed or markedly improved ulcers. Excluded Chaloner 2004, reason noted as 'other'.
VA Health Care 2012 ¹³	+	Included Harding 2011. Excluded Chaloner 2004, as review excluded studies not published in a peer reviewed journal. Does not add to data already presented.
Chambers 2007 ⁶	+	Included Chaloner 2004. Does not add to data already presented.
<i>Primary evidence: A literature search identified no RCTs that had not already been included in the systematic reviews.</i>		

2.1.3.3 Silver impregnated dressings versus non-antimicrobial dressings

O'Meara 2014¹¹ included eight RCTs that compared silver-impregnated dressings with non-antimicrobial dressings. Two of these were rated as having a low risk of bias overall (Michaels 2009; Kerihuel 2010); one as having a high risk (Jorgensen 2005); and the remaining five were unclear (Wunderlich 1991; Meaume 2005; Munter 2006; Lazareth 2008; Dimakakos 2009).

Outcome – wound infection

Of the two RCTs with a low risk of bias, one excluded patients with infected ulcers at baseline (Kerihuel 2010), and the other excluded patients taking antibiotics (Michaels 2009). Neither reported on outcomes relating to the treatment of wound infection. Of the remaining RCTs: one did not mention baseline ulcer infection status (Wunderlich 1991); three included patients with critically colonised (but not clinically infected) ulcers (Jorgensen 2005; Meaume 2005; Lazareth 2008); one included patients with critically colonised and clinically infected ulcers (Munter 2006); and one included only those with infected ulcers (Dimakakos 2009).

In all eight RCTs, the primary outcomes related to wound healing (such as complete healing and wound healing rate). There was very little data reported relating to change in bacterial colonisation or the treatment of wound infection. One RCT (including participants with critically colonised but not clinically infected ulcers) reported that 39% of those receiving the silver dressing and 17% in the non-antimicrobial dressing group had no remaining signs of bacterial colonisation at 4 weeks (trial authors give no further data or p-values) (Lazareth 2008). A second RCT (which did not describe baseline ulcer infection status) reported a non-significant reduction in colonisation over the whole study period for the silver dressings group, and a reduction starting only at week 2 in the group allocated other topical agents according to the stage of wound healing (Wunderlich 1991).

Outcome – wound healing and adverse effects

The remaining results, as presented by O'Meara 2014 are summarised below:

- Four RCTs provided data on complete healing at 4 to 12 weeks (Wunderlich 1991; Jorgensen 2005; Dimakakos 2009; Michaels 2009). Three RCTs stated that they provided compression to all participants as a concurrent treatment, and one did not mention compression. Data from all four RCTs was pooled, indicating that 90/213 (42%) participants healed on silver and 76/211 (36%) healed on non-antimicrobial dressings (RR 1.17; 95% CI 0.95 to 1.45). This difference is not statistically significant.
- Michaels 2009 also reported on additional healing related outcomes (complete healing at 6 and 12 months, time to healing and ulcer recurrence). No evidence of a difference was detected between the groups.
 - Complete healing at 6 months: RR 1.10; 95% CI 0.96 to 1.28
 - Complete healing at 12 months: RR 1.05; 95% CI 0.94 to 1.16
 - Median time to healing estimates were 67 days for silver dressings and 58 days for non-antimicrobial dressings (p=0.408 reported by Michaels 2009)
 - Ulcer recurrence within the first year: RR 0.80; 95% CI 0.38 to 1.70
- The other four RCTs provided outcome data on change in wound surface area. In all these RCTs, the trial authors stated that all participants received concurrent compression therapy. Two RCTs (Meaume 2005; Lazareth 2008) were pooled for absolute change in ulcer surface area at 4 weeks, indicating a between group difference in favour of silver (difference in means -4.7cm^2 ; 95% CI -8.46 to -0.94). The data for percentage change in ulcer area was not suitable for meta-analyses: one trial suggested there was evidence of a difference in favour of silver (Lazareth 2008), the other did not detect a statistically significant difference between groups (Meaume 2005). The same two RCTs were pooled for the outcome of healing rate, but no evidence of a difference was detected between the groups (pooled difference

in means -0.12cm^2 per day; 95% CI -0.28 to 0.03). The other two RCTs provided only limited data.

- Six RCTs reported on adverse events (Jorgensen 2005; Münter 2006; Lazareth 2008; Dimakakos 2009; Michaels 2009; Kerihuel 2010). Pooled data from four RCTs did not suggest any evidence of a difference in the number of adverse events between the groups (RR 0.69; 95% CI 0.36 to 1.33). The most commonly reported adverse event in both groups was maceration and other indications of worsening of the peri-ulcer area.
- Three RCTs reported change in health-related quality of life (Jorgensen 2005; Münter 2006; Michaels 2009). Michaels 2009 reported that they found no evidence of between-group differences at 1, 3, 6 and twelve months (using EQ-5D and SF-6D). The other two RCTs also reported that they detected no difference between the two groups using EQ-5D (but the data presented was more limited).

Some other systematic reviews reported on the studies included in the O'Meara 2014 review, but did not add anything to the data already presented^{1, 3-6, 8, 10, 12-14, 16}.

A further RCT (Romanelli 2005) was identified from one of the systematic reviews, Lo 2009⁸. Lo 2009 included a non-blinded RCT (n=109), which compared a foam dressing to a silver-impregnated foam dressing in people with critically colonised (but not clinically infected) chronic venous or mixed arterial/venous ulcers. This trial was not eligible for inclusion in the O'Meara 2014 review as the primary outcome did not relate to wound healing, but was on health-related quality of life (measured using odour, leakage, comfort during wear and pain). Lo 2009 stated that the RCT did not include a sample size estimation and that the analysis was not intention-to-treat. Lo 2009 reported that the results of the study favour treatment with silver. However, the detail presented was insufficient, and so no conclusions can be drawn from this. The quality issues highlighted by Lo 2009 meant that the RCT is unlikely to contribute to the body of evidence. Therefore, the fulltext was not obtained for further analysis for this HTA.

Table 13: Summary of evidence: venous ulcers – Silver impregnated dressings versus non-antimicrobial dressings

Reference	Quality	Main results (of relevance to this section)
O'Meara 2014 ¹¹	++	Included eight RCTs. In all, the primary outcomes related to wound healing. No between-group differences were detected for most wound healing outcomes. Some short-term surrogate measures of healing suggested benefit of silver dressings compared with non-AWDs, whilst others did not detect any differences. No between-group differences were detected for adverse effects and health-related quality of life.
AHRQ 2014 ¹	++	Included the RCT by Michaels (2009), which was already included in O'Meara (2014). Excluded the other RCTs in O'Meara (2014). However, overall conclusions of both reviews are the same.
VA Health Care 2012 ¹³	+	Included three RCTs already identified by the O'Meara (2014) review (Jorgensen 2005, Dimakakos 2009, Michaels 2009). Does not add to data already presented.
Moore 2011 ¹⁰	+	Included one RCT already identified by the O'Meara (2014) (Jogensen 2005). Does not add to data already presented.
Carter 2010 ⁴	+	Included five RCTs already identified by the O'Meara (2014) review (Wunderlich 1991, Jorgensen 2005, Meaume 2005, Münter 2006,

		Lazareth 2008). Does not add to data already presented.
Storm-Versloot 2010 ¹⁶	++	Included one RCT (Wunderlich 1991). Does not add to the data already presented.
Lo 2009 ⁸	+	Included three RCTs (Jorgensen 2005, Meaume 2005, Münter 2006) already identified by O'Meara (2014), and a further RCT (Romanelli 2005) that was not eligible for inclusion in O'Meara (2014).
Chaby 2007 ⁵	+	Included two RCTs already identified by O'Meara (2014) (Jorgensen 2005, Meaume 2005). Does not add to data already presented.
Chambers 2007 ⁶	+	Included four RCTs already identified by O'Meara (2014) (Wunderlich 1991, Jorgensen 2005, Meaume 2005, Münter 2006). Does not add to data already presented.
Vermeulen 2007 ¹⁴	++	Included three RCTs already identified by O'Meara (2014) (Jorgensen 2005, Meaume 2005, Münter 2006). Does not add to data already presented.
O'Meara 2000 ¹²	++	Included one RCT already identified by the more recent O'Meara review (Wunderlich 1991). Does not add to data already presented.
Bradley 1999 ³	++	Included one RCT already identified by the more O'Meara (2014) review (Wunderlich 1991). Does not add to data already presented.
<i>Primary evidence: A literature search identified no RCTs that had not already been included in the systematic reviews.</i>		

2.1.3.4 Cadexomer iodine versus silver impregnated dressings

Refer to section 2.1.1.4

2.1.3.5 Silver oxide ointment versus standard wound care

An RCT, conducted in Italy, was identified by one of the reviews (Belcaro 2010)¹³. It included people with both diabetic and venous ulcers (the data for 82 people with venous ulcers has been presented here). It compared standard care to treatment with silver oxide ointment twice daily. The trial was rated by the authors of the review as 'fair quality'; this seems generous as they also stated that the allocation concealment method and evidence of blinding was unclear.

Outcome – wound healing

The percentage of venous ulcers healed at 4 weeks was higher in the group treated with silver ointment than the group receiving standard care, and this difference was statistically significant (42% versus 22%; RR 2.05; 95% CI 1.02 to 4.14; p<0.05).

Table 14: Summary of evidence: venous ulcers – silver oxide ointment versus standard wound care

Reference	Quality	Main results (of relevance to this section)
VA Health Care 2012 ¹³	+	Included one RCT (Belcaro 2010) which compared silver oxide ointment with standard wound care. Reported a statistically significant difference in number of venous ulcers healed at 4 weeks, in favour of silver oxide.
<i>Primary evidence: A literature search identified no RCTs that had not already been included in the systematic reviews.</i>		

2.1.3.6 Membranous dressing with silver ions versus hydrocolloid dressing Unna's boot

The literature search for this HTA identified one further RCT (Kucharzewski 2013)¹⁷, published too late to be included in the systematic reviews. This RCT has a high risk of bias: the randomisation method and how allocation was concealed is not clearly described, it is not clear whether a sample size calculation was conducted, and it is not stated whether the outcome assessors were blinded to the treatment received.

The study consisted of 58 people with chronic venous ulceration, who had previously been treated with no positive result for at least 2 years in regional dermatological and surgical ambulatory care clinics. The authors stated that no treatment of superficial reflux had been done before application of the dressings. Participants were randomised to receive treatment with a membranous dressing with silver ions (Textus Bioactiv® by Biocell GmbH Germany), or with a hydrocolloid dressing Unna's boot. Dressings were changed every 7 days. All participants received compression therapy, but the silver group received elastic compression therapy and the hydrocolloid group non-elastic compression. The authors reported that all ulcers healed after seven weeks in the group treated with Textus Bioactiv® dressings; and in the group treated with the hydrocolloid dressing Unna's boot it took 16 weeks before all ulcers healed. These results are not reliable.

2.1.3.7 Update searches

An update search run in January 2015 did not highlight any systematic reviews or RCTs that add to the results presented.

2.1.4 Venous ulcers: 'Other' AWDs

Very little was identified relating to the treatment of venous ulcers with the 'other' AWDs detailed in our inclusion criteria.

O'Meara 2014¹¹ included nine RCTs on 'other' AWDs, but only one of these was relevant to this HTA (Fumal 2002). This RCT was rated as having an unclear risk of bias, and included 17 people with two leg ulcers. Participants acted as their own control. Application of 5% chlorhexidine digluconate solution with usual care was compared to usual care alone. Usual care was defined as hydrocolloid dressing and a 'compressive bandage' (no other details given). Treatment duration was 6 weeks. Median time to healing was reported as 14 weeks (range 7 to 17 weeks) for the intervention group, and 15 weeks (range 7 to 19 weeks) for those allocated to usual care alone. No p-value was given, but the authors report that the between-group difference is not statistically significant.

A literature search for this HTA highlighted one additional RCT (Vanscheidt 2012)²¹. This study has an unclear risk of bias, with unclear randomisation and blinding, and an analysis that was not intention-to-treat. It included 126 people with infected chronic venous ulcers, treated with either octenidine dihydrochloride/phenoxyethanol (OHP) or Ringer solution. Treatment lasted over a maximum of 12 weeks. The study reported that there was no evidence of a between-group difference for median time to complete ulcer healing (92 days in OHP group compared to 87 days in Ringer solution group; p=0.952). They also reported that fewer adverse events were observed with the Ringer group (17% versus 29%; no p-value given).

Table 15: Summary of systematic reviews: venous ulcers – ‘other’ AWDs

Reference	Quality	Main results (of relevance to this section)
O’Meara 2014 ¹¹	++	Included nine RCTs on ‘other’ AWDs. Only one of these related to an AWD that is detailed in the inclusion criteria. It reported no difference between 5% chlorhexidine digluconate solution and usual care for the outcome of ‘mean time to healing’.
AHRQ 2014 ¹	++	Included no studies on ‘other’ AWDs, as detailed by our inclusion criteria.
SIGN 2010 ¹⁹	++	Reported in an earlier version of the O’Meara 2014 review.
Australian and New Zealand 2011 ¹⁸	++	Reported in an earlier version of the O’Meara 2014 review.
<i>Primary evidence: A literature search highlighted one additional RCT (Vanscheidt 2012). This included people with infected chronic venous ulcers. It reported no evidence of a between-group difference for median time to healing in groups treated with OHP or with Ringer solution.</i>		

2.1.4.1 Update searches

An update search run in January 2015 did not highlight any systematic reviews or RCTs that add to the results presented.

3.0 Arterial leg ulcers: All AWDs

One systematic review of acceptable quality searched for RCTs that evaluated the effects of silver products on arterial ulcers¹³. The review authors identified none that focused solely on arterial ulcers. They identified three ‘fair quality’ RCTs that included ulcers of mixed venous/arterial etiologies (Fumal 2002; Jorgensen 2005; Miller 2010). These three RCTs were included in section 2.0 on venous ulcers.

No other systematic reviews or RCTs were identified that focused solely on the use of AWDs in arterial ulcers.

Table 16: Arterial Ulcers: Summary of systematic reviews and meta-analyses

Reference	Quality	Main results (of relevance to this section)
VA Health Care 2012 ¹³	+	Included no RCTs that focused solely on arterial ulcers. Included three RCTs that included ulcers of mixed etiologies. These did not provide evidence that silver products improved ulcer healing in this patient group.
<i>Primary evidence: A literature search identified no RCTs that had not already been included in the systematic reviews.</i>		

3.1 Update searches

An update search run in January 2015 did not highlight any systematic reviews or RCTs that add to the results presented.

4.0 Foot ulcers in people with diabetes

4.1 Foot ulcers in people with diabetes: Iodine

Seven systematic reviews^{7, 15, 22-26} and one NICE guideline based on a systematic review²⁷ were identified that included evidence on the use of iodine products in foot ulcers in people who have diabetes. Five of these were rated as high quality^{7, 22, 24, 26, 27}, with the remaining three as acceptable quality^{15, 23, 25}.

None of the reviews were focused entirely on iodine products for foot ulcers in people with diabetes. For example, some included a variety of interventions²²⁻²⁷, and some included various different wound types^{7, 15}. The outcomes of interest also varied between the reviews. In all but one review, the authors stated that the main outcomes of interest related to wound healing^{7, 15, 22-24, 26}. Mason 1999 did not specifically state what outcomes they were focussing on, but appear to have extracted all outcomes reported in the primary studies²⁵. With regards to wound infection, Vermeulen 2010¹⁵ included bacterial load or wound infection (along with wound healing) as their primary outcomes; and Nelson 2006²⁶ also included 'bacterial profile of ulcer' as an outcome. Only the data relevant to this section of the HTA has been extracted from these reviews. For more details on the content of the reviews, please refer to the evidence tables (Appendix 4).

From the eight sources of secondary evidence identified, only three RCTs reported on the use of iodine products on foot ulcers in people who have diabetes.

Outcome – wound infection

None of the RCTs reported on outcomes relating to wound infection

Outcomes – wound healing, adverse effects and other outcomes reported by authors

Rather than summarising the results of these by outcome, the results of each RCT has been detailed separately:

- Jeffcoate 2009: This was included in two of the reviews^{22, 23}. A systematic review by Dumville (2012)²² judged this trial to be at "low risk of bias for three key domains" (randomisation sequence, allocation concealment and blinded outcome assessment). This is in agreement with the appraisal by Game (2012)²³, who stated that the RCT was of good quality.

This multi-centred RCT, conducted in the UK, included people with both type 1 and type 2 diabetes who had a foot ulcer present for at least 6 weeks (n=317). It excluded people with infection of the bone or soft tissue infection requiring systemic antibiotics, among many other exclusions. Participants were randomised to treatment with one of three dressings: a fibrous-hydrocolloid dressing, an iodine-impregnated dressing (povidone iodine), or a non-adherent dressing.

The authors reported no evidence of a difference in the number of ulcers healed at week 24 in the group treated with the iodine-impregnated dressing (48/108; 44%) compared with the group treated with the fibrous-hydrocolloid dressing (46/103;

45%). Dumville 2012 reported the RR as 1.00 (95% CI 0.74 to 1.34). The mean time to healing was 127.8 (SD 54.2) days for the iodine-impregnated dressing group, and 125.8 (SD 55.9) days for the fibrous-hydrocolloid dressing group. There was no difference in quality of life or in recurrence rates, and both groups had similar numbers of serious and non-serious adverse events.

- Shukrimi 2008: This was included in two of the reviews^{7, 23}. This study is described more in the next section (foot ulcers in people who have diabetes: honey). In summary, it is a lower quality trial which was conducted in Malaysia. It included 30 people with Wagner grade II diabetic foot ulcers. It reported that the mean time to surgical closure was not statistically different in groups treated with either honey daily or povidone-iodine soaked gauze.
- Apelqvist 1996: This RCT was included in five of the reviews^{15, 24-27}. It is of lower quality, with reporting of withdrawals and allocation concealment lacking²⁴⁻²⁶. However, the outcomes were assessed by two independent physicians blinded to the treatment received by the participants.

It was an open RCT, conducted in Sweden (n=41). It included people with Wagner grade 1 or 2 diabetic foot ulcers, and outcomes were assessed over a 12-week period. It compared topically applied cadexomer iodine and standard care to a standard topical treatment (which included gentamicin solution, streptodornase/streptokinase, or dry saline gauze). Oral antibiotics were used in participants if there were signs of clinical infection and special footwear was offered.

In this RCT, there was no evidence of a difference in the number of participants who required surgical intervention in the standard treatment group (5/18; 28%) and the cadexomer iodine group (3/17; 18%). A systematic review (Nelson 2006) reported a RR for surgery of 0.64 (95% CI 0.19 to 2.07)²⁶. Furthermore, there was no evidence of a difference in the number of participants whose ulcer was completely healed (11% in standard treatment group versus 29% in the cadexomer iodine group). Nelson 2006 reported a RR for complete healing of 2.65 (95% CI 0.68 to 10.89)²⁶. Finally, there was no evidence of a difference in the outcome of “wound area reduction of at least 50% or improvement in Wagner grade” between the two groups (71% in the iodine group and 72% in the standard care group; RR 0.98, 95% CI 0.64 to 1.49)²⁶.

A search for the primary evidence did not highlight any additional RCTs.

Table 17: Summary of evidence: foot ulcers in people who have diabetes and iodine

Reference	Quality	Main Results (of relevance to this section)
Jull <i>et al</i> (2013) ⁷	++	Included one lower quality RCT of relevance (n=30) (Shukrimi 2008). Included patients with Wagner grade II diabetic foot ulcers. Compared treatment with honey and gauze dressings to povidone-iodine and gauze dressings. There was no evidence of a between-group difference for the outcome of ‘mean time to surgical closure’.
Dumville <i>et al</i>	++	Included one good quality RCT of relevance (n=317) (Jeffcoate 2009). Reported no evidence of a difference in the number of ulcers healed

(2012b) ²²		in a group treated with an iodine-impregnated dressing compared with a group treated with a fibrous-hydrocolloid dressing. The mean time to healing was 127.8 days for the iodine-impregnated dressing group, and 125.8 days for the fibrous-hydrocolloid dressing group.
Game <i>et al</i> (2012) ²³	+	Included the RCTs by Jeffcoate 2009 and Shukrimi 2008. Does not add to data already presented.
Vermeulen <i>et al</i> (2010) ¹⁵	+	Included one lower quality RCT of relevance (n=41) (Apelqvist 1996). Included patients with Wagner grade 1 or 2 diabetic foot ulcers. Compared cadexomer iodine (Iodosorb [®]) dressings with standard care of gentamicin solution/streptodornase/streptokinase or dry saline dressing. Reported no evidence of a difference between the groups for surgical revision and complete ulcer healing at 12 weeks.
Hinchliffe <i>et al</i> (2008) ²⁴	++	Included the RCT by Apelqvist 1996. Does not add to data already presented.
Nelson <i>et al</i> (2006) ²⁶	++	Included the RCT by Apelqvist 1996. The detail of this RCT has largely been taken from this review.
NICE (2003) ²⁷	++	Included the RCT by Apelqvist 1996. Does not add to data already presented.
Mason (1999) ²⁵	+	Included the RCT by Apelqvist 1996. Does not add to data already presented.
<i>Primary evidence: A literature search identified no RCTs that had not already been included in the systematic reviews.</i>		

4.1.1 Update searches

An update search run in January 2015 did not highlight any systematic reviews or RCTs that add to the results presented.

4.2 Foot ulcers in people with diabetes: Honey

Two systematic reviews (Game 2012²³ and Jull 2013⁷) were identified that considered the use of honey in foot ulcers in people who have diabetes. Jull 2013, a Cochrane review, was rated as high quality, scoring well on all criteria on the SIGN methodology checklist. Game 2012 was rated as acceptable quality. For more details on the quality of the reviews, refer to Appendix 3.

Neither review was focused solely on honey and foot ulcers in people with diabetes: the review by Jull 2013 included a number of different wound types (both acute and chronic)⁷; and Game 2012 included a number of different interventions for healing foot ulcers in people with diabetes²³.

The primary outcomes of the review by Jull 2013 were 'time to complete wound healing' and 'proportion of participants with completely healed wounds'. The primary outcomes reported by Game 2012 were 'healing', 'time to healing', 'reduction in ulcer area' and 'amputation'. Neither review reported on outcomes relating to the treatment of localised wound infection.

Outcome – wound healing

Both reviews identified the same RCT on the use of honey in foot ulcers in people with diabetes (Shukrimi 2008). Jull 2013⁷ rated the RCT as having an "unclear risk of bias". Game 2012²³ also describe the study as small and of "poor design".

The RCT was carried out in Malaysia, and included 30 people with Wagner grade 2 diabetic foot ulcers. Participants were allocated to either treatment with honey and gauze dressing, or to povidone-iodine and gauze dressing, following surgical debridement and background treatment with antibiotics. The mean time to surgical closure was 14.4 days in the honey-treated group and 15.4 days in the povidone-iodine group. The difference was not statistically significant (though no p-value was reported).

The primary literature search for this HTA highlighted one additional study, reported as an RCT (Kamaratos 2014)²⁸. It included 63 participants who had neuropathic diabetic foot ulcers and were being treated in the outpatient setting. The study compared manuka honey-impregnated dressings with conventional dressings. Participants were followed up on a weekly basis for 16 weeks. The study has a high risk of bias. Participants were enrolled into the treatment groups in an alternating fashion. This is not random, and prevents allocation to treatment groups being concealed. In addition, the study is described as ‘double blinded’, but it is not clear who was blinded.

The trial authors reported that after 16 weeks, 97% (31/32) of ulcers treated with honey dressings healed, compared to 90% (28/31) of ulcers treated with conventional dressings. This difference is not statistically significant (p=0.4). Evidence of a difference, in favour of the honey group, was reported for the mean duration of healing (31 days versus 43 days; mean difference 12 days; 95% CI -10.7 to -8.7, p<0.05).

Outcome – wound infection

Kamaratos *et al* also reported that in the honey group, 78.13% of ulcers became ‘sterile’ during the first week compared to 35.5% in the conventional dressing group (p-value not reported). The authors state that manuka-impregnated honey dressings represent an effective treatment for foot ulcers in people with diabetes, but this conclusion should be treated with caution.

Table 18: Summary of evidence: foot ulcers in people who have diabetes and honey

Reference	Quality	Main Results (of relevance to this section)
Jull <i>et al</i> (2013) ⁷	++	Included one lower quality RCT of relevance (n=30) (Shukrimi 2008). Included patients with Wagner grade 2 diabetic foot ulcers. Compared treatment with honey and gauze dressings to povidone-iodine and gauze dressings. There was no evidence of a between-group difference for mean time to surgical closure.
Game <i>et al</i> (2012) ²³	+	Identified the same RCT (Shukrimi 2008), and so does not add to the data already presented.
<i>Primary literature: An additional trial was identified (Kamaratos 2014; n=63). This was reported as an RCT, but the way in which people were allocated to treatments was not random. This compared treatment with honey-impregnated dressings to conventional dressings, and reported no statistically significant difference for the number of ulcers healed; and a statistically significant difference, in favour of honey, for mean duration of healing. These results are not reliable.</i>		

4.2.1 Update searches

An update search run in January 2015 did not highlight any systematic reviews or RCTs that add to the results presented.

4.3 Foot ulcers in people with diabetes: Silver

In 2006, a Cochrane review was published on the use of silver-based wound dressings and topical agents in treating diabetic foot ulcers²⁹. The primary outcomes included 'signs and symptoms of clinical infection' and three endpoints relating to wound healing. The authors identified no studies (RCTs or controlled trials) that met the inclusion criteria.

Eight more recent systematic reviews that included evidence on the use of silver products in foot ulcers in people who have diabetes were identified^{4, 8, 10, 13, 16, 22, 23, 30}. Three of these were rated as high quality^{16, 22, 30}, with the remaining five as acceptable quality. None of these included treatment of localised wound infection as an outcome.

Together, these eight systematic reviews included only four RCTs on the use of silver products in foot ulcers in people who have diabetes. As none of the reviews included data on the treatment of localised wound infection, the fulltext of the RCTs were checked to ensure that outcomes relating to wound infection were extracted. As the comparisons were different in each study, it was not feasible to present the results by outcome. Instead, the four RCTs have been summarised separately:

All outcomes

- *Belcaro (2010)*: This RCT was identified by one of the reviews¹³. It was conducted in Italy, and included people with both diabetic and venous ulcers (the data for foot ulcers in 66 people with diabetes has been presented here). It compared standard care to treatment with silver oxide ointment twice daily. The trial was rated by the authors of the review as 'fair quality'; this seems generous as they also stated that the allocation concealment method and whether or not there was blinding was unclear.

The percentage of diabetic ulcers healed at 4 weeks was higher in the group treated with silver ointment than the group receiving standard care. This difference was statistically significant (39% versus 16%; absolute risk difference (ARD) 23%; 95% CI 2% to 43%; $p < 0.05$). It should be noted that this confidence interval is wide, being consistent with an ARD of as little as 2%, or as much as 43%. No adverse events were recorded in the study.

- *Jacobs (2008)*: This RCT was included in three of the reviews^{13, 16, 23}. It was conducted in the USA, and included people with Wagner grade 1 or 2 diabetic foot ulcers at least 3cm in diameter ($n=40$). It excluded people with clinical evidence of local infection. Silver sulfadiazine cream was used in the control group, with the intervention group being treated with oak bark extract. The study was rated by the reviews as lower quality, with randomisation and allocation method being unclear. Furthermore, while the trial is reported as blinded, the review authors stated that it was not clear who was blinded.

After 6 weeks of treatment, the wound diameter of the oak bark extract collective

group had decreased 72.5%, and the wound diameter in the silver sulfadiazine cream group had decreased 54.7%. This difference was not statistically significant ($p=0.059$). A review also reported no evidence of a between group difference in the number of healed ulcers at 6 weeks (40% versus 30% respectively; RR 0.75 [95% CI 0.32 to 1.77]; no p -value).

- *Jude (2007)*: This was included in seven of the reviews^{4, 8, 13, 16, 22, 23, 30}. It is a European multi-centred RCT ($n=134$) comparing a calcium-alginate dressing to a fibrous-hydrocolloid dressing with 1.2% ionic silver. It included people with type 1 or 2 diabetes. The Cochrane reviews^{16, 22, 30} rated it overall as having an ‘unclear risk of bias’ due to the allocation method being inadequately described, and there being no mention of blinding of the participants, personnel and outcome assessors.

At 8 weeks, there was no evidence of a difference between the groups for: the number of ulcers healed; the mean time to healing; healing velocity; per cent reduction in area; and global assessment of healing. The number of people experiencing one or more adverse event, and the mean number of dressing changes, was similar in both groups. The change in ulcer depth was better in the fibrous-hydrocolloid with silver group (0.25cm versus 0.13 cm; $p=0.042$), however, the method for assessing depth (cotton-tipped swab) was criticised as imprecise by Game 2012²³. Subgroup analyses based on the location and type of ulcer (neuropathic or neuroischemic) were non-significant. The only significant finding was a greater percentage of ulcers healed or improved (92% versus 50%; $p=0.02$) in the silver dressing group among patients taking systemic antibiotics at baseline.

The RCT also reported on wound infection, but this was not picked up in the systematic reviews as it was not one of their outcomes. In the silver group, nine participants had clinically infected ulcers at baseline, compared to 13 in the calcium-alginate group. The trial authors reported that eight of the nine infections resolved in the silver group, compared to 10 out of 13 in the calcium-alginate group ($p=0.48$)³¹.

- *Viswanathan (2011)*: This small RCT ($n=40$), conducted in India, was included in one review¹³. The control group were treated with silver sulfadiazine cream, while the treatment group were treated with a polyherbal treatment. The study was rated by the review authors as ‘fair quality’. Again, this assessment seems generous as the review authors reported that the allocation method and blinding was unclear, and that the analysis was not intention-to-treat. No evidence of a difference was reported between the groups for ‘time to healing’ and ‘ulcer recurrence’. No participants experienced adverse events.

A search of the primary literature highlighted one additional RCT (Gottrup 2013)³². This included 39 people who had foot ulcers associated with diabetes (Wagner grade 2 or 3). It compared treatment with a collagen/oxidised regenerated cellulose (ORC)/silver therapy to standard care. The study lasted 14 weeks. The randomisation method used was acceptable, and allocation concealment was ensured using sealed envelopes. However it is not clear if anyone was blinded to the treatments and the analysis was not intention to treat.

The authors hypothesised that the collagen/ORC elements of the intervention would facilitate wound healing by normalising the microenvironment and correcting biochemical imbalances in chronic wounds; and that the silver element would act as an antimicrobial. The main results were:

- More wounds in the collagen/ORC/silver group reached 50% wound closure by week 4 compared with the control group (79% [19/24] versus 43% [6/14], $p=0.035$).
- “At the end of the study, 91% of wounds treated with collagen/ORC/silver treatment group compared with 69% of wounds in the control group either healed or showed a reduction in wound size of at least 50% (no p-value given)”³².
- “At each week throughout the 14 week study, the proportion of healed wounds in the collagen/ORC/silver group was higher than that in the control group (not significant $p>0.05$). At week 14, 52% (12/23) of wounds in the collagen/ORC/silver group had healed compared with 31% (4/13) in the control group”³².
- “There were no reported adverse events in relation to the use of collagen/ORC/silver. Five adverse events were reported in the control group. There were four cases of withdrawal from the study because of infection. One adverse event was filed as the wound showed clinical signs of infection; this patient was administered antibiotic treatment and went on to complete the study”³².
- The authors also reported that the sum of matrix metalloproteinase-9 and elastase concentration was higher in nonresponders (people whose wound had not reduced by at least 50%) compared with responders (people whose wound had reduced in size by at least 50%) at baseline ($p=0.0705$; not statistically significant) and week 4 ($p=0.012$).

Table 19: Summary of systematic reviews: foot ulcers in people who have diabetes and silver

Reference	Quality	Main Results (of relevance to this section)
Dumville <i>et al</i> (2012a) ³⁰	++	Included an RCT with an ‘unclear risk of bias’ (Jude 2007). Comparing groups of people with diabetic ulcers treated with silver fibrous-hydrocolloid dressings or calcium-alginate dressings, there was no evidence of a difference in the number of ulcers healed at 8 weeks, or in time to healing.
Dumville <i>et al</i> (2012b) ²²	++	Included the RCT by Jude (2007), and does not add to the data presented.
Game <i>et al</i> (2012) ²³	+	Included the RCT by Jude (2007). Also included a low quality RCT (3/9) by Jacobs (2008), which reported no evidence of a difference in healed diabetic ulcers when treated with oak bark extract versus silver sulfadiazine cream.
VA Health Care <i>et al</i> (2012) ¹³	+	Included both RCTs by Jude and Jacobs. Included two further ‘fair quality’ RCTs (Belcaro 2010; Viswanathan 2011). Belcaro 2010 reported that the percentage of ulcers healed at 4 weeks was significantly higher in a group treated with silver ointment, compared to standard care. Viswanathan 2011 reported that there was no evidence of a difference between groups treated with silver sulfadiazine cream and a polyherbal treatment for: time to healing and ulcer recurrence.
Moore <i>et al</i> (2011) ¹⁰	+	Included a single-armed study on a sustained silver releasing dressing, Contreet foam (Rayman 2005). This does not add to the data already presented.

Storm-Versloot <i>et al</i> (2010) ¹⁶	++	Included the RCTs by Jude 2007 and Jacobs 2008. These do not add to the data already presented.
Carter <i>et al</i> (2010) ⁴	+	Included the RCT by Jude (2007). This does not add to the data already presented.
Lo <i>et al</i> (2009) ⁸	+	Included the RCT by Jude (2007). This does not add to the data already presented.
Bergin <i>et al</i> (2006) ²⁹	++	This review did not identify any CCTs or RCTs that evaluated the effects of silver-containing dressings and topical agents on infection in foot ulcers in people with diabetes.
<i>Primary literature: An additional RCT was identified (Gottrup 2013; n=39). At each week throughout the 14 week study, the proportion of healed wounds in the collagen/ORC/silver group was higher than that in the control group, but the difference was not statistically significant (p>0.05). While some benefits were noted in the intervention group, the small study size means that the results need to be treated with caution.</i>		

4.3.1 Update searches

An update search run in January 2015 did not highlight any systematic reviews or RCTs that add to the results presented.

4.4 Foot ulcers in people with diabetes – other AWDs

Six systematic reviews^{5, 12, 23-26}, and one guideline based on a systematic review²⁷ were identified that had inclusion criteria that meant that studies on ‘other’ AWDs would have been picked up. However, five of these did not identify any studies on ‘other’ AWDs that meet the inclusion criteria for this HTA.

Two reviews^{12, 26} included an unpublished RCT by Vandeputte (1996). This compared a hydrogel dressing with dry gauze dressings irrigated with chlorhexidine in 29 people with foot ulcers associated with diabetes. Additional systemic antibiotics and topical treatments/antiseptics were available to all participants as required. The trial authors reported statistically significant improvements, in favour of the hydrogel group, for healing outcomes (for more details refer to evidence table, Appendix 4). However, the review authors highlight some methodological problems with this study (eg it is not clear if the analysis was intention-to-treat, whether assessments were blinded, and whether the ulcers were comparable at baseline). Also, the fact that the participants were treated with additional topical antimicrobial treatments (most commonly povidone-iodine cream), makes the results difficult to interpret.

Table 20: Summary of systematic reviews: foot ulcers in people who have diabetes and other AWDs

Reference	Quality	Main Results (of relevance to this section)
Game <i>et al</i> (2012) ²³	+	Included no studies on ‘other’ AWDs, as detailed by our inclusion criteria.
Hinchliffe <i>et al</i> (2008) ²⁴	++	Included no studies on ‘other’ AWDs, as detailed by our inclusion criteria.
Chaby <i>et al</i> (2007) ⁵	+	Included no studies on ‘other’ AWDs, as detailed by our inclusion criteria.
Nelson <i>et</i>	++	Included one RCT which compared a hydrogel with dry gauze

<i>aI</i> (2006) ²⁶		irrigated with chlorhexidine (Vandeputte 1996). This reported more ulcer healing with hydrogel, although it is not clear if the analysis was intention-to-treat, whether assessments were blinded, or whether the results were comparable at baseline.
NICE (2003)	++	Included no studies on 'other' AWDs, as detailed by our inclusion criteria.
O'Meara 2000 ¹²	++	Included the RCT by Vandeputte (1996)
Mason (1999) ²⁵	+	Included no studies on 'other' AWDs, as detailed by our inclusion criteria.
<i>Primary evidence: A literature search identified no RCTs that had not already been included in the systematic reviews.</i>		

4.4.1 Update searches

An update search run in January 2015 did not highlight any systematic reviews or RCTs that add to the results presented.

5.0 Pressure ulcers

5.1 Pressure ulcers - Iodine

Nine systematic reviews were identified^{12, 15, 33-39}, five of which were part of clinical guidelines^{33-35, 37, 39}. All of these reviews were rated as being of high or acceptable quality, but all the primary evidence that they collectively included was of low methodological quality. In addition, most outcomes related to wound healing, and very little was reported on wound infection. A search of the primary literature highlighted no RCTs that had not already been included in the systematic reviews.

The most recent review comes from NICE guidelines on the prevention and management of pressure ulcers, published in 2014³⁷. The guideline included 36 RCTs evaluating topical agents for treating pressure ulcers, and in three the intervention of interest was an iodine product. It is not feasible to present the results by outcome, and so each RCT has been summarised separately:

All outcomes

- Kaya 2005: Included hospital patients with a spinal cord injury and at least one pressure ulcer (n=49). The results suggested no evidence of a difference between hydrogel and povidone-iodine dressings for mean rate of healing of pressure ulcers.
- Kim 1996: Included people with a grade one or two pressure ulcers, and compared treatment with povidone iodine soaked gauze to hydrocolloid dressings (n=44). This study reported that povidone-iodine solution was not as beneficial as a hydrocolloid dressing for: proportion of patients with complete healing; mean healing speed; and proportion of people with hypergranulation. However, NICE reported that none of these differences were statistically significant.
- Moberg 1983: This included hospitalised adults with a deep or superficial pressure ulcers (n=34). It compared treatment for 3 weeks with cadexomer iodine or standard treatment. The study reported that cadexomer iodine is a more effective treatment for

the outcome of ‘proportion of pressure ulcers reduced by 50%’ (50% vs. 5.6%; RR 9; 95% CI 1.26 to 64.33). No statistically significant differences were reported for the outcomes of: ‘mean cm² decrease in ulcer area after 3 weeks’; and ‘mean percentage reduction in ulcer area after 3 weeks’.

Another guideline, from Belgium (2013), reported on the same three RCTs³⁴. It also included an additional RCT (Kucan 1981), which included 45 hospitalised patients with a pressure ulcer. Participants were randomised to one of three treatments: silver sulfazidine cream (1%), povidone-iodine solution, or physiologic saline. The authors reported on the number of people who reached a bacterial count below a certain level (<10⁵ per gram) during 3 weeks of treatment. The group treated with silver sulfazidine cream scored the best (silver group 15/15; povidone-iodine group 7/11; saline group 11/14). For the difference in mean values of bacterial levels for povidone-iodine and silver sulfazidine, a p-value of p<0.01 in favour of silver sulfazidine was reported (no other details given in review). For the outcome of ‘proportion of patients clinically responding within 3 weeks’, a p-value in favour of silver sulfazidine was reported, when compared to povidone iodine (p≤0.022) (no other details given in review)³⁴.

Five of the other reviews^{15, 33, 35, 36, 38} broadly included the same body of evidence (see evidence tables, Appendix 4, for more details). The recommendations from the guidelines vary, but are all ultimately based on low quality evidence. Four additional RCTs were identified from the other reviews^{12, 36, 39} (Barrois 1992; Toba 1997, Worsley 1991, Huchon 1992), but none are of sufficient quality to draw any firm conclusions. Overall, the clinical evidence base is too weak to support or refute the use of iodine products in the treatment of localised infection in pressure ulcers.

Table 21: Summary of systematic reviews: pressure ulcers and iodine

Reference	Quality	Main Results (of relevance to this section)
NICE 2014 ³⁷	++	Included three RCTs of lower methodological quality (Kaya 2005; Kim 1996; Moberg 1983). Overall, there was no strong evidence to support or refute the use of iodine products (povidone-iodine and cadexomer iodine), compared to hydrogel, hydrocolloid dressings and standard treatment.
KCE 2013 ³⁴	+	Included four RCTs of lower methodological quality (Kaya 2005; Kim 1996; Moberg 1983; Kucan 1981), three of which were included in the NICE review. Overall, there was no strong evidence to support or refute iodine products (povidone-iodine and cadexomer iodine), compared to hydrogel, hydrocolloid dressings and standard treatment.
Pan Pacific Guideline 2012 ³³	++	Included the reviews by Vermeulen 2010 ¹⁵ and Reddy 2008 ¹⁵ .
Vermeulen <i>et al</i> 2010 ¹⁵	+	Included three RCTs (Kaya 1996, Kucan 1981, Moberg 1983), and does not add to the data already presented.
NPUAP & EPUAP 2009 ³⁵	++	Includes one RCT (Kaya 2010), and does not add to the data already presented.
Ontario Health Technology 2009 ³⁶	++	Included two RCTs (Kim 1996, Barrois 1992), one of which was included in the more recent reviews. Barrois 1992 (n=76) reported no evidence of a difference in the number of ulcers healed in groups treated with povidone iodine (9/38) or a hydrocolloid

		dressing (10/38).
Reddy <i>et al</i> 2008 ³⁸	++	Included three RCTs (Kim 1996, Kaya 2005, Moberg 1983), and does not add to the data already presented.
RCON & NICE 2005 ³⁹	++	Included three RCTs of lower methodological quality (Toba 1997; Worsley 1991; Huchon 1992), none of which were included in the more recent reviews. None are of sufficient quality to draw firm conclusions.
O'Meara <i>et al</i> 2000 ¹²	++	Included three RCTs (Toba 1997, Worsley 1991, Huchon 1992), which were already reported on in RCON & NICE guideline.
<i>Primary evidence: A literature search identified no RCTs that had not already been included in the systematic reviews.</i>		

5.1.1 Update searches

An update search run in January 2015 did not highlight any systematic reviews or RCTs that add to the results presented.

5.2 Pressure ulcers: Honey

Seven systematic reviews were identified that evaluated the use of topical honey, or honey-impregnated dressings in people with pressure ulcers^{7, 33-38}. These were all rated as being of high or acceptable quality.

From all the reviews, only two low quality RCTs of relevance were identified.

Outcome – wound infection

Neither of the RCTs reported outcomes relating to the treatment of localised wound infection.

Outcome – wound healing

The first RCT (Weheida 1991), was conducted in Egypt, and included 40 hospitalised orthopaedic patients with uninfected grade I or II pressure ulcers of at least 2cm in diameter. The authors defined a Grade I ulcer as a moist irregular partial-thickness ulcer confined to epidermis and dermis; and a Grade II ulcer as full-thickness ulcer descending into subcutaneous tissue. Participants were randomised to receive either a honey dressing or a saline soaked dressing, both applied daily for 10 days. Mean time to healing favoured the honey-treated group (8.2 days versus 9.93 days; MD -1.73; 95% CI -1.09 to -2.37). While this difference is statistically significant, the clinical significance of a mean difference of 1.73 days is questionable.

The second RCT (Günes 2007) included hospitalised patients aged 18 years or older with stage II or III pressure ulcers. It included 27 people with 50 ulcers. Honey was compared to ethoxydiaminoacridine and nitrofurazone, a treatment that is not used in clinical practice in the UK³⁷. Treatment continued until the wound healed or for a maximum of 5 weeks. The results indicated that honey was associated with a statistically significant improvement in pressure ulcer severity ($p < 0.001$); percentage reduction in ulcer size (56% versus 13%; $p < 0.001$); and proportion of ulcers healed (5/25 versus 0/25; $p < 0.001$).

For more details on both of these RCTs, please refer to the evidence tables (Appendix 4).

A search of the primary literature highlighted no further RCTs.

Table 22: Summary of systematic reviews: pressure ulcers and honey

Reference	Quality	Main Results (of relevance to this section)
NICE 2014 ³⁷	++	Included one low quality RCT (Günes 2007). Honey was compared to a treatment not used in UK clinical practice. Pressure ulcer severity improved more, and healing outcomes were better, in the group treated with honey compared with ethoxy-diamoacridine and nitrofurazone dressings..
KCE (2013) ³⁴	+	Included the RCT by Günes 2007, and does not add to the data already presented.
Jull 2013	++	Included one low quality RCT (Weheida 1991). Mean time to healing was better in a group treated with honey, compared to a group treated with saline soaked gauze. While the difference showed statistical significance, the clinical significance needs to be considered.
Pan Pacific Guideline 2012 ³³	++	Included the reviews by Jull 2013 ⁷ and Reddy 2008 ³⁸ .
NPUAP & EPUAP 2009 ³⁵	++	Included the RCT by Günes 2007, and does not add to the data already presented.
Ontario Health Technology 2009 ³⁶	++	Included the RCT by Günes 2007, and does not add to the data already presented.
Reddy <i>et al</i> 2008 ³⁸	++	Included the RCT by Günes 2007, and does not add to the data already presented.
<i>Primary evidence: A literature search identified no RCTs that had not already been included in the systematic reviews.</i>		

5.2.1 Update searches

An update search run in January 2015 did not highlight any systematic reviews or RCTs that add to the results presented.

5.3 Pressure ulcer: Silver

Eight systematic reviews were identified^{4, 5, 8, 33-37}, four of which were part of clinical guidelines^{33-35, 37}.

The most recent evidence comes from a NICE guideline, published in 2014³⁷. The guideline considered a number of dressing types and topical agents, and included four low quality RCTs that evaluated silver containing products in the treatment of pressure ulcers. In one, the outcome was the 'percentage decrease in infection score' (Trial 2010). In the remaining three RCTs the outcomes related to wound healing (Chuangsuwanich 2011; Münter 2006; Meaume 2005).

Outcome – wound infection

Trial 2010 included adults (≥ 18 years) with ulcers and one or more signs of local infection. A variety of wound types were included. The data presented here relates to 24 people who had pressure ulcers. The intervention group were treated for 2 weeks with a silver alginate matrix dressing, and the comparison group were treated for the same length of time with a silver-free alginate dressing. The RCT did not detect a difference between the groups for percentage reduction in infection score (52% in the silver alginate group versus 50% in the alginate group; no other details, including p-values, provided).

Outcome – wound healing

Meaume 2005 also compared a silver alginate dressing to a silver-free alginate dressing. It included 28 patients aged over 65 with a stage III or IV pressure ulcer (the RCT also included people with leg ulcers, but the data presented here just relates to pressure ulcers). The wounds were not infected at baseline. The RCT reported that in pressure ulcers treated with the silver alginate dressing, there was greater wound reduction after 4 weeks (31.6% versus 13.9%), and a greater reduction in wound severity score (30.7% versus 17.5%). However, no statistical analysis was presented, and so there is little that can be concluded from these results. Other outcomes were reported on (eg proportion of patients with ulcer aggravation, and proportion on patients with poor acceptability and/or tolerability), however the small numbers and lack of statistical analyses do not allow any conclusions to be drawn.

Münter 2006 included 619 patients, 43 of whom had a grade II or III pressure ulcer (the data presented here relates to these 43 patients). It compared treatment with a silver-releasing foam dressing (changed weekly or dependent on exudate) to local best practice (eg foams/alginate, hydrocolloids, silver dressings, and other AWDs). At the end of 4 weeks of treatment, the group treated with silver-releasing foam had greater reduction in ulcer area (58.5% versus 33.3%). Again, no estimate of precision was presented.

Chuangsuwanich 2011 included 40 people with a grade III or IV pressure ulcer. It compared treatment with a silver mesh dressing to silver sulfadiazine cream. The NICE guideline reported that this comparison was irrelevant, as both intervention and control contained silver (although they also compared costs, which is relevant). No statistically significant differences were reported for: mean healing rate (%) at 8 weeks; percentage reduction in PUSH score at 8 weeks; complications; adverse events; and all cause mortality.

Another guideline from Belgium (KCE 2013)³⁴ reported on the same four RCTs, and a further low quality RCT by Kucan 1981. The Kucan 1981 RCT has been reported in a previous section of this HTA (section 4.1; pressure ulcers – iodine). None of the other reviews^{4, 5, 8, 33, 35, 36} included any studies that not already been picked up by NICE 2014 and KCE 2013.

A search of the primary literature highlighted no further RCTs.

Table 23: Summary of systematic reviews: pressure ulcers and silver

Reference	Quality	Main Results (of relevance to this section)
NICE 2014 ³⁷	++	Included four low quality RCTs (Meaume 2005; Münter 2006; Trial 2010; Chuangsuwanich 2011). Overall the evidence was insufficient to recommend, or not recommend, silver sulfadiazine cream over silver dressing; silver alginate dressings over silver-free alginate dressings; or silver-releasing foam over best practice.
KCE	+	Included five low quality RCTs (Meaume 2005; Münter 2006; Trial

(2013) ³⁴		2010; Chuangsuwanich 2011; Kucan 1981), four of which were included in NICE 2014. Overall, the evidence presented is insufficient to support or refute the use of silver containing products.
Pan Pacific Guideline 2012 ³³	++	Their search was limited to systematic reviews, and they did not identify any investigating the role of topical silver preparations for treating pressure ulcers.
Carter <i>et al</i> 2010 ⁴	+	Included two RCTs (Meaume 2005; Münter 2006). These were included in NICE 2014 and KCE 2013.
NPUAP & EPUAP 2009 ³⁵	++	Included one RCT (Meaume 2005), which was included in NICE 2014 and KCE 2013.
Ontario Health Technology 2009 ³⁶	++	Included two RCTs (Meaume 2005; Münter 2006). These were included in NICE 2014 and KCE 2013.
Lo <i>et al</i> 2009 ⁸	+	Included two RCTs (Meaume 2005; Münter 2006). These were included in NICE 2014 and KCE 2013.
Chaby <i>et al</i> 2007 ⁵	+	Included one RCT (Meaume 2005), which was included in NICE 2014 and KCE 2013.
<i>Primary evidence: A literature search identified no RCTs that had not already been included in the systematic reviews.</i>		

5.3.1 Update searches

An update search run in January 2015 did not highlight any systematic reviews or RCTs that add to the results presented.

5.4 Pressure ulcers: Other AWDs

No systematic reviews were identified that focused solely on the use of ‘other’ AWDs in pressure ulcers. Seven systematic reviews (five of which were part of clinical guidelines) were identified that included, or at least searched for, studies on ‘other’ AWDs in the treatment of pressure ulcers^{12, 33-35, 37-39}. However, in most instances, the AWDs did not meet the inclusion criteria for this HTA.

One guideline from Belgium, based on a systematic review, included an RCT that compared treatment with a polyhexadine dressing to a polyhexadine swab (Wild 2012)³⁴. It included 30 people with grade II, III or IV pressure ulcers with long-term intractable MRSA. The RCT had some limitations, including no *a priori* sample size calculation and no measure of statistical difference between the groups. The percentage reduction in pain score was higher in the group treated with polyhexadine dressings (82.4% versus 52.6%); and the proportion of patients whose MRSA was eradicated was higher in the polyhexadine dressings group (15/15 versus 10/15). No robust conclusions can be drawn based on this small study.

No guidelines were able to recommend one AWD over another.

Table 24: summary of systematic reviews: pressure ulcers and ‘other’ AWDs

Reference	Quality	Main Results (of relevance to this section)
NICE	++	Included several RCTs on AWDs other than iodine, silver or

2014 ³⁷		honey. However, none met the inclusion criteria for this HTA.
KCE (2013) ³⁴	+	Included several RCTs on AWDs other than iodine, silver or honey. Only one met the inclusion criteria for this HTA (Wild 2012). The percentage reduction in pain score, and proportion of patients whose MRSA was eradicated, was better with polyhexadine dressings compared to polyhexadine swabs in people who had MRSA colonised pressure ulcers.
Pan Pacific Guideline 2012 ³³	++	Did not identify any systematic reviews investigating the role of 'other' AWDs in promoting healing of pressure ulcers.
NPUAP & EPUAP 2009 ³⁵	++	Included RCTs on AWDs other than iodine, silver or honey. However, none met the inclusion criteria for this HTA.
Reddy <i>et al</i> 2008 ³⁸	++	Included several RCTs on AWDs other than iodine, silver or honey. However, none met the inclusion criteria for this HTA.
RCON & NICE 2005 ³⁹	++	Included several RCTs on AWDs other than iodine, silver or honey. However, none met the inclusion criteria for this HTA.
O'Meara <i>et al</i> 2000 ¹²	++	Included several RCTs on AWDs other than iodine, silver or honey. However, none met the inclusion criteria for this HTA.
<i>Primary evidence: A literature search identified no RCTs that had not already been included in the systematic reviews.</i>		

5.4.1 Update searches

An update search run in January 2015 did not highlight any systematic reviews or RCTs that add to the results presented.

6.0 Dehisced surgical wounds and wounds healing by secondary intention: all AWDs

Very little evidence was identified from the systematic reviews on the use of AWDs in dehisced surgical wounds, or wounds healing by secondary intention. The evidence that was identified related to wound healing; there was nothing on the treatment of localised infection.

A Cochrane review assessed the effectiveness of dressings (AWDs and non-AWDs) and topical agents on surgical wounds healing by secondary intention⁴⁰. This included 13 small and lower-quality RCTs, of which three were of relevance to this section (Williams 1981, Guillotreau 1996, Viciano 2000). In all, the participants had an excised pilonidal sinus, and the comparators were: silastic foam cavity dressing versus gauze soaked in 0.5% aqueous solution of chlorhexidine (n=80; Williams 1981); calcium alginate rope versus povidone iodine packing soaked gauze (n=70; Guillotreau 1996); and hydrocolloid dressing versus povidone iodine soaked gauze (n=38; Viciano 2000). The conclusions based on these RCTs are as follows:

- There is no clear evidence of a difference between foam and 0.5% chlorhexidine-soaked gauze in terms of healing. Patients may experience less discomfort and require fewer nursing visits with foam.
- There is insufficient evidence of a difference in healing rates in patients treated with calcium alginate rope versus povidone-iodine soaked gauze. "Gauze may be associated with less satisfaction and more pain but more research is needed"⁴⁰.

- “There is no evidence of a difference in the effects of hydrocolloid and povidone-iodine soaked gauze on wound healing. Hydrocolloid dressings may be associated with lower pain levels, particularly in the first week, than gauze”⁴⁰.

These conclusions are likely to be reliable, as they come from a well-conducted review with a transparent methodology. For more details on the results of the individual RCTs, please refer to the evidence tables (Appendix 4).

In addition, one RCT (Jurczak 2007) was included in three systematic reviews^{4, 10, 15}. This compared a silver impregnated hydrofiber dressing to a povidone-iodine soaked gauze dressing in 67 participants with open surgical or traumatic wounds left to heal by secondary intention. It included dehisced wounds, surgically reopened wounds, and incised and draining abscesses. Dressing changes were completed as clinically indicated (at least once every seven days) and were used until complete healing or for up to 2 weeks. The review by Carter *et al*⁴ reported that there was no statistically significant between-group differences for the healing parameters at 2 weeks (complete wound healing, mean time to heal, wound size reduction, or adjusted wound depth); although there were slight advantages in the silver-treated participants. Mean time to heal in both groups was approximately 14 days. The review by Moore *et al* added the following detail: ‘Hydrofiber Ag dressing was significantly better than povidone-iodine gauze for ability to manage pain, overall comfort, wound trauma on dressing removal, exudate handling and ease of use’¹⁰; (no data of p-values were presented).

In summary, the evidence is insufficient to support or refute the use of any one AWD in people with dehisced surgical wounds, or wounds healing by secondary intention.

Table 25: summary of systematic reviews: dehisced surgical wounds and wounds healing by secondary intention and all AWDs

Reference	Quality	Main Results (of relevance to this section)
Jull <i>et al</i> 2013 ⁷	++	Did not identify any RCTs of relevance to this section of the HTA
Moore <i>et al</i> 2011	+	Included one RCT (Jurczak 2007, n=67), on patients with open surgical wounds or traumatic wounds healing by secondary intention. Reported that: ‘Hydrofiber Ag dressing was significantly better than povidone-iodine gauze for ability to manage pain, overall comfort, wound trauma on dressing removal, exudate handling and ease of use’.
Carter <i>et al</i> 2010	+	Included the RCT by Jurczak, and reported between-group differences for the healing parameters were not statistically significant between the groups at 2 weeks.
Vermeulen <i>et al</i> 2010	+	Included the RCT by Jurczak 2007, does not add to the data already presented.
Vermeulen <i>et al</i> 2004	++	Included three RCTs in people with excision of a pilonidal sinus (Williams 1981; Guillotreau 1996; Viciano 2000).
<i>Primary evidence: A literature search identified no RCTs that had not already been included in the systematic reviews.</i>		

6.1 Update searches

An update search run in January 2015 did not highlight any systematic reviews or RCTs that add to the results presented.

7.0 Guideline recommendations

The following table summarises all of the recommendations in the different guidelines identified in the systematic review search. The grade of recommendation has been given, but the grading system in each guideline is different (for example, a B-grade recommendation from SIGN is based on something different to a B-grade recommendation from the Australian and New Zealand clinical guidelines). For more information on the grading systems used, please refer to the individual guidelines.

Guideline	Wound Type	Antimicrobial type	Recommendation
SIGN 2010	Chronic venous leg ulcers	Iodine	<i>Recommendation not made</i> <i>'There is insufficient consistent evidence on which to base a recommendation for either cadexomer iodine or povidone iodine.'</i>
Australian and New Zealand Clinical Guidelines 2011	Venous leg ulcers	Iodine	B-grade recommendation Cadexomer iodine could be used to promote healing in VLUs when there is known increased microbial burden.
SIGN 2010	Chronic venous leg ulcers	Honey	B- grade recommendation: Honey dressings are not recommended in the routine treatment of patients with venous leg ulcers.
Australian and New Zealand Clinical Guidelines 2011	Venous leg ulcers	Honey	A-grade recommendation: Honey offers no benefits over standard care in promoting healing in VLUs.
SIGN 2010	Chronic venous leg ulcers	Silver	A-grade recommendation: Silver dressings are not recommended in the routine treatment of patients with venous leg ulcers.
Australian and New Zealand Clinical Guidelines 2011	Venous leg ulcers	Silver	C-grade recommendation: Silver products offer no benefit over standard care in reducing the healing time of VLUs.
SIGN 2010	Chronic venous leg ulcers	Other/All	There is insufficient evidence on which to base a recommendation for mupirocin, peroxide and topical phenytoin. Good Practice Point: Routine long term use of topical antiseptics and antimicrobials is not recommended.
Australian and New Zealand Clinical Guidelines	Venous leg ulcers	Other/All	B-grade recommendation: Topical antimicrobial agents should not be used in the standard care of VLUs with no clinical signs of infection. Consensus-based recommendation:

2011			<p>There may be a role for judicious use of topical antimicrobials when there is known or suspected increased microbial burden.</p> <p>Consensus-based recommendation: Use topical antibiotics judiciously in managing VLU as there is a concern that their use is associated with antibiotic resistance and sensitivities.</p> <p>B-grade recommendation: No specific dressing product is superior for reducing healing time in VLUs. Select dressings based on clinical assessment of the ulcer, cost, access and patient/health professional preferences.</p>
Lipsky 2012	Foot ulcers in people with diabetes	Other/All	We do not advocate using topical antimicrobials for treating most clinically uninfected wounds (strong recommendation, low-quality evidence).
NICE 2003	Foot ulcers in people with diabetes	Other/All	<p>D-grade recommendation: In the absence of strong evidence of clinical or cost effectiveness, healthcare professionals should use wound dressings that best match clinical experience, patient preference, and the site of the wound, and consider the cost of the dressings.</p> <p>D-grade recommendation: Wounds should be closely monitored and dressings changed regularly.</p>
NPUAP & EPUAP 2009	Pressure ulcers	Cadexomer Iodine	<p>Consider use of cadexomer iodine dressings in moderately to highly exudating pressure ulcers. (Strength of Evidence = C)</p> <p>Avoid use of cadexomer iodine in individuals with iodine sensitivity and in those with thyroid disease. (Strength of Evidence = C)</p> <p>Avoid use of cadexomer iodine in large-cavity ulcers that require frequent (daily) dressing changes. (Strength of Evidence = C)</p>
Pan Pacific Guideline 2012	Pressure ulcers	Cadexomer iodine	C-grade recommendation Cadexomer iodine could be used to promote healing in pressure injuries when there is a known increased microbial burden.
NPUAP & EPUAP 2009	Pressure ulcers	Honey	Consider use of dressings impregnated with medical-grade honey for the treatment of Category/Stage II and III pressure ulcers. (Strength of Evidence = C)
Pan Pacific Guideline 2012	Pressure ulcers	Honey	D-grade recommendation Consider using topical medical grade honey to promote healing in pressure injuries.
NPUAP & EPUAP 2009	Pressure ulcers	Silver	<p>Consider use of silver dressings for pressure ulcers that are infected or heavily colonized. (Strength of Evidence = B)</p> <p>Consider use of silver dressings for ulcers at high risk of infection. (Strength of Evidence = B)</p> <p>Avoid prolonged use of silver dressings; discontinue when the infection is controlled. (Strength of Evidence = C)</p> <p>Consider use of silver sulfadiazine (Silvadene[®]) in heavily contaminated or infected pressure ulcers until definitive debridement is accomplished. (Strength of Evidence = C)</p>

Pan Pacific Guideline 2012	Pressure ulcers	Silver	Consensus based recommendation Consider using topical silver to promote healing in pressure injuries.
NICE 2014	Pressure ulcers	Other/All	<p><u>Topical antimicrobials and antiseptics</u> Do not routinely use topical antiseptics or antimicrobials to treat pressure ulcers in adults.</p> <p><u>Dressings</u> Discuss with adults with a pressure ulcer and, if appropriate, their family or carers, what type of dressing should be used, taking into account:</p> <ul style="list-style-type: none"> - Pain and tolerance - Position of the ulcer - Amount of exudates - Frequency of dressing change <p>Consider using a dressing for adults that promoted a warm, moist wound healing environment to treat grade 2, 3 and 4 pressure ulcers. Do not offer gauze dressings to treat a pressure ulcer in adults.</p>
KCE 2013	Pressure ulcers	Other/All	<p>The strength of this recommendation is ‘weak’, and the level of evidence is ‘very low’. Consider improving wound healing environment by using modern dressings and topical agents (e.g. hydrocolloids, hydrogels, hydrofibres, foams, alginates, silver dressings) instead of basic dressing types (e.g. gauze, paraffin gauze and simple dressing pads).</p> <p>As clinical studies did not demonstrate the superiority of one type of modern dressing and topical agent over another, decisions about which type of modern dressing/topical agent to use should be based on:</p> <ul style="list-style-type: none"> o Ulcer assessment (condition of wound: tissue, exudate, depth, degree of infection, odor, pain, wound edges and wound environment); o General skin assessment; o Treatment objective; o Dressing characteristics; o Previous positive effect of particular dressing/topical agent; o Manufacturer’s indications for use and contraindications; o Risk of adverse events; o Patient preferences (lifestyle, abilities and comfort).
NPUAP & EPUAP 2009	Pressure ulcers	Other/All	<p>Consider the use of topical antiseptics that are properly diluted and appropriate for pressure ulcers. Antiseptics should be used for a limited time period to control the bacterial bioburden, clean the ulcer, and reduce surrounding inflammation. The professional should be knowledgeable about proper dilutions, as well as risks of toxicity and adverse reactions. (Strength of Evidence = C) See Clinical Practice Guideline for additional details.</p> <p>Consider the use of topical antiseptics for pressure ulcers that are not expected to heal and are critically colonized. (Strength of Evidence = C)</p> <p>Consider the use of topical antimicrobial silver or medical-grade honey dressings for pressure ulcers infected with multiple organisms, because these dressings offer broad</p>

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			<p>antimicrobial coverage. However, before applying a honey dressing, make sure that the individual is not allergic to honey, bee products, or bee stings. (Strength of Evidence = C)</p> <p>Limit the use of topical antibiotics on infected pressure ulcers, except in special situations. (Strength of Evidence = C)</p>
RCON & NICE 2005	Pressure ulcers	Other/All	<p>1++ level of evidence: There is insufficient evidence to indicate whether antimicrobials are effective in the treatment of pressure ulcers.</p> <p>No economic evaluations assessing antimicrobials for the treatment of pressure ulcers were found.</p> <p>The results summarised in this review are based on findings from small trials with methodological problems. Therefore, much of the required research needs replication in larger, well-designed studies using contemporary interventions for antimicrobial activity.</p>
Pan Pacific Guideline 2012	Pressure ulcers	Other/All	<p>Consensus based recommendation</p> <p>Toxic topical antiseptic agents should not be used in the standard care of pressure injuries. Antiseptic solutions with no demonstrated toxicity should be considered in the treatment of pressure injuries with clinical evidence of infection or critical colonisation.</p> <p>Consensus based recommendation</p> <p>Topical antibiotics are best avoided in the management of pressure injuries as there is a concern that their use is associated with antibiotic resistance and sensitivities.</p>

8.0 Summary of results

Venous leg ulcers: iodine

Cadexomer iodine

A good quality systematic review included 11 RCTs (12 comparisons), encompassing 962 participants, that evaluated the use of cadexomer iodine in the treatment of venous leg ulcers¹. All 11 RCTs had a high or unclear risk of bias. Comparisons were: standard care (seven RCTs); hydrocolloid dressing (one RCT); paraffin gauze dressing (one RCT); dextranomer (two RCTs); and silver-impregnated dressing (one RCT).

The evidence on the use of cadexomer-iodine in the treatment of localised wound infection in venous leg ulcers was insufficient (in terms of quality and quantity) to draw any conclusions.

The primary outcomes of the review related to wound healing (in particular, 'time to complete wound healing', 'proportion of ulcers healed during follow-up' and 'change in ulcer size'). Healing outcomes were better for cadexomer iodine when compared with standard care, however the incidence of adverse effects was greater for those receiving cadexomer iodine. The adverse events reported included itching, pain, eczema, pruritus, rashes and difficulty removing cadexomer iodine from the ulcer. Other comparisons did not detect differences in terms of healing¹.

Two guidelines reported on an earlier version of this systematic review (which included largely the same evidence base). A SIGN guideline on chronic venous leg ulcers stated that there is inconsistent evidence on which to base a recommendation for cadexomer iodine². Another guideline from Australia and New Zealand makes the following B-grade recommendation¹ for venous leg ulcers (VLUs): 'Cadexomer iodine could be used to promote healing in VLUs when there is known increased microbial burden'³.

Povidone-iodine

A good quality systematic review included six RCTs (seven comparisons), encompassing 639 participants, that evaluated the use of povidone-iodine preparations in the treatment of venous ulcers¹. All six RCTs had a high or unclear risk of bias. Comparisons were: dextranomer (one RCT); growth factor (one RCT); hydrocolloid dressing (three RCTs); paraffin gauze dressing (one RCT); and moist or foam dressings given according to ulcer status (one RCT).

Overall, the evidence reported relating to the use of povidone-iodine in the treatment of localised wound infection in venous leg ulcers was insufficient (in terms of quality and quantity) to draw any conclusions. One RCT, with a high risk of bias, reported that the average eradication time for *Staphylococcus aureus* was shorter in a group treated with dextranomer, compared to a group treated with povidone-iodine.

There was no evidence from healing data to suggest a difference between treatment groups (estimates either indicated no difference, or were not reliable)¹.

ⁱⁱ Australian and New Zealand guidelines describe B-grade recommendations as: 'good evidence — body of evidence can be trusted to guide practice in most situations'³

Based on an earlier version of this systematic review (which included largely the same evidence base), a SIGN guideline on chronic venous leg ulcers stated that there is inconsistent evidence on which to base a recommendation for povidone-iodine².

Venous leg ulcers: honey

A good quality systematic review included two RCTs, encompassing 476 participants, that evaluated the use of honey in the treatment of venous ulcers¹. Comparisons were: manuka honey topical application versus hydrogel (one RCT; high risk of bias); and honey-impregnated calcium alginate versus usual care (one RCT; low risk of bias).

Overall, the evidence reported relating to the use of honey preparations in the treatment of localised wound infection in venous leg ulcers was insufficient (in terms of quality and quantity) to draw any conclusions. The RCT evaluating manuka honey topical application excluded participants with clinically infected wounds at baseline, but reported that some wounds were colonised with MRSA. No difference was detected between groups for eradication of MRSA at 4 weeks¹.

Pooled data suggested no evidence of a difference between groups for the outcome of complete healing at 12 weeks. Furthermore, the RCT evaluating honey-impregnated calcium alginate reported no evidence of a difference between groups for time to healing and mean percentage change in ulcer area¹.

Based on the same evidence, a SIGN guideline on chronic venous leg ulcers gives a B-grade recommendationⁱⁱ: 'Honey dressings are not recommended in the routine treatment of patients with venous leg ulcers'². A guideline from Australia and New Zealand gives an A-grade recommendationⁱⁱⁱ: 'Honey offers no benefits over standard care in promoting healing in VLUs'³.

Venous leg ulcers: silver

A good quality systematic review included 12 RCTs (13 comparisons), encompassing 1,514 participants, that evaluated the use of silver in the treatment of venous ulcers¹. Two of these had a low risk of bias, nine had an unclear risk of bias, and one had a high risk of bias. Silver sulphadiazine cream was compared with: usual care (one RCT); placebo (one RCT); growth factor (one RCT); and non-adherent dressing (one RCT). Silver-impregnated dressings were compared with alternative silver dressings (one RCT) and non-antimicrobial dressings (eight RCTs).

Overall, the evidence reported relating to the use of silver preparations in the treatment of localised wound infection in venous leg ulcers was insufficient (in terms of quality and quantity) to draw any conclusions.

For other outcomes, the review reported that 'there was no difference between treatment groups for most healing outcomes; some short-term surrogate measures of healing suggested benefit of silver dressings compared with non-antimicrobial dressings, whilst

ⁱⁱ SIGN defines a B-grade recommendation as being: based on high quality case-control or cohort studies, or systematic reviews of case-control or cohort studies; or extrapolated from high quality or well conducted RCTs, or systematic reviews of RCTs.²

ⁱⁱⁱ Australian and New Zealand guidelines describe A-grade recommendations as: 'excellent evidence — body of evidence can be trusted to guide practice.'³

others suggested no between-group difference. Data on secondary outcomes suggested no difference between silver-impregnated dressings and non-antimicrobial dressings for adverse effects and changes in health-related quality of life scores¹.

Four additional RCTs were identified from other systematic reviews, and from a search of the primary literature. Comparisons were: silver-impregnated dressing versus alternative silver-impregnated dressing (one RCT); silver-impregnated foam dressing versus foam dressing (one RCT); silver oxide ointment versus standard care (one RCT); and a membranous dressing with silver ions versus hydrocolloid dressing Unna's boot (one RCT). These do not alter the evidence base.

A SIGN guideline on chronic venous ulcers gave the following A-grade recommendation^{iv}: 'Silver dressings are not recommended in the routine treatment of patients with venous leg ulcers'². Guidelines from Australia and New Zealand give a C-grade recommendation^v: 'Silver products offer no benefit over standard care in reducing the healing time of VLU's'³.

Venous leg ulcers: other AWDs

A good quality systematic review included nine RCTs on 'other AWDs' but only one was of relevance to this HTA¹. This RCT had an unclear risk of bias. It reported no statistically significant difference between 5% chlorhexidine digluconate solution and usual care for the outcome of 'mean time to healing'.

The SIGN guideline on chronic venous leg ulcers gave the following good practice point: 'Routine long term use of topical antiseptics and antimicrobials is not recommended'². Similarly, guidelines from Australia and New Zealand recommend that topical antimicrobial agents should not be used in the standard care of venous ulcers with no clinical signs of infection³. However, they also make the following consensus-based recommendation: 'There may be a role for judicious use of topical antimicrobials when there is known or suspected increased microbial burden'³.

Arterial leg ulcers: all AWDs

One systematic review searched for RCTs that evaluated the effects of silver products on arterial ulcers⁴. None were identified that focused solely on arterial ulcers. Three RCTs were identified that included ulcers of mixed venous/arterial aetiologies, but these were addressed in the venous ulcers section.

Foot ulcers in people with diabetes: iodine

Seven systematic reviews and one NICE guideline based on a systematic review were identified that included evidence on the use of iodine products in foot ulcers in people who have diabetes. Together, these highlighted three RCTs. One was rated as having a low risk of bias, and two as being of poor quality. Comparisons were: a fibrous-hydrocolloid dressing versus an iodine impregnated dressing (povidone-iodine) or a non-adherent dressing (one RCT; low risk of bias); honey daily versus povidone-iodine soaked gauze (one RCT; poor

^{iv} SIGN defines an A-grade recommendation as being based on: at least one high quality RCT, or systematic review of RCTs; or more than one well-conducted RCTs, or systematic reviews of RCTs.²

^v Australian and New Zealand guidelines describe C-grade recommendations as: 'Some evidence — body of evidence provides some support for recommendation(s) but care should be taken in its application'.³

quality); and cadexomer iodine dressings versus a standard topical treatment (one RCT; poor quality).

No evidence was reported relating to the use of iodine preparations in the treatment of localised wound infection in foot ulcers in people who have diabetes.

The primary outcomes related to wound healing. There was no statistically significant difference between the treatment groups for most healing outcomes.

Foot ulcers in people with diabetes: honey

Two systematic reviews^{5, 6} report on the same small RCT (n=30) with an unclear risk of bias. This detected no statistically significant difference in the mean time to surgical closure in groups treated with either honey and gauze dressings or povidone-iodine and gauze dressings.

A primary literature search identified another RCT, which has a high risk of bias⁷. This compared manuka-honey impregnated dressings with conventional dressings. No statistically significant difference was reported between groups for the outcome of 'ulcers healed at 16 weeks'. A statistically significant between-group difference, in favour of honey, was reported for the mean duration of healing.

The evidence of the use of honey in the treatment of localised wound infection in foot ulcers in people with diabetes was insufficient (in terms of quality and quantity) to draw any conclusions.

Foot ulcers in people with diabetes: silver

Eight systematic reviews highlighted four RCTs on the use of silver products in foot ulcers in people who have diabetes. A search of the primary literature highlighted one additional RCT of relevance. All of the RCTs had methodological short-comings. Comparisons were: standard care versus silver oxide ointment (one RCT); silver sulfadiazine cream versus oak bark extract (one RCT); calcium-alginate dressing versus a fibrous-hydrocolloid dressing with 1.2% ionic silver (one RCT); silver sulfadiazine cream versus polyherbal treatment (one RCT); and collagen/ORC/silver therapy versus standard care (one RCT).

In one RCT, eight out of nine infections resolved in a group treated with a fibrous-hydrocolloid dressing with 1.2% ionic silver, and 10 out of 13 resolved in the calcium-alginate group (p=0.48).

The primary outcomes in all the RCTs related to wound healing. In most, there was no statistically significant difference between the treatment groups for various healing outcomes. In one, the percentage of diabetic ulcers healed at 4 weeks was higher in the group treated with silver ointment than the group receiving standard care, and the difference reached statistical significance. Another RCT reported some wound-healing benefits in a group treated with collagen/ORC/silver therapy compared to standard care, but this study is small.

For healing outcomes and the treatment of localised infection, the evidence is insufficient (in terms of quality or quantity) to support or refute the use of silver-based preparations in foot ulcers in people with diabetes.

Foot ulcers in people with diabetes: other AWDs

Two reviews included a small unpublished RCT that compared a hydrogel dressing with dry gauze dressings irrigated with chlorhexidine^{8,9}. The trial authors reported statistically significant improvements, in favour of the hydrogel group, for healing outcomes and infection incidence. However, methodological concerns with this study means that the results need to be treated with caution.

Pressure ulcers: iodine

A NICE guideline on the prevention and management of pressure ulcers, from 2014, included three RCTs which evaluated the treatment of pressure ulcers with iodine preparations. All studies were of low methodological quality. Comparisons were: hydrogel versus povidone-iodine; hydrocolloid versus povidone-iodine; and cadexomer iodine versus standard treatment.

Two of the RCTs reported no statistically significant differences between the groups for wound healing outcomes. The remaining RCT reported that cadexomer iodine is a more effective treatment, compared to standard care, for the outcome of 'proportion of pressure ulcers reduced by 50%'; but also reported no statistically significant difference for 'mean cm² decrease in ulcer area after 3 weeks' and 'mean percentage reduction in ulcer area after 3 weeks'.

Some additional RCTs were identified by other systematic reviews, but overall the clinical evidence base is weak.

Two guidelines made recommendations relating to the use of cadexomer iodine in pressure ulcers. A guideline from the National Pressure Ulcer Advisory Panel & European Pressure Ulcer Advisory Panel (NPUAP & EPUAP) makes the following C-grade recommendations (they define a C-grade recommendation as one based on indirect evidence and/or expert opinion):

- 'Consider the use of cadexomer iodine dressings in moderately to highly exuding pressure ulcers'
- Avoid use of cadexomer iodine in individuals with iodine sensitivity and in those with thyroid disease'
- 'Avoid the use of cadexomer iodine in large-cavity ulcers that require frequent (daily) dressing changes'¹⁰.

Furthermore, a Pan Pacific Guideline makes the following C-grade recommendation^{vi}: 'Cadexomer iodine could be used to promote healing in pressure injuries when there is a known increased microbial burden'¹¹.

Pressure ulcers: honey

Seven systematic reviews highlighted two low quality RCTs on the use of topical honey, or honey-impregnated dressings, in people with pressure ulcers. The comparisons were: honey

^{vi} Pan Pacific guidelines define a C-grade recommendation as: 'Some evidence - body of evidence provides some support for recommendation(s) but care should be taken in its application'.¹¹

dressing versus a saline soaked dressing (one RCT); and honey versus a treatment not used in clinical practice in the UK (one RCT).

Neither RCT reported outcomes related to the treatment of localised wound infection. Both RCTs reported improvements in wound healing outcomes in the honey group (although in one the clinical significance of this improvement was questionable).

Guidelines from the NPUAP & EPUAP make the following C-grade recommendation: 'Consider the use of dressings impregnated with medical-grade honey for the treatment of Category/Stage II and III pressure ulcers'¹⁰. Pan-Pacific guidelines give a D-grade recommendation^{vii}: 'Consider using topical medical grade honey to promote healing in pressure injuries'¹¹.

Pressure ulcers: silver

Eight systematic reviews, four of which were part of clinical guidelines, were identified. Collectively, these highlighted five low-quality RCTs that evaluated silver containing products in the treatment of pressure ulcers. Comparisons were: silver alginate dressing versus silver free alginate dressing (two RCTs); silver-releasing foam versus best practice (one RCT); silver mesh versus silver sulfadiazine cream (one RCT); and silver sulfadiazine cream versus povidone iodine versus physiologic saline (one RCT).

In one trial, the outcome was the 'percentage decrease in infection score'. It did not detect evidence of a difference between groups treated with a silver alginate dressing or a silver-free alginate dressing (52% versus 50%, respectively. No p-value given).

In the remaining RCTs, the outcomes related to wound healing. These suggested some advantage of using silver dressings over non-silver dressings, however the methodological short-comings of the RCTs means that the results need to be treated with caution.

Guidelines from the NPUAP & EPUAP¹⁰ make the following recommendations^{viii}:

- "Consider use of silver dressings for pressure ulcers that are infected or heavily colonized. (Strength of Evidence = B)"
- "Consider use of silver dressings for ulcers at high risk of infection. (Strength of Evidence = B)"
- "Avoid prolonged use of silver dressings; discontinue when the infection is controlled. (Strength of Evidence = C)"
- "Consider use of silver sulfadiazine (Silvadene®) in heavily contaminated or infected pressure ulcers until definitive debridement is accomplished. (Strength of Evidence = C)"

Furthermore, Pan Pacific guidelines make the following consensus based recommendation: 'Consider using topical silver to promote healing in pressure injuries'¹¹.

Pressure ulcers: other AWDs

^{vii} Pan Pacific guidelines define a D-grade recommendation as: 'weak evidence - body of evidence is weak and recommendation must be applied with caution'¹¹.

^{viii} NPUAP & EPUAP define a B-grade recommendation as being supported by direct evidence from properly designed series; and a C-grade recommendation as being based on indirect evidence and/or expert opinion¹⁰.

No evidence that could inform decision making was identified on the use of other AWDs in the treatment of pressure ulcers.

Some guidelines make recommendations on the use of antimicrobials and antiseptics more generally. For example: NICE 2014 recommends against the routine use of topical antiseptics or antimicrobials to treat pressure ulcers in adults¹². In addition, guidelines from Belgium (2013) state: 'Consider improving wound healing environment by using modern dressings and topical agents (e.g. hydrocolloids, hydrogels, hydrofibres, foams, alginates, silver dressings) instead of basic dressing types (e.g. gauze, paraffin gauze and simple dressing pads)¹³.

Dehisced surgical wounds and wound healing by secondary intention: all AWDs

No evidence relating to the use of AWDs in the treatment of localised wound infection in dehisced surgical wounds or wounds healing by secondary intention was identified.

For outcomes relating to wound healing, a good quality Cochrane review included three RCTs on 'other' AWDs of relevance to this HTA. In all, the participants had an excised pilonidal sinus, and the comparisons were: silastic foam cavity dressing versus gauze soaked in 0.5% aqueous solution of chlorhexidine; calcium alginate rope versus povidone iodine packing soaked gauze; and hydrocolloid dressing versus povidone iodine soaked gauze. Overall, the evidence was insufficient to support or refute the use of any one AWD in people with dehisced surgical wounds, or wounds healing by secondary intention.

An additional RCT was identified. This compared a silver impregnated hydrofiber dressing to a povidone-iodine soaked gauze dressing in 67 people with open surgical wounds or traumatic wounds left to heal by secondary intention. No evidence of a difference was reported for any of the healing parameters, although slight advantages were reported in the silver-treated group.

9.0 Discussion

With regards to the treatment of localised wound infection:

- For all chronic wound types included in this review, the current evidence base is insufficient to draw conclusions on the use of AWDs to treat localised wound infection.

With regards to wound healing:

- For all chronic wound types included in this review, the current evidence base either
 - does not support the use of AWDs; or
 - is insufficient to draw conclusions on the routine use of AWDs.

On the whole, the included guidelines recommend against the use of AWDs in the routine treatment of clinically uninfected chronic wounds. When the guidelines did recommend AWDs as an option, it was almost always for wounds with known or suspected increased microbial burden. This is in accordance with BNF 68, which states that: ‘Medical grade honey has antimicrobial and anti-inflammatory properties. Dressings impregnated with iodine can be used to treat clinically infected wounds. Dressings containing silver should be used only when clinical signs or symptoms of infection are present’¹⁴.

However, evidence suggests that in clinical practice AWDs are used widely in chronic wounds, regardless of whether they are clinically infected at the outset of treatment¹. Some of the included guidelines also cautioned against the long-term use of AWDs, stating that they should only be used for a limited period of time, or until the infection has cleared. It has been argued that long-term use of some AWDs is not only unnecessary, it may actually impede wound healing¹⁵. Again, it is not clear if AWDs are used for an appropriate duration of time in clinical practice.

Wound infection as a primary outcome

Most of the studies evaluating the use of AWDs in chronic wounds have endpoints relating to wound healing (for example complete ulcer healing, time to healing or change in ulcer size). However, there is some disagreement in the literature about how appropriate this is, given that all chronic wounds are difficult to heal¹⁵. The argument given is that the primary purpose of AWDs is not to promote healing, but is to reduce wound bioburden and to treat local infection before it escalates into a systemic infection. With this in mind, the clinical experts for the HTA advised that the most appropriate primary outcomes for the literature review should relate to wound infection (namely, resolution of localised wound infection, improvement in signs and symptoms of wound infection, and reduction of bioburden). This is supported by a document published by the European Wound Management Association: ‘Wound infection is a valid primary, but most often secondary, endpoint’¹⁶.

The use of wound infection-related outcomes in this HTA was associated with significant challenges. Most importantly, they were not reported on in many studies. In the studies that did include wound infection related outcomes, they were almost always reported as secondary outcomes, with the studies normally being designed around the primary outcome of healing. There is no one exact definition of wound infection in the literature, and so we accepted all definitions used by the authors. The wound infection outcomes used in the

studies varied, and included: bacterial growth (using swabs); eradication of certain bacterial organisms; average eradication time; signs of bacterial colonisation; and resolved infection. The baseline wound infection status of the participants included in the studies varied. Some studies included people with infected wounds, some excluded them, and in many studies eligibility for inclusion based on wound infection status was not mentioned. Furthermore, some studies included people on oral/systemic antibiotics, others excluded them, and some did not mention antibiotic use.

Ulcer infection and wound healing

According to O'Meara et al, the relationship between ulcer infection and wound healing is unclear¹. They discuss two RCTs that assess the impact of wound infection or bacterial colonisation on healing: 'For bacterial colonisation, one study showed a statistically significant association between positive post-treatment wound cultures and lower healing rates (Alinovi 1986), whilst the other suggested that bacterial contamination of ulcers with *Staphylococcus aureus* did not appear to delay healing (Huovinen 1994)¹. Three of the RCTs (evaluating cadexomer iodine) included in the O'Meara analysis also assessed the association between ulcer infection and healing (Skog 1983, Moss 1987, Miller 2010). These all suggested that improved healing rates were associated with reduced bioburden with certain bacterial species; but all were small studies and so the results may not be reliable.

Quality of the research

This literature review highlighted several up-to-date and high quality systematic reviews of relevance. The conclusions of the included reviews are likely to be reliable. However, the studies included within the reviews were generally methodologically weak. Many were small, and clinical heterogeneity often prevented meta-analyses. There is no reason specific to chronic wounds or AWDs that should prevent good quality RCTs being conducted. Many of the RCTs included in the reviews were published before the CONSORT statement, which may explain why they did not meet expected standards.

Of all the studies included in the reviews, only four were judged by the review authors as having a low risk of bias (Michaels 2009; Kerihuel 2010; Jeffcoate 2009; Jull 2008). Despite being at a low risk of bias, some discussion surrounding the RCT by Michaels 2009 (otherwise known as the VULCAN trial) have been reported in the literature¹⁷. In this RCT, 213 people with venous ulcers were randomised to treatment with either a silver dressing (any one of the following: Aquacel® Ag, Acticoat™, Acticoat™ 7, Acticoat™ Absorbent, Contreet® Foam and Urgotul® SSD) or any non-antimicrobial wound dressing. The study found no difference between the groups for the number of ulcers healed at 12 weeks, overall median time to healing, or various secondary endpoints. The authors concluded that there was no evidence to support the routine use of silver-donating dressings beneath compression for venous ulceration¹⁸. This RCT was well conducted, and the conclusion is likely to be reliable.

Leaper and Drake 2011 argue that the VULCAN study did not use silver dressings as recommended¹⁷. They state that the main purpose of silver dressings (and other AWDs) is not to promote wound healing, but is to 'prevent the progression of critical colonisation, infection or recurrence of infection in those patients who have chronic wounds and are at increased risk...or to treat established localised or spreading infection in chronic wounds'¹⁷.

They also state that AWDs should be discontinued when signs of infection resolve, and prolonged use is possibly counterproductive to healing. The VULCAN study used silver dressings for a prolonged period (up to 12 weeks). It excluded people who were receiving oral or parenteral antibiotic treatment, but otherwise does not mention wound infection status.

In response to these challenges, the authors of the VULCAN study stated that the design of the trial was based on a survey of current practice of AWDs and a review of advice given in manufacturers' literature. They argue that the advice that AWDs be used on groups 'at high risk of infection' could be applied to any patient with an open wound.

The conclusion of the VULCAN study is justified and reasonable; there is no evidence to support the routine use of silver-donating dressings beneath compression for venous ulceration. However, the VULCAN study did not evaluate the short-term use of silver dressings in venous ulcers with signs of localised infection. It is possible that there are some sub-groups in whom the use of AWDs may be clinically effective, but there is a need for well conducted trials in this area.

The three other studies rated by the review authors as having a low risk of bias also had primary outcomes relating to wound healing (Jull 2008; Kerihuel 2010; Jeffcoate 2009). None of the trials reported on outcomes relating to the treatment of localised wound infection, or the reduction of bioburden.

Limitations of this review

This HTA has a very broad scope, with many interventions meeting the eligibility criteria for inclusion. In addition to the different antimicrobials, there is a variety of ways in which the antimicrobials can be delivered (for example gauze, foams, creams, hydrocolloids). We also included several types of chronic wounds, eligible comparators, and outcome measures. This has made combining the results into a succinct narrative challenging. It also meant that considering all the evidence beyond systematic reviews and RCTs was not feasible in the time available. During the protocol stage, the scope of the HTA was discussed with topic experts, and was considered during an open consultation period. Those consulted stressed that it would be helpful to produce a report that considers all these interventions and wounds types together, in the hope that it can inform on which AWD should be used in which circumstance and for how long. Unfortunately the clinical evidence reviewed does not give clear direction.

Given the scope of the review, a decision was made to focus on good quality systematic reviews and meta-analyses. A search for RCTs was done in order to update the included reviews, but other study types were not searched for (for example observational studies). This approach freed up time and resource to work on examining the patient and organisational issues in more detail. It seemed more appropriate to invest time in these other areas of the HTA, rather than searching through lower quality evidence. Other reviews in wound care have been criticised for not including lower levels of evidence; with conclusions of 'more research is required' being seen as frustrating and unhelpful to clinical practice¹⁹. However, as the HTA considers the topic beyond just clinical evidence, the decision to limit this section to review and RCT evidence was justified.

The decision to not include *in-vitro* studies was challenged when the protocol was consulted on. As stated above, it was felt that the extra effort and resource taken to look at this type of evidence would mean that less time could be spent on other parts of the HTA. While *in-vitro* studies are undoubtedly helpful in developing our understanding around chronic wounds, infection and antimicrobials, they cannot be used to support clinical-based recommendations.

Most of the published evidence relates to venous ulcers, therefore some of the other ulcer types are not as well represented in this clinical effectiveness section.

Articles were not eligible for inclusion if they were not available in English. The time and resource to translate non-English articles was not available. One HTA was identified in the literature search, and from the abstract appeared to be good quality, but the fulltext was only available in Swedish.

Appendix 1: Strategies for literature search

Secondary and grey literature

Internet searches were undertaken to identify HTAs, systematic reviews and other evidence based reports.

Clinical effectiveness

The following sources were searched in January 2014:

- Adelaide Health Technology Assessment
<http://www.adelaide.edu.au/ahta/>
- Agency for Healthcare Research and Quality (AHRQ)
<http://www.ahrq.gov/>
- AHRQ National Guideline Clearing House
<http://www.guideline.gov/>
- Aggressive Research Intelligence Facility (ARIF)
<http://www.arif.bham.ac.uk/>
- Alberta Heritage Foundation for Medical Research
<http://www.ahfmr.ab.ca/>
- American Academy of Dermatology
<http://www.aad.org/>
- American Academy of Family Physicians
<http://www.aafp.org/>
- American College of Certified Wound Specialists
<http://www.theccws.org/>
- American College of Physicians
<http://www.acponline.org/>
- American Professional Wound Care Association
<http://www.apwca.org/>
- American Society of Dermatology
<http://www.asd.org/>
- Association for the Advancement of Wound Care
<http://www.aawconline.org/>
- Australasian College of Dermatologists
<http://www.dermcoll.asn.au/>
- Australasian Wound and Tissue Repair Society
<http://www.awtrs.org/>
- Australian National Health and Medical Research Council
<http://www.nhmrc.gov.au/guidelines/index.htm>
- Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S)
<http://www.surgeons.org/racs/research-and-audit/asernip-s/asernip-s-publications>
- Australian Wound Management Association
<http://www.awma.com.au/>
- Bandolier
<http://www.jr2.ox.ac.uk/bandolier>
- Belgian Healthcare Knowledge Centre (KCE)

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- <https://kce.fgov.be/>
- [British Association of Dermatologists](http://www.bad.org.uk/)
- [British Society for Paediatric Dermatology](http://www.bspd.org/)
- [Canadian Agency for Drugs and Technologies in Health \(CADTH\)](http://www.cadth.ca/)
- [Canadian Association of Wound Care](http://www.cawc.net/)
- [Canadian Dermatology Association](http://www.dermatology.ca/)
- [Canadian Institutes of Health Research](http://www.cihr-irsc.gc.ca/e/43989.html)
- [Centers for Medicare and Medicaid Services](http://www.cms.gov/medicare-coverage-database/indexes/technology-assessments-index.aspx?TAId=85&bc=AAAQAAAAAAAA&)
- [Centre for Clinical Effectiveness \(Monash\)](http://www.southernhealth.org.au/page/Health_Professionals/CCE/Evidence_reviews/)
- [NICE Clinical Knowledge Summaries](http://www.cks.nhs.uk/home)
- [CMA Infobase](http://www.cma.ca/index.cfm/ci_id/54316/la_id/1.htm)
- [Cochrane Database of Systematic Reviews](http://onlinelibrary.wiley.com/cochranelibrary/search/advanced)
- [Database of Abstracts of Reviews of Effects \(DARE\)](http://onlinelibrary.wiley.com/cochranelibrary/search/advanced)
- [Dermatology Nurses Association](http://www.dnanurse.org/)
- [Dynamed](http://web.a.ebscohost.com/dynamed)
- [ECRI](http://www.ecri.org/)
- [eGuidelines](http://www.eguidelines.co.uk/)
- [European Pressure Ulcer Advisory Panel \(EPUAP\)](http://www.epuap.org/)
- [European Tissue Repair Society](http://www.etrso.org/)
- [European Wound Management Association \(EWMA\)](http://www.ewma.org/)
- [Euroscan](http://www.euroscan.org.uk/)
- [EVIDENT database](https://evident.has-sante.fr/has/login.xhtml)
- [EVIP Net](http://global.evipnet.org/search/evipnet/index.php)
- [Google](http://www.google.co.uk/)
- [Guidelines and Audit Implementation Network \(GAIN\)](http://www.gain-ni.org/index.php/audits/guidelines)

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- Guidelines International Network (GIN)
<http://www.g-i-n.net/>
- Health Evidence Network
<http://www.euro.who.int/hen>
- Health Information and Quality Authority (HIQA)
<http://www.hiqa.ie/>
- Health Quality Ontario
<http://www.hqontario.ca/>
- Health Services Assessment Collaboration (HSAC)
<http://www.healthsac.net/>
- Health Systems Evidence
<http://www.mcmasterhealthforum.org/healthsystemsevidence/>
- HTA database
<http://onlinelibrary.wiley.com/cochranelibrary/search/advanced>
- Institute for Clinical Evaluative Sciences (ICES)
<http://www.ices.on.ca/webpage.cfm>
- International Society of Dermatology
<http://www.intsocderm.org/>
- Japanese Society for Wound Healing
http://www.jswh.com/english2/index_e.html
- Liverpool Reviews and Implementation Group (LRIG)
<http://www.liv.ac.uk/lrig/>
- Madox Horizon Scanning Reports
<http://madox.org/horizon-scanning-reports>
- McGill University Health Center Technology Assessment Unit
<http://www.mcgill.ca/tau/>
- Medicaid Evidence Based Decisions Project (MED)
<http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/med/index.cfm>
- Medical Dermatology Society
<http://www.meddermsociety.org/>
- Medical Research Council (MRC)
<http://www.mrc.ac.uk/>
- Medical Services Advisory Committee (Australia)
<http://www.msac.gov.au/>
- National Health and Medical Research Council (NHMRC)
<http://www.nhmrc.gov.au/publications/index.htm>
- National Horizon Scanning Centre
<http://www.nhsc-healthhorizons.org.uk/>
- National Institute for Health and Clinical Excellence (NICE)
<http://www.nice.org.uk/>
- National Pressure Ulcer Advisory Panel (NPUAP)
<http://www.npuap.org/>
- New Zealand Dermatological Society
<http://www.dermnetnz.org/>
- New Zealand Guidelines Group
<http://www.nzgg.org.nz/>
- New Zealand Wound Care Society
<http://www.nzwcs.org.nz/>
- NHS Evidence

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- <https://www.evidence.nhs.uk/>
- [NIHR HTA Programme](http://www.nchta.org/)
<http://www.nchta.org/>
- [Ottawa Hospital Research Institute](http://www.ohri.ca/hta/)
<http://www.ohri.ca/hta/>
- [Peel Health Library](http://www.peelregion.ca/health/library/literature-reviews.asp)
<http://www.peelregion.ca/health/library/literature-reviews.asp>
- [Peninsula Technology Assessment Group \(PenTAG\)](http://medicine.exeter.ac.uk/pentag/)
<http://medicine.exeter.ac.uk/pentag/>
- [Primary Care Dermatology Society](http://www.pcds.org.uk/)
<http://www.pcds.org.uk/>
- [Public Health Wales](http://www.wales.nhs.uk/sitesplus/888/home)
<http://www.wales.nhs.uk/sitesplus/888/home>
- [PubMed Clinical Queries](http://www.ncbi.nlm.nih.gov/pubmed/clinical)
<http://www.ncbi.nlm.nih.gov/pubmed/clinical>
- [Royal College of Nursing Clinical Guidelines](http://www.rcn.org.uk/development/practice/clinicalguidelines)
<http://www.rcn.org.uk/development/practice/clinicalguidelines>
- [Sax Institute](http://www.saxinstitute.org.au/)
<http://www.saxinstitute.org.au/>
- [Scottish Dermatological Society](http://www.scottish-dermatology.org.uk/)
<http://www.scottish-dermatology.org.uk/>
- [Scottish Intercollegiate Guidelines Network \(SIGN\)](http://www.sign.ac.uk/)
<http://www.sign.ac.uk/>
- [Sheffield Technology Assessment Group](https://www.shf.ac.uk/scharr/sections/heds/collaborations/tag)
<https://www.shf.ac.uk/scharr/sections/heds/collaborations/tag>
- [Southampton Health Technology Assessment Centre](http://www.southampton.ac.uk/shtac)
<http://www.southampton.ac.uk/shtac>
- [Tissue Viability Online](http://www.tissueviabilityonline.com/)
<http://www.tissueviabilityonline.com/>
- [Tissue Viability Society](http://www.tvs.org.uk/)
<http://www.tvs.org.uk/>
- [TRIP Database](http://www.tripdatabase.com/)
<http://www.tripdatabase.com/>
- [UpToDate](http://www.uptodate.com/home/index.html)
<http://www.uptodate.com/home/index.html>
- [US National Institutes of Health](http://www.nih.gov/)
<http://www.nih.gov/>
- [VA Technology Assessment Program](http://www.va.gov/vatap/)
<http://www.va.gov/vatap/>
- [West Midlands Health Technology Assessment Collaboration](http://www.wmhtac.bham.ac.uk/)
<http://www.wmhtac.bham.ac.uk/>
- [World Union of Wound Healing Societies](http://www.wuwhs.org/)
<http://www.wuwhs.org/>
- [Wound Healing Society](http://www.woundheal.org/)
<http://www.woundheal.org/>
- [Wound Ostomy and Continence Nurses Society](http://www.wocn.org/)
<http://www.wocn.org/>

Manufacturer websites

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Websites of the following manufacturers of antimicrobial wound dressings were searched in January 2014:

- [Molnlycke Health Care](#)
- [Smith & Nephew](#)
- [Convatec](#)
- [Johnson & Johnson Medical](#)
- [Systagenix Wound Management Ltd](#)
- [Unomedical Ltd](#)
- [Coloplast](#)
- [Urgo Ltd](#)
- [Hartmann \(Paul\)](#)
- [3M Healthcare](#)
- [Braun Medical](#)
- [Crawford Pharm](#)
- [Derma Sciences Europe Ltd](#)
- [Activa Healthcare](#)
- BSN
- Lohmann Raucher
- Schulke
- Advancis
- Danetre
- Medihoney
- Aspen Medica
- Medlogic
- Covidien
- Archimed

Cost effectiveness

The following sources were searched for economic studies and reports in January 2014:

- [Audit Scotland](http://www.audit-scotland.gov.uk/)
- [CEA registry](https://research.tufts-nemc.org/cear4/default.aspx)
- [Centre for Health Economics](http://www.york.ac.uk/inst/che/)
- [Centre for Health Economics and Policy Analysis](http://www.chepa.org/)
- [EconLIT](http://www.econlit.org/)
- [ESHER \(University of Newcastle\)](http://www.ncl.ac.uk/nubs/research/centres/esher/)
- [Health and Social Care Information Centre](http://www.hscic.gov.uk/)

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- [Health Economic Evaluations Database \(HEED\)](http://www3.interscience.wiley.com/cgi-bin/mrwhome/114130635/HOME)
<http://www3.interscience.wiley.com/cgi-bin/mrwhome/114130635/HOME>
- [Health Economics and Decision Science \(University of Sheffield\)](http://www.shef.ac.uk/scharr/sections/heds)
<http://www.shef.ac.uk/scharr/sections/heds>
- [Health Economics Group \(University of East Anglia\)](http://www.med.uea.ac.uk/research/research_econ/welcome.htm)
http://www.med.uea.ac.uk/research/research_econ/welcome.htm
- [Health Economics Research Centre \(University of Oxford\)](http://www.herc.ox.ac.uk/)
<http://www.herc.ox.ac.uk/>
- [Health Economics Research Group \(Brunel University\)](http://www.brunel.ac.uk/about/acad/herg)
<http://www.brunel.ac.uk/about/acad/herg>
- [Health Economics.com](http://www.healtheconomics.com/)
<http://www.healtheconomics.com/>
- [Institute of Health Economics \(Canada\)](http://www.ihe.ca/)
<http://www.ihe.ca/>
- [International Health Economics Association](https://www.healtheconomics.org/)
<https://www.healtheconomics.org/>
- [London School of Economics and Political Science](http://www.lse.ac.uk/)
<http://www.lse.ac.uk/>
- [NHS Economic Evaluations Database \(NHS EED\)](http://onlinelibrary.wiley.com/cochranelibrary/search/advanced)
<http://onlinelibrary.wiley.com/cochranelibrary/search/advanced>
- [NHS Finance Manual](http://www.info.doh.gov.uk/doh/finman.nsf)
<http://www.info.doh.gov.uk/doh/finman.nsf>
- [Paediatric Economic Database Evaluation \(PEDE\) database](http://pede.ccb.sickkids.ca/pede/index.jsp)
<http://pede.ccb.sickkids.ca/pede/index.jsp>
- [Prescription Services, NHS Business Services Authority](http://www.nhsbsa.nhs.uk/PrescriptionServices/810.aspx)
<http://www.nhsbsa.nhs.uk/PrescriptionServices/810.aspx>
- [RePEc](http://repec.org/)
<http://repec.org/>
- [Southampton University Economics Department](http://www.economics.soton.ac.uk/)
<http://www.economics.soton.ac.uk/>
- [University of Melbourne Centre for Health Policy Programs and Economics](http://healthprograms.unimelb.edu.au/)
<http://healthprograms.unimelb.edu.au/>
- [University of Sydney Health Economics Research and Evaluation](http://www.chere.uts.edu.au/)
<http://www.chere.uts.edu.au/>
- [WHO-CHOICE](http://www.who.int/choice/en/)
<http://www.who.int/choice/en/>
- [York Health Economics Consortium](http://www.yhec.co.uk/)
<http://www.yhec.co.uk/>

Patient issues (including safety issues)

The following sources were searched in April 2014:

- [Australian Commission on Safety and Quality in Health Care](http://www.safetyandquality.gov.au/)
<http://www.safetyandquality.gov.au/>
- [Australian Patient Safety Foundation](http://www.apsf.net.au/)
<http://www.apsf.net.au/>
- [Better Together \(Scottish Patient Experience Programme\)](#)

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- http://www.bettertogetherscotland.com/bettertogetherscotland/CCC_FirstPage.jsp
- [Campbell Collaboration](http://www.patientsafetyinstitute.ca/English/Pages/default.aspx)
<http://www.patientsafetyinstitute.ca/English/Pages/default.aspx>
 - [Canadian Patient Safety Institute](http://www.patientsafetyinstitute.ca/English/Pages/default.aspx)
<http://www.patientsafetyinstitute.ca/English/Pages/default.aspx>
 - [Centre for Qualitative Research](http://www.bournemouth.ac.uk/cqr/)
<http://www.bournemouth.ac.uk/cqr/>
 - [Centre for Research Excellence in Patient Safety](http://www.crepatientsafety.org.au/)
<http://www.crepatientsafety.org.au/>
 - [Cochrane Consumer Network \(CCNet\)](http://www.cochrane.org/consumers/homepage.htm)
<http://www.cochrane.org/consumers/homepage.htm>
 - [Community Health Exchange \(CHEX\)](http://www.chex.org.uk/)
<http://www.chex.org.uk/>
 - [Developing Patient Partnerships](http://dpp.org.uk/)
<http://dpp.org.uk/>
 - [Equality Evidence Finder](http://www.scotland.gov.uk/Topics/People/Equality/Equalities/DataGrid)
<http://www.scotland.gov.uk/Topics/People/Equality/Equalities/DataGrid>
 - [Equality in Health Managed Knowledge Network](http://www.equalityinhealth.scot.nhs.uk/home.aspx?referer=AAS&un=nouusername)
<http://www.equalityinhealth.scot.nhs.uk/home.aspx?referer=AAS&un=nouusername>
 - [Federal Drugs Administration](http://www.fda.gov/)
<http://www.fda.gov/>
 - [Health Talk Online](http://www.healthtalkonline.org/)
<http://www.healthtalkonline.org/>
 - [Institute for Safe Medication Practices](http://www.ismp.org/)
<http://www.ismp.org/>
 - [Institute of Medicine](http://www.iom.edu/)
<http://www.iom.edu/>
 - [International Alliance of Patients' Organizations](http://www.patientsorganizations.org/index.pl)
<http://www.patientsorganizations.org/index.pl>
 - [Involve](http://www.invo.org.uk/)
<http://www.invo.org.uk/>
 - [James Lind Alliance](http://www.lindalliance.org/)
<http://www.lindalliance.org/>
 - [Joint Commission: Patient Safety](http://www.jointcommission.org/topics/patient_safety.aspx)
http://www.jointcommission.org/topics/patient_safety.aspx
 - [King's Patient Safety and Service Quality Research Centre](http://www.kingspssq.org.uk/)
<http://www.kingspssq.org.uk/>
 - [MedlinePlus: Patient Safety](http://www.nlm.nih.gov/medlineplus/patientsafety.html)
<http://www.nlm.nih.gov/medlineplus/patientsafety.html>
 - [MHRA](http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=5)
http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=5
 - [National Association for Patient Participation](http://www.napp.org.uk/)
<http://www.napp.org.uk/>
 - [National Coordinating Council for Medication Error Reporting and Correction](#)

Clinical effectiveness – full write-up

- <http://www.nccmerp.org/>
- [National Patient Safety Agency \(NPSA\)](http://www.npsa.nhs.uk/)
<http://www.npsa.nhs.uk/>
- [National Patient Safety Foundation](http://www.npsf.org/)
<http://www.npsf.org/>
- [National Voices](http://www.nationalvoices.org.uk/)
<http://www.nationalvoices.org.uk/>
- [NHS Centre for Involvement](http://www.nhscentreforinvolvement.nhs.uk/)
<http://www.nhscentreforinvolvement.nhs.uk/>
- [NHS Improving Quality](http://www.england.nhs.uk/ourwork/qual-clin-lead/nhsiq/)
<http://www.england.nhs.uk/ourwork/qual-clin-lead/nhsiq/>
- [NHS Surveys](http://www.nhssurveys.org/)
<http://www.nhssurveys.org/>
- [Patient Opinion](http://www.patientopinion.org.uk/)
<http://www.patientopinion.org.uk/>
- [Patient Safety Board, Royal College of Surgeons \(Edinburgh\)](http://www.patientsafetyboard.org/)
<http://www.patientsafetyboard.org/>
- [Patient Safety Research Group](http://www.abdn.ac.uk/psrg/)
<http://www.abdn.ac.uk/psrg/>
- [Patient UK Discussion Forums](http://www.patient.co.uk/forums/)
<http://www.patient.co.uk/forums/>
- [Patient Views](http://www.patient-view.com/)
<http://www.patient-view.com/>
- [Patients Accelerating Change](http://www.cgsupport.nhs.uk/Programmes/Patients_Accelerating_Change_Program)
http://www.cgsupport.nhs.uk/Programmes/Patients_Accelerating_Change_Program
- [Patients Association](http://www.patients-association.org.uk/)
<http://www.patients-association.org.uk/>
- [Picker Institute](http://www.pickereurope.org/)
<http://www.pickereurope.org/>
- [Royal College of Nursing: Patient Safety](http://www.rcn.org.uk/development/practice/patient_safety)
http://www.rcn.org.uk/development/practice/patient_safety
- [Scottish Patient Safety Alliance](http://www.patientsafetyalliance.scot.nhs.uk/)
<http://www.patientsafetyalliance.scot.nhs.uk/>
- [Scottish Patient Safety Research Network](http://www.spsrn.ac.uk/)
<http://www.spsrn.ac.uk/>
- [Veterans Association National Center for Patient Safety](http://www.patientsafety.gov/)
<http://www.patientsafety.gov/>
- [World Alliance for Patient Safety](http://www.who.int/patientsafety/en/)
<http://www.who.int/patientsafety/en/>
- [Youth Talk Online](http://www.youthhealthtalk.org/)
<http://www.youthhealthtalk.org/>

Organisational issues

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The following sources were searched in June 2014:

- Chief Scientist Office
<http://www.cso.scot.nhs.uk/>
- Healthcare Improvement Scotland
http://www.healthcareimprovementscotland.org/welcome_to_healthcare_improvem.aspx
- Health Services Research Unit (Aberdeen)
<http://www.abdn.ac.uk/hsru/>
- ISD Scotland
http://www.isdscotland.org/isd/CCC_FirstPage.jsp
- National Procurement Scotland
<http://www.nhsscotlandprocurement.scot.nhs.uk/>
- NHS Education for Scotland
<http://www.nes.scot.nhs.uk/>
- Scottish Government
<http://www.scotland.gov.uk/Topics/Health>
- Scottish Public Health Observatory (ScotPHO)
<http://www.scotpho.org.uk/>
- Scottish Health On the Web (SHOW)
<http://www.show.scot.nhs.uk/>
- Health Facilities Scotland
<http://www.hfs.scot.nhs.uk/>
- Health Protection Scotland
<http://www.hps.scot.nhs.uk/>
- Health Scotland
<http://www.healthscotland.com/>
- Health Foundation
<http://www.health.org.uk/>
- King's Fund
<http://www.kingsfund.org.uk/>
- NHS Improving Quality
<http://www.england.nhs.uk/ourwork/qual-clin-lead/nhsiq/>
- NIHR Service Delivery and Organisation Programme
<http://www.sdo.nihr.ac.uk/>

Bibliographic database searches

The following databases were searched to identify additional systematic reviews and primary studies:

- MEDLINE (Ovid)
- MEDLINE in Process (Ovid)
- EMBASE (Ovid) *[Not searched for cost effectiveness]*
- CINAHL (EBSCOHost)

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- PsychInfo (EBSCOHost) [*Patient issues searches only*]
- Web of Science (ISI)
- Cochrane Central Register of Controlled Trials (CENTRAL, Cochrane Library)

Search 1: AWD systematic reviews

Database: MEDLINE

Database coverage: 1946 to present with daily update

Platform: Ovid

Date of search: 20 January 2014

1. exp "Wounds and Injuries"/
2. wound*.tw.
3. Chronic Disease/
4. (chronic illness* or chronically ill or chronic disease*).tw.
5. exp Skin Ulcer/
6. ulcer*.tw.
7. exp Venous Insufficiency/
8. Varicose Ulcer/
9. ((venous or varicose) adj3 ulcer*).tw.
10. Diabetic Foot/
11. "diabetic foot".tw.
12. or/1-11
13. exp Anti-Infective Agents/
14. (antimicrobial* or "anti-microbial*").tw.
15. (antibacterial* or "anti-bacterial*").tw.
16. (antiseptic* or "anti-septic*" or antiinfective or "anti-infective").tw.
17. (bacteri?cidal or bacteri?static).tw.
18. Chlorhexidine/
19. (chlorhexidine or chlorhexidene or dialkylcarbomoyl chloride or "di-alkylcarbomoyl chloride").tw.
20. (glucose oxidase or lactoperoxidase or microcid).tw.
21. Honey/

Clinical effectiveness – full write-up

22. honey.tw.
23. Iodine/
24. iodine.tw.
25. octenidine.tw.
26. (PHMB or polihexanide or polyhexanide).tw.
27. "polymethylene biguanide".tw.
28. Silver/
29. exp Silver Compounds/
30. silver.tw.
31. or/13-30
32. exp Bandages/
33. Alginates/
34. Ointments/
35. Hydrogel/
36. (bandage* or dressing*).tw.
37. (alginate* or carboxymethylcellulose).tw.
38. (foam* or gauze*).tw.
39. (hydrocolloid* or hydrogel*).tw.
40. "low adher* acetate*".tw.
41. (ointment* or paste* or gel*).tw.
42. (pad or tulle or viscose net or viscose mesh).tw.
43. topical*.tw.
44. or/32-43
45. 31 and 44
46. 12 and 45
47. Meta-Analysis as Topic/
48. meta analy\$.tw.
49. metaanaly\$.tw.
50. Meta-Analysis/
51. (systematic adj (review\$1 or overview\$1)).tw.

Clinical effectiveness – full write-up

52. exp Review Literature as Topic/
53. or/47-52
54. cochrane.ab.
55. embase.ab.
56. (psyclit or psychlit).ab.
57. (psycinfo or psychinfo).ab.
58. (cinahl or cinhal).ab.
59. science citation index.ab.
60. bids.ab.
61. cancerlit.ab.
62. or/54-61
63. reference list\$.ab.
64. bibliograph\$.ab.
65. hand-search\$.ab.
66. relevant journals.ab.
67. manual search\$.ab.
68. or/63-67
69. selection criteria.ab.
70. data extraction.ab.
71. 69 or 70
72. Review/
73. 71 and 72
74. Comment/
75. letter/
76. Editorial/
77. animal/
78. human/
79. 77 not (77 and 78)
80. or/74-76,79
81. 53 or 62 or 68 or 73

Clinical effectiveness – full write-up

82. 81 not 80

83. 46 and 82

84. limit 83 to (yr="1990 -Current" and english)

Search 2: AWD systematic reviews (company name)

Database: MEDLINE

Database coverage: 1946 to present with daily update

Platform: Ovid

Date of search: 20 January 2014

1. exp "Wounds and Injuries"/
2. wound*.tw.
3. Chronic Disease/
4. (chronic illness* or chronically ill or chronic disease*).tw.
5. exp Skin Ulcer/
6. ulcer*.tw.
7. exp Venous Insufficiency/
8. Varicose Ulcer/
9. ((venous or varicose) adj3 ulcer*).tw.
10. Diabetic Foot/
11. "diabetic foot".tw.
12. or/1-11
13. "3M healthcare".tw.
14. activa.tw.
15. advancis.tw.
16. archimed.tw.
17. "aspen medica".tw.
18. braun.tw.
19. BSN.tw.
20. convatec.tw.

Clinical effectiveness – full write-up

21. covidien.tw.
22. "crawford pharma".tw.
23. danetre.tw.
24. "derma sciences".tw.
25. hartmann.tw.
26. "johnson and johnson".tw.
27. "lohmann raucher".tw.
28. medlogic.tw.
29. molnlycke.tw.
30. schulke.tw.
31. "smith and nephew".tw.
32. systagenix.tw.
33. unomedical.tw.
34. urgo.tw.
35. or/13-34
36. 12 and 35
37. Meta-Analysis as Topic/
38. meta analy\$.tw.
39. metaanaly\$.tw.
40. Meta-Analysis/
41. (systematic adj (review\$1 or overview\$1)).tw.
42. exp Review Literature as Topic/
43. or/37-42
44. cochrane.ab.
45. embase.ab.
46. (psyclit or psychlit).ab.
47. (psycinfo or psychinfo).ab.
48. (cinahl or cinhal).ab.
49. science citation index.ab.
50. bids.ab.

Clinical effectiveness – full write-up

51. cancerlit.ab.
52. or/44-51
53. reference list\$.ab.
54. bibliograph\$.ab.
55. hand-search\$.ab.
56. relevant journals.ab.
57. manual search\$.ab.
58. or/53-57
59. selection criteria.ab.
60. data extraction.ab.
61. 59 or 60
62. Review/
63. 61 and 62
64. Comment/
65. letter/
66. Editorial/
67. animal/
68. human/
69. 67 not (67 and 68)
70. or/64-66,69
71. 43 or 52 or 58 or 63
72. 71 not 70
73. 36 and 72
74. 36 and 72
75. 36 and 72

Search 3: AWD systematic reviews (brand-names)

Database: MEDLINE

Database coverage: 1946 to present with daily update

Clinical effectiveness – full write-up

Platform: Ovid

Date of search: 20 January 2014

1. exp "Wounds and Injuries"/
2. wound*.tw.
3. Chronic Disease/
4. (chronic illness* or chronically ill or chronic disease*).tw.
5. exp Skin Ulcer/
6. ulcer*.tw.
7. exp Venous Insufficiency/
8. Varicose Ulcer/
9. ((venous or varicose) adj3 ulcer*).tw.
10. Diabetic Foot/
11. "diabetic foot".tw.
12. or/1-11
13. (acticoat or actisorb).tw.
14. (coloplast or cutimed sorbact).tw.
15. flaminol.tw.
16. (inadine or iodasorb or iodoflex or iodozyme).tw.
17. octenilin.tw.
18. (physiotulle ag or polymem silver or prontosan).tw.
19. "vliwaktiv ag".tw.
20. (urgocell or urgosorb or urgotul or urgotul SSD).tw.
21. (suprasorb or tegaderm or telfa or therabond).tw.
22. (algitel or algitel).tw.
23. (algivon or allevyn or aquacel).tw.
24. (askina or atrauman).tw.
25. (bactigras or biatain).tw.
26. (kendal AMD or kendal antimicrobial dressing* or kendal anti-microbial dressing*).tw.
27. (medihoney or melgisorb or mepilex or mesalt or mesitran).tw.
28. (seasorb or silvercel or silverseal or sorbact or sorbsan).tw.

Clinical effectiveness – full write-up

29. or/13-28
30. 12 and 29
31. Meta-Analysis as Topic/
32. meta analy\$.tw.
33. metaanaly\$.tw.
34. Meta-Analysis/
35. (systematic adj (review\$1 or overview\$1)).tw.
36. exp Review Literature as Topic/
37. or/31-36
38. cochrane.ab.
39. embase.ab.
40. (psyclit or psychlit).ab.
41. (psycinfo or psychinfo).ab.
42. (cinahl or cinhal).ab.
43. science citation index.ab.
44. bids.ab.
45. cancerlit.ab.
46. or/38-45
47. reference list\$.ab.
48. bibliograph\$.ab.
49. hand-search\$.ab.
50. relevant journals.ab.
51. manual search\$.ab.
52. or/47-51
53. selection criteria.ab.
54. data extraction.ab.
55. 53 or 54
56. Review/
57. 55 and 56
58. Comment/

Clinical effectiveness – full write-up

59. letter/
60. Editorial/
61. animal/
62. human/
63. 61 not (61 and 62)
64. or/58-60,63
65. 37 or 46 or 52 or 57
66. 65 not 64
67. 30 and 66
68. limit 67 to (yr="1990 -Current" and english)

Search 4: AWD cost effectiveness

Database: MEDLINE

Database coverage: 1946 to present with daily update

Platform: Ovid

Date of search: 30 January 2014

1. exp "Wounds and Injuries"/
2. wound*.tw.
3. Chronic Disease/
4. (chronic illness* or chronically ill or chronic disease*).tw.
5. exp Skin Ulcer/
6. ulcer*.tw.
7. exp Venous Insufficiency/
8. Varicose Ulcer/
9. ((venous or varicose) adj3 ulcer*).tw.
10. Diabetic Foot/
11. "diabetic foot".tw.
12. or/1-11

Clinical effectiveness – full write-up

13. exp Anti-Infective Agents/
14. (antimicrobial* or "anti-microbial*").tw.
15. (antibacterial* or "anti-bacterial*").tw.
16. (antiseptic* or "anti-septic*" or antiinfective or "anti-infective").tw.
17. (bacteri?cidal or bacteri?static).tw.
18. Chlorhexidine/
19. (chlorhexidine or chlorhexidene or dialkylcarbomoyl chloride or "di-alkylcarbomoyl chloride").tw.
20. (glucose oxidase or lactoperoxidase or microcid).tw.
21. Honey/
22. honey.tw.
23. Iodine/
24. iodine.tw.
25. octenidine.tw.
26. (PHMB or polihexanide or polyhexanide).tw.
27. "polymethylene biguanide".tw.
28. Silver/
29. exp Silver Compounds/
30. silver.tw.
31. or/13-30
32. exp Bandages/
33. Alginates/
34. Ointments/
35. Hydrogel/
36. (bandage* or dressing*).tw.
37. (alginate* or carboxymethylcellulose).tw.
38. (foam* or gauze*).tw.
39. (hydrocolloid* or hydrogel*).tw.
40. "low adher* acetate*".tw.
41. (ointment* or paste* or gel*).tw.

Clinical effectiveness – full write-up

42. (pad or tulle or viscose net or viscose mesh).tw.
43. topical*.tw.
44. or/32-43
45. 31 and 44
46. 12 and 45
47. ECONOMICS/
48. "Costs and Cost Analysis"/
49. Cost Allocation/
50. Cost-Benefit Analysis/
51. Cost Control/
52. Cost Savings/
53. Cost of Illness/
54. Cost Sharing/
55. "Deductibles and Coinsurance"/
56. Medical Savings Accounts/
57. Health Care Costs/
58. Direct Service Costs/
59. Drug Costs/
60. Employer Health Costs/
61. Hospital Costs/
62. Health Expenditures/
63. Capital Expenditures/
64. Value of Life/
65. exp Economics, Hospital/
66. exp Economics, Medical/
67. Economics, Nursing/
68. Economics, Pharmaceutical/
69. exp "Fees and Charges"/
70. exp BUDGETS/
71. (low adj cost).mp.

Clinical effectiveness – full write-up

72. (high adj cost).mp.
73. (health?care adj cost\$).mp.
74. (fiscal or funding or financial or finance).tw.
75. (cost adj estimate\$).mp.
76. (cost adj variable).mp.
77. (unit adj cost\$).mp.
78. (economic\$ or pharmaco-economic\$ or price\$ or pricing).tw.
79. or/47-78
80. 46 and 79
81. Economics/
82. exp "Costs and Cost Analysis"/
83. Economics, Dental/
84. exp Economics, Hospital/
85. Economics, Medical/
86. Economics, Nursing/
87. Economics, Pharmaceutical/
88. (economic* or cost or costs or costly or costing or price or prices or pricing or pharmaco-economic*).tw.
89. (expenditure* not energy).tw.
90. (value adj1 money).ti,ab.
91. budget*.tw.
92. or/81-91
93. ((energy or oxygen) adj cost).tw.
94. (metabolic adj cost).tw.
95. ((energy or oxygen) adj expenditure).tw.
96. 93 or 94 or 95
97. 92 not 96
98. 46 and 97
99. 80 or 98
100. limit 99 to (yr="1990 -Current" and english)

Search 5: AWD patient issues

Database: MEDLINE

Database coverage: 1946 to present with daily update

Platform: Ovid

Date of search: 7 April 2014

1. exp "Wounds and Injuries"/
2. wound*.tw.
3. Chronic Disease/
4. (chronic illness* or chronically ill or chronic disease*).tw.
5. exp Skin Ulcer/
6. ulcer*.tw.
7. exp Venous Insufficiency/
8. Varicose Ulcer/
9. ((venous or varicose) adj3 ulcer*).tw.
10. Diabetic Foot/
11. "diabetic foot".tw.
12. or/1-11
13. exp Anti-Infective Agents/
14. (antimicrobial* or "anti-microbial").tw.
15. (antibacterial* or "anti-bacterial").tw.
16. (antiseptic* or "anti-septic*" or antiinfective or "anti-infective").tw.
17. (bacteri?cidal or bacteri?static).tw.
18. Chlorhexidine/
19. (chlorhexidine or chlorhexidene or dialkylcarbomoyl chloride or "di-alkylcarbomoyl chloride").tw.
20. (glucose oxidase or lactoperoxidase or microcid).tw.
21. Honey/
22. honey.tw.

Clinical effectiveness – full write-up

23. Iodine/
24. iodine.tw.
25. octenidine.tw.
26. (PHMB or polihexanide or polyhexanide).tw.
27. "polymethylene biguanide".tw.
28. Silver/
29. exp Silver Compounds/
30. silver.tw.
31. or/13-30
32. exp Bandages/
33. Alginates/
34. Ointments/
35. Hydrogel/
36. (bandage* or dressing*).tw.
37. (alginate* or carboxymethylcellulose).tw.
38. (foam* or gauze*).tw.
39. (hydrocolloid* or hydrogel*).tw.
40. "low adher* acetate*".tw.
41. (ointment* or paste* or gel*).tw.
42. (pad or tulle or viscose net or viscose mesh).tw.
43. topical*.tw.
44. or/32-43
45. 31 and 44
46. 12 and 45
47. limit 46 to (yr="1990 -Current" and english)
48. exp Consumer Participation/
49. ((patient\$ or consumer\$) adj3 (participat\$ or decisi\$ or decid\$)).ti,ab.
50. "Patient Acceptance of Health Care"/
51. exp attitude to health/
52. consumer satisfaction/

Clinical effectiveness – full write-up

53. exp *Consumer Satisfaction/
54. Patient Preference/
55. "patient-focused".ti,ab.
56. "patient-centered".ti,ab.
57. "patient-centred".ti,ab.
58. (patient adj3 (attitude\$ or preference\$)).ti,ab.
59. "patient satisfaction".ti.
60. cooperative behavior/
61. exp self-efficacy/
62. self-efficacy.ti,ab.
63. exp adaptation, psychological/
64. coping.ti,ab.
65. ("self-perception" or "self-concept").ti,ab.
66. exp health education/
67. patient education as topic/
68. exp attitude to health/
69. health knowledge, attitudes, practice/
70. "informed choice".ti,ab.
71. "shared decision making".ti,ab.
72. empowerment.tw.
73. ("focus group" adj3 (patient\$ or parent\$ or famil\$ or spouse\$)).ti,ab.
74. *"Quality of Life"/
75. "Quality of Life"/px [Psychology]
76. (QoL or "quality of life").ti.
77. personal autonomy/
78. self concept/
79. Consumer Advocacy/
80. freedom/
81. needs assessment/
82. patient advocacy/

Clinical effectiveness – full write-up

83. self-help groups/
84. life change events/
85. attitude to death/
86. patient-centered care/
87. exp professional-patient relations/
88. self care/
89. self-management.ti.
90. ((patient\$ or consumer\$ or parent\$ or famil\$ or spouse\$) adj (attitude\$ or involvement or desir\$ or perspective\$ or activation or view\$ or preference\$)).ti,ab.
91. "expert patient".ti,ab.
92. or/48-91
93. exp decision making/
94. exp communication/
95. stress, psychological/
96. emotions/
97. vignette*.ti,ab.
98. or/93-97
99. exp Patients/px [Psychology]
100. (patient\$ or consumer\$).ti.
101. or/99-100
102. 98 and 101
103. "focus group\$".ti,ab.
104. focus groups/
105. narration/
106. qualitative.ti.
107. or/103-106
108. 92 or 102 or 107
109. 47 and 108
110. from 109 keep 1-114
111. exp Mortality/

Clinical effectiveness – full write-up

112. Morbidity/
113. (mortality or morbidity).ti.
114. Incidence/
115. Prevalence/
116. (inciden* or prevalen*).ti.
117. Demography/
118. Censuses/
119. exp Population Surveillance/
120. "age of onset"/
121. age distribution/
122. Age Factors/
123. age.ti.
124. exp sex distribution/
125. Sex Factors/
126. (sex or gender).ti.
127. "Emigration and Immigration"/
128. Minority Groups/
129. culture/ or cultural characteristics/
130. exp Population Groups/
131. (ethnic* or cultur* or minorit*).ti.
132. epidemiologic factors/
133. Income/
134. (income or salar* or earning*).ti.
135. ep.fs.
136. eh.fs.
137. burden.ti.
138. "Quality of Life"/
139. (sociodemographic* or socio-demographic* or social demographic* or "social and demographic").tw.
140. (socioeconomic or socio-economic or (social and economic)).ti.

Clinical effectiveness – full write-up

141. "Activities of Daily Living"/
142. px.fs.
143. (psychological or psychosocial or emotional).ti.
144. exp Socioeconomic Factors/
145. Work/
146. employment/ or unemployment/
147. Occupations/
148. (employment or earning* or workplace or productivity).tw.
149. work.ti.
150. or/111-149
151. 47 and 150
152. exp Great Britain/
153. ("great britain" or "united kingdom" or UK or GB).tw.
154. (London or Birmingham or Bristol or Oxford or Cambridge or Manchester or Leeds or York or Newcastle or Sheffield or Liverpool or Coventry or Leicester or Nottingham).tw.
155. (Cardiff or Swansea or Belfast).tw.
156. (england or english or wales or welsh or "northern ireland" or irish).tw.
157. (scotland or scottish or scots).tw.
158. (Glasgow or Edinburgh or Stirling or Dundee or Perth or Inverness or Aberdeen).tw.
159. (Argyll or Ayresshire or Arran or Dumfries or Galloway or Lothian or Highland or Clyde or Fife or "Forth valley" or Orkney or Hebride* or Borders or Shetland or "Western isles" or Grampian or Lanarkshire or Tayside).tw.

Search 6: AWD adverse effects

Database: MEDLINE

Database coverage: 1946 to present with daily update

Platform: Ovid

Date of search: 18 June 2014

1. exp "Wounds and Injuries"/

Clinical effectiveness – full write-up

2. wound*.tw.
3. Chronic Disease/
4. (chronic illness* or chronically ill or chronic disease*).tw.
5. exp Skin Ulcer/
6. ulcer*.tw.
7. exp Venous Insufficiency/
8. Varicose Ulcer/
9. ((venous or varicose) adj3 ulcer*).tw.
10. Diabetic Foot/
11. "diabetic foot".tw.
12. or/1-11
13. exp Anti-Infective Agents/
14. (antimicrobial* or "anti-microbial").tw.
15. (antibacterial* or "anti-bacterial").tw.
16. (antiseptic* or "anti-septic*" or antiinfective or "anti-infective").tw.
17. (bacteri?cidal or bacteri?static).tw.
18. Chlorhexidine/
19. (chlorhexidine or chlorhexidene or dialkylcarbomoyl chloride or "di-alkylcarbomoyl chloride").tw.
20. (glucose oxidase or lactoperoxidase or microcid).tw.
21. Honey/
22. honey.tw.
23. Iodine/
24. iodine.tw.
25. octenidine.tw.
26. (PHMB or polihexanide or polyhexanide).tw.
27. "polymethylene biguanide".tw.
28. Silver/
29. exp Silver Compounds/
30. silver.tw.

Clinical effectiveness – full write-up

31. or/13-30
32. exp Bandages/
33. Alginates/
34. Ointments/
35. Hydrogel/
36. (bandage* or dressing*).tw.
37. (alginate* or carboxymethylcellulose).tw.
38. (foam* or gauze*).tw.
39. (hydrocolloid* or hydrogel*).tw.
40. "low adher* acetate*".tw.
41. (ointment* or paste* or gel*).tw.
42. (pad or tulle or viscose net or viscose mesh).tw.
43. topical*.tw.
44. or/32-43
45. 31 and 44
46. 12 and 45
47. limit 46 to (yr="1990 -Current" and english)
48. *Patient Safety/
49. Patient Harm/
50. (safe or safety).ti,ab.
51. (side effect* or undesirable effect*).ti,ab.
52. harm*.ti,ab.
53. (tolerability or toxicity).ti,ab.
54. (adverse adj2 (effect* or reaction* or event* or outcome*)).ti,ab.
55. or/48-54
56. ae.fs.
57. (pain* or discomfort).ti.
58. (bleed* or blood loss or h?emorrhag*).ti.
59. (dermatitis or skin inflammation or skin irritation).ti.
60. ((skin or ulcer or wound or dermat* or tissue) adj2 deteriorat*).ti.

Clinical effectiveness – full write-up

61. (erythema or (red* adj2 skin)).ti.
62. (edema or oedema).ti.
63. (edema or oedema).ti.
64. exudate*.ti.
65. (pruritis or itch*).ti.
66. (exanthema or (skin rash* or dermat* rash*)).ti.
67. eczema.ti.
68. sting*.ti.
69. (allergy or allergies or allergic or hypersensitiv* or hyper-sensitiv*).ti.
70. ((wound or ulcer or skin or dermat* or tissue) adj2 (erosion or erod*)).ti.
71. burning.ti.
72. ((local* or wound or ulcer or tissue or dermat*) adj3 infect*).ti.
73. ((wound or ulcer or tissue) adj3 contaminat*).ti.
74. or/57-73
75. human/ not animal/
76. 55 or 56 or 74
77. 47 and 76
78. 75 and 77

Search 7: AWD qualitative studies (patient issues)

Database: MEDLINE

Database coverage: 1946 to present with daily update

Platform: Ovid

Date of search: 2 July 2014

1. exp "Wounds and Injuries"/
2. wound*.tw.
3. Chronic Disease/
4. (chronic illness* or chronically ill or chronic disease*).tw.

Clinical effectiveness – full write-up

5. exp Skin Ulcer/
6. ulcer*.tw.
7. exp Venous Insufficiency/
8. Varicose Ulcer/
9. ((venous or varicose) adj3 ulcer*).tw.
10. Diabetic Foot/
11. "diabetic foot".tw.
12. or/1-11
13. exp Anti-Infective Agents/
14. (antimicrobial* or "anti-microbial*").tw.
15. (antibacterial* or "anti-bacterial*").tw.
16. (antiseptic* or "anti-septic*" or antiinfective or "anti-infective").tw.
17. (bacteri?cidal or bacteri?static).tw.
18. Chlorhexidine/
19. (chlorhexidine or chlorhexidene or dialkylcarbomoyl chloride or "di-alkylcarbomoyl chloride").tw.
20. (glucose oxidase or lactoperoxidase or microcid).tw.
21. Honey/
22. honey.tw.
23. Iodine/
24. iodine.tw.
25. octenidine.tw.
26. (PHMB or polihexanide or polyhexanide).tw.
27. "polymethylene biguanide".tw.
28. Silver/
29. exp Silver Compounds/
30. silver.tw.
31. or/13-30
32. exp Bandages/
33. Alginates/

Clinical effectiveness – full write-up

34. Ointments/
35. Hydrogel/
36. (bandage* or dressing*).tw.
37. (alginate* or carboxymethylcellulose).tw.
38. (foam* or gauze*).tw.
39. (hydrocolloid* or hydrogel*).tw.
40. "low adher* acetate*".tw.
41. (ointment* or paste* or gel*).tw.
42. (pad or tulle or viscose net or viscose mesh).tw.
43. topical*.tw.
44. (fabric or polyester* or soft polymer).ti,ab.
45. ((silicone or starch based) adj2 dress*).tw.
46. or/32-45
47. 31 and 46
48. 12 and 47
49. exp Interviews as Topic/
50. exp Attitude to Health/
51. exp Observation/
52. qualitative research/
53. Narration/
54. exp Nursing Research/
55. exp Tape Recording/
56. experience*.ti,ab.
57. interview*.ti,ab.
58. qualitative*.ti,ab.
59. theme*.ti,ab.
60. analytic memo.ti,ab.
61. anecdote*.ti,ab.
62. audiotape*.ti,ab.
63. (conceptual adj2 (categor* or framework*)).ti,ab.

Clinical effectiveness – full write-up

64. (concurrent adj2 (analys* or data)).ti,ab.
65. confirmability.ti,ab.
66. content analys*.ti,ab.
67. (comparative adj2 (analys* or method*)).ti,ab.
68. convenience sampl*.ti,ab.
69. data saturation.ti,ab.
70. ((descriptive or document) adj2 analys*).ti,ab.
71. emergent theor*.ti,ab.
72. ((semistructured or semi-structured or unstructured or informal or in-depth or indepth or face-to-face or structured or guid*) adj3 (discussion* or questionnaire*)).ti,ab.
73. (ethnograph* or ethnological or ethnomethodol* or ethnonursing research).ti,ab.
74. exploratory design.ti,ab.
75. (field notes or fieldwork or field work or key informant*).ti,ab.
76. focus group*.ti,ab.
77. grounded theor*.ti,ab.
78. hermeneutic.ti,ab.
79. (inductive adj2 (analys* or grounded or reasoning)).ti,ab.
80. informational redundancy.ti,ab.
81. (iterative adj2 approach*).ti,ab.
82. interpretive.ti,ab.
83. life histor*.ti,ab.
84. maximum variation sampl*.ti,ab.
85. (meta-ethnography or metaethnography).ti,ab.
86. (narrative* or narration or metanarrative* or meta-narrative*).ti,ab.
87. naturalistic.ti,ab.
88. observation*.ti,ab.
89. (open-ended or open coding).ti,ab.
90. phenomen*.ti,ab.
91. ((purposeful or purposive or quota) adj2 sampl*).ti,ab.
92. saturation.ti,ab.

Clinical effectiveness – full write-up

93. selective coding.ti,ab.
94. (semistructured or semi-structured).ti,ab.
95. snowball sampling.ti,ab.
96. symbolic interactionism.ti,ab.
97. (tape record* or taped discussion*).ti,ab.
98. thematic.ti,ab.
99. (theoretical adj2 (grounding or sampl* or model* or saturation)).ti,ab.
100. transcendental phenomenology.ti,ab.
101. (transcrib* or transcript*).ti,ab.
102. triangulation.ti,ab.
103. verbatim.ti,ab.
104. (video tape* or videotap*).ti,ab.
105. or/49-104
106. 12 and 46 and 105
107. 12 and 47 and 105
108. 106 or 107

Search 8: AWD primary studies (venous ulcers)

Database: MEDLINE

Database coverage: 1946 to present with daily update

Platform: Ovid

Date of search: 7 July 2014

1. Varicose Ulcer/
2. exp Venous Insufficiency/
3. ((venous or varicose or stasis) adj3 ulcer*).ti,ab.
4. "venous insufficien*".ti,ab.
5. or/1-4
6. Iodine/

Clinical effectiveness – full write-up

7. exp Iodine Compounds/
8. iodine.ti,ab.
9. or/6-8
10. Honey/
11. honey*.ti,ab.
12. 10 or 11
13. Silver/
14. exp Silver Compounds/
15. silver*.ti,ab.
16. or/13-15
17. exp Bandages/
18. Alginates/
19. Ointments/
20. Hydrogel/
21. (bandage* or dressing*).ti,ab.
22. (alginate* or carboxymethylcellulose).ti,ab.
23. (foam* or gauze*).ti,ab.
24. (hydrocolloid* or hydrogel*).ti,ab.
25. "low adher* acetate*".ti,ab.
26. (ointment* or paste* or gel*).ti,ab.
27. (pad or tulle or viscose net or viscose mesh).ti,ab.
28. topical*.ti,ab.
29. (fabric* or polyester* or soft polymer).ti,ab.
30. (silicone or starch based).ti,ab.
31. or/17-30
32. 5 and 9 and 31
33. limit 32 to (yr="2009 -Current" and english)
34. 5 and 12 and 31
35. limit 34 to (yr="1990 -Current" and english)
36. 5 and 16 and 31

Clinical effectiveness – full write-up

37. limit 36 to (yr="1990 -Current" and english)
38. randomized controlled trial.pt.
39. controlled clinical trial.pt.
40. randomized.ab.
41. placebo.ab.
42. clinical trials as topic.sh.
43. randomly.ab.
44. trial.ti.
45. or/38-44
46. exp animals/ not humans.sh.
47. 45 not 46
48. 33 and 47
49. 35 and 47
50. 37 and 47

Search 9: AWD primary studies (pressure ulcers)

Database: MEDLINE

Database coverage: 1946 to present with daily update

Platform: Ovid

Date of search: 7 July 2014

1. Pressure Ulcer/
2. (pressure adj3 ulcer*).ti,ab.
3. (pressure adj3 sore*).ti,ab.
4. (bed sore* or bedsore*).ti,ab.
5. (decubitus adj3 ulcer*).ti,ab.
6. or/1-5
7. Iodine/
8. exp Iodine Compounds/

Clinical effectiveness – full write-up

9. iodine.ti,ab.
10. or/7-9
11. Honey/
12. honey*.ti,ab.
13. 11 or 12
14. Silver/
15. exp Silver Compounds/
16. silver*.ti,ab.
17. or/14-16
18. exp Bandages/
19. Alginates/
20. Ointments/
21. Hydrogel/
22. (bandage* or dressing*).ti,ab.
23. (alginate* or carboxymethylcellulose).ti,ab.
24. (foam* or gauze*).ti,ab.
25. (hydrocolloid* or hydrogel*).ti,ab.
26. "low adher* acetate*".ti,ab.
27. (ointment* or paste* or gel*).ti,ab.
28. (pad or tulle or viscose net or viscose mesh).ti,ab.
29. topical*.ti,ab.
30. (fabric* or polyester* or soft polymer).ti,ab.
31. (silicone or starch based).ti,ab.
32. or/18-31
33. randomized controlled trial.pt.
34. controlled clinical trial.pt.
35. randomized.ab.
36. placebo.ab.
37. clinical trials as topic.sh.
38. randomly.ab.

Clinical effectiveness – full write-up

39. trial.ti.
40. or/33-39
41. exp animals/ not humans.sh.
42. 40 not 41
43. 6 and 10 and 32
44. limit 43 to (yr="2013 -Current" and english)
45. 42 and 44
46. 6 and 13 and 32
47. limit 46 to (yr="2013 -Current" and english)
48. 42 and 47
49. 6 and 17 and 32
50. limit 49 to (yr="2013 -Current" and english)
51. 42 and 50

Search 10: AWD primary studies (diabetic ulcers)

Database: MEDLINE

Database coverage: 1946 to present with daily update

Platform: Ovid

Date of search: 7 July 2014

1. Diabetic Foot/
2. (diabetic foot or diabetic feet).ti,ab.
3. (diabet* adj3 ulcer*).ti,ab.
4. (diabet* adj5 wound*).ti,ab.
5. or/1-4
6. Iodine/
7. exp Iodine Compounds/
8. iodine.ti,ab.
9. or/6-8

Clinical effectiveness – full write-up

10. Honey/
11. honey*.ti,ab.
12. 10 or 11
13. Silver/
14. exp Silver Compounds/
15. silver*.ti,ab.
16. or/13-15
17. exp Bandages/
18. Alginates/
19. Ointments/
20. Hydrogel/
21. (bandage* or dressing*).ti,ab.
22. (alginate* or carboxymethylcellulose).ti,ab.
23. (foam* or gauze*).ti,ab.
24. (hydrocolloid* or hydrogel*).ti,ab.
25. "low adher* acetate*".ti,ab.
26. (ointment* or paste* or gel*).ti,ab.
27. (pad or tulle or viscose net or viscose mesh).ti,ab.
28. topical*.ti,ab.
29. (fabric* or polyester* or soft polymer).ti,ab.
30. (silicone or starch based).ti,ab.
31. or/17-30
32. randomized controlled trial.pt.
33. controlled clinical trial.pt.
34. randomized.ab.
35. placebo.ab.
36. clinical trials as topic.sh.
37. randomly.ab.
38. trial.ti.
39. or/32-38

Clinical effectiveness – full write-up

40. exp animals/ not humans.sh.
41. 39 not 40
42. 5 and 9 and 31
43. limit 42 to (yr="2009 -Current" and english)
44. 41 and 43
45. 5 and 12 and 31
46. limit 45 to (yr="1990 -Current" and english)
47. 41 and 46
48. 5 and 16 and 31
49. limit 48 to (yr="2005 -Current" and english)
50. 41 and 49

Search 11: AWD primary studies (surgical wounds and all ulcer types)

Database: MEDLINE

Database coverage: 1946 to present with daily update

Platform: Ovid

Date of search: 5 August 2014

1. Varicose Ulcer/
2. exp Venous Insufficiency/
3. ((venous or varicose or stasis) adj3 ulcer*).ti,ab.
4. "venous insufficien*".ti,ab.
5. or/1-4
6. Pressure Ulcer/
7. (pressure adj3 ulcer*).ti,ab.
8. (pressure adj3 sore*).ti,ab.
9. (bed sore* or bedsore*).ti,ab.
10. (decubitus adj3 ulcer*).ti,ab.
11. or/6-10

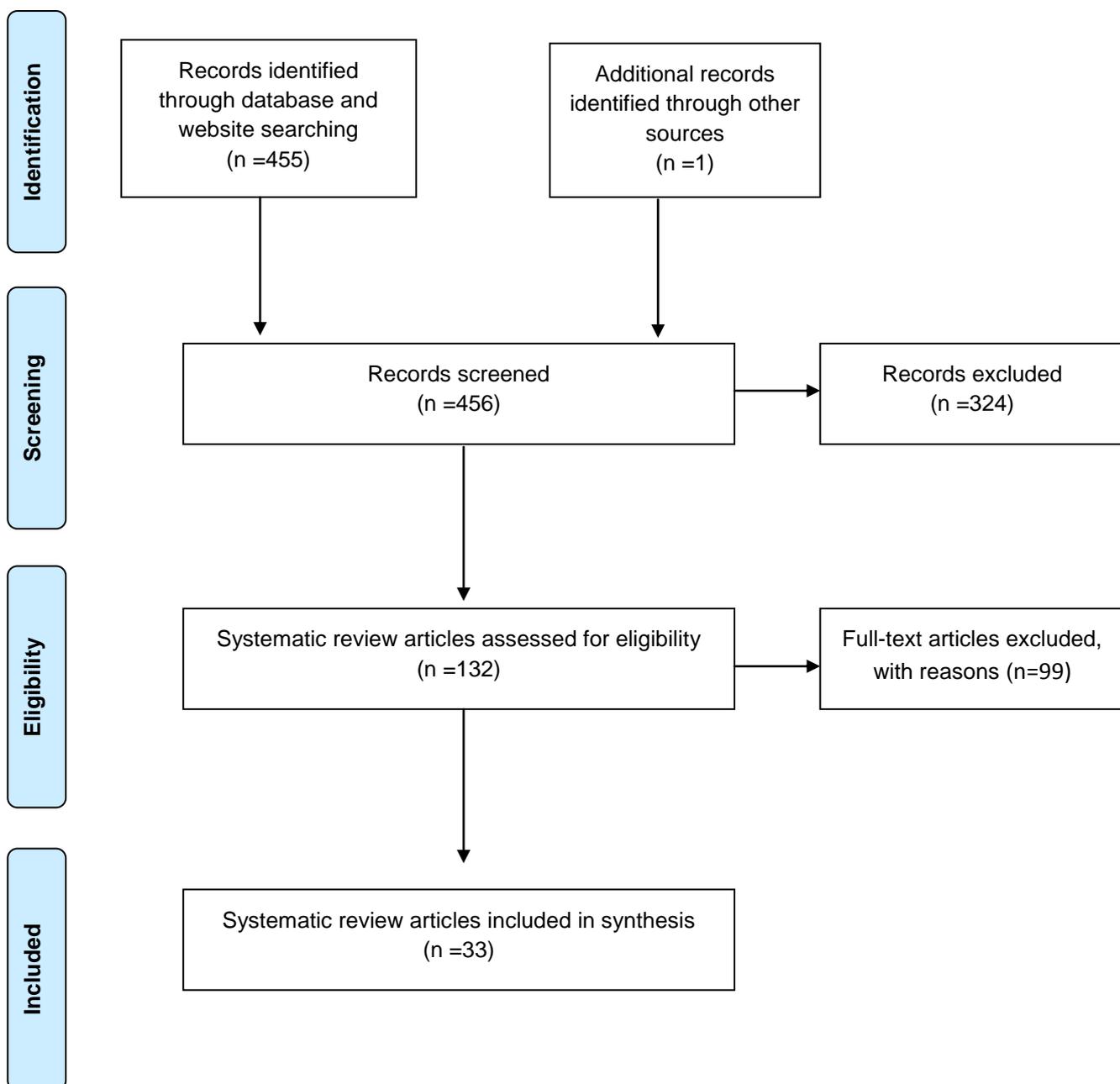
Clinical effectiveness – full write-up

12. Diabetic Foot/
13. (diabetic foot or diabetic feet).ti,ab.
14. (diabet* adj3 ulcer*).ti,ab.
15. (diabet* adj5 wound*).ti,ab.
16. or/12-15
17. exp Skin Ulcer/
18. ulcer*.ti,ab.
19. Surgical Wound Dehiscence/
20. exp Wound Infection/
21. ((chronic* or surg* or postoperat* or "post-operat*") adj3 wound*).ti,ab.
22. (wound* adj3 dehisc*).ti,ab.
23. or/17-22
24. 5 or 11 or 16 or 23
25. Chlorhexidine/
26. (chlorhexidine or chlorhexidene).ti,ab.
27. (dialkylcarbomoyl chloride or "di-alkylcarbomoyl chloride" or dialkylcarbomoyl chloride or "di-alkylcarbomoyl chloride" or DACC).ti,ab.
28. (glucose oxidase or lactoperoxidase or microcid or flaminol or "enzyme alginogel*").ti,ab.
29. (octenidine or octenidene).ti,ab.
30. (PHMB or polihexanide or polyhexanide or polyhexamide or polihexamide).ti,ab.
31. or/25-30
32. 24 and 31
33. randomized controlled trial.pt.
34. controlled clinical trial.pt.
35. randomized.ab.
36. placebo.ab.
37. clinical trials as topic.sh.
38. randomly.ab.
39. trial.ti.
40. or/33-39

Clinical effectiveness – full write-up

41. exp animals/ not humans.sh.
42. 40 not 41
43. 32 and 42
44. limit 43 to (yr="1990 -Current" and english)

Appendix 2: Flow chart and summary of included and excluded systematic reviews



Adapted from: PRISMA – Transparent Reporting of Systematic Reviews and Meta-analyses. Available from: <http://www.prisma-statement.org/>

Clinical effectiveness – full write-up

Abbotts, J. (2013). "Are silver dressings clinically effective and cost effective for the healing of infected wounds and the prevention of wound infection relative to other types of dressing?". http://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/shtg_scoping_reports/technologies_scoping_report_12.aspx	Exclude – this is a rapid review (scoping report). It is not a systematic review
Adderley, U. and R. Smith (2007). "Topical agents and dressings for fungating wounds." Cochrane Database Syst Rev(2): CD003948.	Exclude – this is on fungating malignant wounds – not chronic wounds
Agency for Healthcare Research and Quality (2012). Chronic Venous Ulcers: A Comparative Effectiveness Review of Treatment Modalities.	Exclude - protocol
Agency for Healthcare Research and Quality (2014). "Chronic venous ulcers:A comparative effectiveness review of treatment modalities."	Include
Al-Benna, S., Y. Al-Ajam, et al. (2009). "The evidence base for the wound healing properties of honey." Burns 35: S21-S22.	Exclude – this is just an abstract
Alguire, P. C. and B. M. Mathes (1997). "Chronic venous insufficiency and venous ulceration." Journal of General Internal Medicine 12(6): 374-383.	Exclude – not a systematic review
Angel DE, Morey P, et al. (2008). "The great debate over iodine in wound care continues: a review of the literature." from http://www.awma.com.au/journal/1601_01.pdf .	Exclude – not a systematic review
Arzt, H., I. Fromantin, et al. (2012). "Which medical device and/or which local treatment are to be used, as of 2012, in patients with infected pressure sore? Developing French guidelines for clinical practice." Ann Phys Rehabil Med 55(7): 498-507.	Exclude – not enough detail given about the included studies. Would need to look them all up
Australian Wound Management Association. (2012). "Pan Pacific clinical practice guideline for the prevention and management of pressure injury." from http://www.awma.com.au/publications/2012_AWMA_Pan_Pacific_Guidelines.pdf .	Include
Australian Wound Management Association Inc and New Zealand Wound Care Society. (2011). "Australian and New Zealand clinical practice guideline for prevention and management of venous leg ulcers." from http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/ext003_venous_leg_ulcers_aust_nz_0.pdf .	Include
Bandolier. (2007). "Update on honey therapy: 2007." from http://www.medicine.ox.ac.uk/bandolier/booth/alternat/honey07.html .	Exclude – this is not a systematic review
Bardy, J., N. J. Slevin, et al. (2008). "A systematic review of honey uses and its potential value within oncology care." Journal of Clinical Nursing 17(19): 2604-2623.	Include
Bates-Jensen, B. M. and C. H. MacLean (2007). "Quality indicators for the care of pressure ulcers in vulnerable elders." Journal of the American Geriatrics Society 55(SUPPL. 2): S409-S416.	Exclude – apart from doing a comprehensive search, this is not a systematic review
Beam, J. W. (2007). "Management of superficial to partial-thickness wounds." Journal of Athletic Training 42(3): 422-424.	Exclude – this is a summary of Wiechula et al (int J Nurs Pract. 2003;9:S9-S17)
KCE, Beeckman D, Matheï C, et al. (2013). "A national guideline for the treatment of pressure ulcers." from https://kce.fgov.be/sites/default/files/page_documents/KCE_203_pressure_ulcers.pdf .	Include
Bergin, S. and P. Wraight (2006) "Silver based wound dressings and topical agents for treating diabetic foot ulcers." Cochrane Database of Systematic Reviews DOI: 10.1002/14651858.CD005082.pub2.	Include
Bolton, L. (2006). "Are silver products safe and effective for chronic wound management?" J Wound Ostomy Continence Nurs 33(5): 469-477.	Exclude – not a systematic review
Bouza, C., A. Munoz, et al. (2005). "Efficacy of modern dressings in the treatment of leg ulcers: A systematic review." Wound Repair and	Exclude – this is looking at modern dressings, but

Regeneration 13(3): 218-229.	not AWDs
Bradley, M., N. Cullum, et al. (1999) "Systematic reviews of wound care management: (2) dressings and topical agents used in the healing of chronic wounds (Structured abstract)." Health Technology Assessment, 1-135.	Include
Brett, D. W. (2006). "A discussion of silver as an antimicrobial agent: alleviating the confusion." Ostomy Wound Manage 52(1): 34-41.	Exclude – not a systematic review
Briggs, M., E. A. Nelson, et al. (2012). "Topical agents or dressings for pain in venous leg ulcers." Cochrane Database of Systematic Reviews(11).	Exclude – this is about analgesia, not antimicrobials
Burrows C, Miller R, et al. (2006). "Best practice recommendations for the prevention and treatment of venous leg ulcers: update 2006." from http://cawc.net/images/uploads/wcc/4-1-vol4no1-BP-VLU.pdf .	Exclude – not a systematic review
Canadian Agency for Drugs and Technologies in Health. (2009). "Antibiotic-impregnated absorbable collagen sponges: clinical effectiveness." from http://www.cadth.ca/media/pdf/K0112_Antibiotic-Impregnated_Sponges_final.pdf .	Exclude – this is a rapid review of the evidence, not a systematic review
Canadian Agency for Drugs and Technologies in Health. (2009). "Medihoney for wound healing: clinical-effectiveness." from http://www.cadth.ca/media/pdf/htis/J0248%20Medihoney%20final.pdf .	Exclude – not a systematic review
Canadian Agency for Drugs and Technologies in Health. (2010). "Silver dressings for the treatment of patients with infected wounds: a review of clinical and cost-effectiveness." from http://www.cadth.ca/media/pdf/I0193_silver_dressings_htis-2.pdf .	Exclude – not a systematic review
Canadian Agency for Drugs and Technologies in Health. (2013). "Dressing materials for the treatment of pressure ulcers in patients in long-term care facilities: a review of the comparative clinical effectiveness and guidelines." from http://www.cadth.ca/media/pdf/htis/dec-2013/RC0496%20Presure%20Ulcer%20Care-Final.pdf .	Exclude – not a systematic review
Carter MJ, Tingley-Kelley K, et al. (2010). "Silver treatments and silver-impregnated dressings for the healing of leg wounds and ulcers: a systematic review and meta-analysis." Journal of the American Academy of Dermatology 63(4): 668-679.	Include
Carter, M. J., K. Tingley-Kelley, et al. (2010) "Silver treatments and silver-impregnated dressings for the healing of leg wounds and ulcers: a systematic review and meta-analysis (Structured abstract)." Journal of the American Academy of Dermatology, 668-679.	Exclude – this is an abstract (the actual paper is included)
Chaby, G., P. Senet, et al. (2007). "Dressings for acute and chronic wounds: a systematic review." Arch Dermatol 143(10): 1297-1304.	Include
Chambers, H., J. C. Dumville, et al. (2007). "Silver treatments for leg ulcers: a systematic review." Wound Repair Regen 15(2): 165-173.	Include
Chrisman, C. A. (2010). "Care of chronic wounds in palliative care and end-of-life patients." International Wound Journal 7(4): 214-235.	Exclude – not a systematic review
Clinical Evidence. (2011). "Pressure ulcers: interventions." from http://clinicalevidence.bmj.com/x/systematic-review/1901/interventions.html .	Exclude – this summarises two reviews (Bradley et al and Reddy et al) that have already been included
Cooper R. (2004). "A review of the evidence for the use of topical antimicrobial agents in wound care." from http://cenormagill.com.br/artigos/A%20review%20of%20the%20evidence%20for%20the%20use%20of%20topical%20antimicrobial%20agents%20in%20wound%20care.pdf .	Exclude – this is not a systematic review
Cray, A. (2010). "Honey treatments for wounds." Journal of Community Nursing 24(2): 22.	This was initially included, and subsequently excluded. When trying to extract data, it became clear that there was insufficient

	detail presented from the individual studies. This is not a systematic review.
CREST. (1998). "Guidelines for the assessment and management of leg ulceration." from http://www.gain-ni.org/images/Uploads/Guidelines/wound-management-leg-ulceration.pdf .	Exclude – this is just recommendations, the accompanying systematic review is not available
CREST. (1998). "Guidelines on the general principles of caring for patients with wounds: recommendations for practice." from http://www.gain-ni.org/images/Uploads/Guidelines/wond-management-wounds.pdf .	Exclude – this is just recommendations, the accompanying systematic review is not available
Cuddigan J. (2009). "NPUAP-EPUAP pressure ulcer prevention and treatment guidelines." from http://www.npuap.org/wp-content/uploads/2012/03/Final-2009-Treatment-Technical-Report1.pdf http://www.epuap.org/guidelines/Final_Quick_Treatment.pdf .	Include
Dat, A. D., F. Poon, et al. (2012). "Aloe vera for treating acute and chronic wounds." Cochrane Database Syst Rev 2: CD008762.	Exclude – not including aloe vera
Dumville, J. C., S. Deshpande, et al. (2012). "Hydrocolloid dressings for healing diabetic foot ulcers." Cochrane Database of Systematic Reviews 2: CD009099.	Include
Dumville, J. C., S. O'Meara, et al. (2012). "Alginate dressings for healing diabetic foot ulcers." Cochrane Database of Systematic Reviews 2: CD009110.	Include
Dynamed. (2013). "Diabetic foot ulcer." from http://search.ebscohost.com/login.aspx?direct=true&db=dme&AN=114270&site=dynamed-live&scope=site .	Exclude – not a systematic review
Dynamed. (2013). "Silver sulfadiazine." from http://search.ebscohost.com/login.aspx?direct=true&db=dme&AN=356476&site=dynamed-live&scope=site .	Exclude – not a systematic review
Dynamed. (2013). "Venous ulcer." from http://search.ebscohost.com/login.aspx?direct=true&db=dme&AN=115837&site=dynamed-live&scope=site .	Exclude – not a systematic review
Dynamed. (2014). "Pressure ulcer." from http://search.ebscohost.com/login.aspx?direct=true&db=dme&AN=116231&site=dynamed-live&scope=site .	Exclude – not a systematic review
Eardley, W. G. P., S. A. Watts, et al. (2012). "Limb Wounding and Antisepsis: Iodine and Chlorhexidine in the Early Management of Extremity Injury." International Journal of Lower Extremity Wounds 11(3): 213-223.	Exclude – this is not a good quality systematic review (limited search), and is not relevant to topic
ECRI. (2013). "TheraBond 3D antimicrobial barrier systems (Choice Therapeutics, Inc.) for wound dressing." from https://members2.ecri.org/Components/Hotline/Documents/IssueFiles/13780.pdf .	Exclude – this is not a systematic review
Ek, A. C., M. Lindgren, et al. (2010) "Silver-releasing dressings in treating chronic wounds (Structured abstract)." Health Technology Assessment Database.	This had to be excluded. It looks very good quality, but the full report is only in Swedish.
European Wound Management Association. (2013). "Antimicrobials and non-healing wounds: evidence, controversies and suggestions." from http://ewma.org/fileadmin/user_upload/EWMA/pdf/EWMA_Projects/Antimicrobial/JWC_EWMA_supplement_NO_CROPS.pdf .	At the data extraction stage – the decision was made to exclude this study. There is insufficient detail to appraise the methodology of the systematic review
Evidence, C. (2011). "Antimicrobial agents (topical)." from	Exclude – we do not

http://clinicalevidence.bmj.com/x/systematic-review/1902/intervention/sr-1902-i23.html .	subscribe to clinical evidence
Fox, C. (2002) "Honey as a dressing for chronic wounds in adults (Provisional abstract)." <i>British Journal of Community Nursing</i> , 530-534.	Exclude- this is an abstract
Fox C (2002). "Honey as a dressing for chronic wounds in adults." <i>British Journal of Community Nursing</i> 7(10): 530-534.	Exclude – following discussion between JK and SHM, the decision was made to exclude this based on methodological quality
Frank, C., I. Bayoumi, et al. (2005). "Approach to infected skin ulcers." <i>Can Fam Physician</i> 51: 1352-1359.	Exclude – this is not a systematic review. It is a review of clinical guidelines
Gajbhiye, V., V. K. Palanirajan, et al. (2009). "Dendrimers as therapeutic agents: A systematic review." <i>Journal of Pharmacy and Pharmacology</i> 61(8): 989-1003.	Exclude – not relevant to the topic
Game, F. L., R. J. Hinchliffe, et al. (2012). "A systematic review of interventions to enhance the healing of chronic ulcers of the foot in diabetes." <i>Diabetes/Metabolism Research Reviews</i> 28 Suppl 1: 119-141.	include
Gottrup, F. and J. Apelqvist (2012). "Present and new techniques and devices in the treatment of DFU: a critical review of evidence." <i>Diabetes Metab Res Rev</i> 28 Suppl 1: 64-71.	Exclude – this is a review of reviews. There is not much description of the methodology either
Greer, N., N. A. Foman, et al. (2013). "Advanced wound care therapies for nonhealing diabetic, venous, and arterial ulcers: a systematic review." <i>Ann Intern Med</i> 159(8): 532-542.	This is a summary of the larger review by VA Health Care (2012) – which has already been included.
Hayes and Inc (2010) "Medihoney dressing (Derma Sciences Inc.) for wound healing (Structured abstract)." <i>Health Technology Assessment Database</i> .	Exclude- unable to access fulltext
Health Quality, O. (2009). "Management of chronic pressure ulcers: an evidence-based analysis." <i>Ont Health Technol Assess Ser</i> 9(3): 1-203.	include
Health Quality Ontario. (2009). "Prevention and management of pressure ulcers." from http://www.hqontario.ca/english/providers/program/mas/tech/reviews/pdf/rev_pup_comp_20090701.pdf .	Exclude – this is two reports. One is relevant – the other does not deal with AWDs
Healthcare Improvement Scotland. (2009). "Prevention and management of pressure ulcers: best practice statement." from http://www.healthcareimprovementscotland.org/our_work/patient_safety/tissue_viability_resources/pressure_ulcer_best_practice.aspx .	Exclude – this is not a systematic review
Healthcare Improvement Scotland. (2013). "Are silver dressings clinically effective and cost effective for the healing of infected wounds and the prevention of wound infection relative to other types of dressing? Technologies scoping report 12." from http://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/shtg_scoping_reports/technologies_scoping_report_12.aspx .	Exclude – this is a scoping report, it is not a systematic review
Hinchliffe, R. J., G. D. Valk, et al. (2008) "A systematic review of the effectiveness of interventions to enhance the healing of chronic ulcers of the foot in diabetes (Structured abstract)." <i>Diabetes Metab Res Rev</i> , S119-s144.	Exclude – this is just an abstract. The actual paper is being included
Hinchliffe, R. J., G. D. Valk, et al. (2008). "A systematic review of the effectiveness of interventions to enhance the healing of chronic ulcers of the foot in diabetes." <i>Diabetes Metab Res Rev</i> 24 Suppl 1: S119-144.	include
Holmes, C., J. S. Wrobel, et al. (2013). "Collagen-based wound dressings	Exclude. Collagen based

Clinical effectiveness – full write-up

for the treatment of diabetes-related foot ulcers: A systematic review." Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 6: 17-29.	dressings is not relevant
Joanne Briggs Institute. (2008). "Pressure ulcers: management of pressure related tissue damage." from http://connect.jbiconnectplus.org/ViewSourceFile.aspx?0=431 .	Exclude –not a systematic review
Jones, K. R. (2009). "Identifying best practices for pressure ulcer management." Journal of Clinical Outcomes Management 16(8): 375-381.	Exclude – not a systematic review
Jull, A. B., N. Walker, et al. (2013). "Honey as a topical treatment for wounds." Cochrane Database of Systematic Reviews 2: CD005083.	Include
Kaltenthaler, E., C. J. Morrell, et al. (1998). "The prevention and treatment of diabetic foot ulcers: A review of clinical effectiveness studies." Journal of Clinical Effectiveness 3(3): 99-104.	Exclude – paper not obtainable
Lazarus, G., M. F. Valle, et al. (2014). "Chronic venous leg ulcer treatment: Future research needs." Wound Repair and Regeneration 22(1): 34-42.	Exclude – this is based on the AHRQ review on chronic venous ulcers, which has already been included
Leaper, D., C. Munter, et al. (2013). "The use of biatain Ag in hard-to-heal venous leg ulcers: meta-analysis of randomised controlled trials." PLoS One 8(7): e67083.	This was originally included, but subsequently excluded due to concerns about methodological quality.
Levin, R. F. (2008). "Translating research evidence for WCET practice: what is the effectiveness of silver impregnated dressings and topical agents for leg ulcers?" World Council of Enterostomal Therapists Journal 28(3): 21-22.	Exclude – paper not obtainable
Levin, R. F. and M. Farren (2010). "Silver dressings and venous leg ulcers." World Council of Enterostomal Therapists Journal 30(3): 41-42.	Exclude – paper not obtainable
Lima, A. F., L. B. Costa, et al. (2011). "Interventions for wound healing among diabetic patients infected with Staphylococcus aureus: a systematic review." Sao Paulo Med J 129(3): 165-170.	Exclude – this is not specifically about AWDs
Lipsky BA, Berendt AR, et al. (2012). "2012 Infectious Diseases of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections." from http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/PDF_Library/2012%20Diabetic%20Foot%20Infections%20Guideline.pdf#search=%22diabetes%22 .	Include – but the sign checklist is not suitable for grading this
Lipsky, B. A., A. R. Berendt, et al. (2004). "Diagnosis and treatment of diabetic foot infections." Clinical Infectious Diseases 39(7): 885-910.	Exclude – there is a more up-to-date version from 2012
Lipsky, B. A. and C. Hoey (2009). "Topical antimicrobial therapy for treating chronic wounds." Clinical Infectious Diseases 49(10): 1541-1549.	Exclude – not a systematic review
Lo, S. F., C. J. Chang, et al. (2009). "The effectiveness of silver-releasing dressings in the management of non-healing chronic wounds: A meta-analysis." Journal of Clinical Nursing 18(5): 716-728.	Include
Lo, S. F., M. Hayter, et al. (2008) "A systematic review of silver-releasing dressings in the management of infected chronic wounds (Structured abstract)." Journal of Clinical Nursing, 1973-1985.	Exclude – this is just the abstract. The full paper is being included
Lo, S. F., M. Hayter, et al. (2008). "A systematic review of silver-releasing dressings in the management of infected chronic wounds." Journal of Clinical Nursing 17(15): 1973-1985.	On trying to extract data, it was apparent that the authors had not presented this from the individual studies (p-values etc). There were other problems with quality- and ultimately, there was no value in including this as there

	were better quality reviews available.
Mao, C. L., A. J. Rivet, et al. (2010). "Update on pressure ulcer management and deep tissue injury." <i>Ann Pharmacother</i> 44(2): 325-332.	Exclude – not a systematic review
Marti-Carvajal, A. J., J. M. Knight-Madden, et al. (2012). "Interventions for treating leg ulcers in people with sickle cell disease: A meta-analysis." <i>West Indian Medical Journal</i> 61: 46.	Exclude – paper not obtainable
Marti-Carvajal Arturo, J., M. Knight-Madden Jennifer, et al. (2012) "Interventions for treating leg ulcers in people with sickle cell disease." <i>Cochrane Database of Systematic Reviews</i> DOI: 10.1002/14651858.CD008394.pub2.	Subsequently decided to exclude – as this patient group is not relevant to the HTA
Mason, J., C. O'Keeffe, et al. (1999). "A systematic review of foot ulcer in patients with type 2 diabetes mellitus. II: Treatment." <i>Diabetic Medicine</i> 16(11): 889-909.	Include
McDonald, A. and P. Lesage (2006). "Palliative management of pressure ulcers and malignant wounds in patients with advanced illness." <i>Journal of Palliative Medicine</i> 9(2): 285-295.	Exclude – this is not a systematic review
Medhi, B., A. Puri, et al. (2008). "Topical application of honey in the treatment of wound healing: A metaanalysis." <i>JK Science</i> 10(4): 166-169.	Exclude – this paper is not methodologically robust
Miller, A. C., R. M. Rashid, et al. (2012). "Silver sulfadiazine for the treatment of partial-thickness burns and venous stasis ulcers." <i>Journal of the American Academy of Dermatology</i> 66(5): e159-e165.	Include
Moore, C. and J. Young (2011) "Effectiveness of silver in wound care treatment." <i>Physical Therapy Reviews</i> , 2011, 16, (3): 201-9	Include
Moore, O. A., L. A. Smith, et al. (2001) "Systematic review of the use of honey as a wound dressing." <i>BMC Complementary and Alternative Medicine</i> .	Exclude – this is not on chronic wounds
Moore, O. A., L. A. Smith, et al. (2001). "Systematic review of the use of honey as a wound dressing." <i>BMC Complementary & Alternative Medicine</i> 1: 2.	Exclude – this is not on chronic wounds
Mwipatayi, B. P., D. Angel, et al. (2004). "The use of honey in chronic leg ulcers: a literature review." <i>Primary Intention: The Australian Journal of Wound Management</i> 12(3): 107.	This was graded as -, therefore was excluded from the study
National Pressure Ulcer Association and European Pressure Ulcer Association. (2008). "Dressings: dressing recommendations for stakeholder review." from http://pressureulcerguidelines.org/therapy/docs/dressings.pdf .	Exclude – this is just recommendations
Nelson, E. A. (2011). "Venous leg ulcers." <i>Clin Evid (Online)</i> 2011.	Exclude – we don't have access to clinical evidence
Nelson EA, O'Meara S, et al. (2006). "A series of systematic reviews to inform a decision analysis for sampling and treating infected diabetic foot ulcers." from http://www.journalslibrary.nihr.ac.uk/_data/assets/pdf_file/0018/64602/FullReport-hta10120.pdf .	Include
Nelson, E. A., S. O'Meara, et al. (2006). "Systematic review of antimicrobial treatments for diabetic foot ulcers." <i>Diabet Med</i> 23(4): 348-359.	Exclude – this is a publication from the HTA by Nelson et al (2006) that is already included
NICE. (2003). "Clinical guidelines for type 2 diabetes: prevention and management of foot problems." from http://www.nice.org.uk/nicemedialive/10934/29242/29242.pdf .	Include
NICE. (2008). "Surgical site infection: prevention and treatment of surgical site infection." from http://www.nice.org.uk/nicemedialive/11743/42378/42378.pdf .	This does not meet the inclusion criteria
NICE (2014). Pressure ulcer guidelines	Include
Noorani, A., N. Rabey, et al. (2010). "Systematic review and meta-analysis of preoperative antisepsis with chlorhexidine versus povidone-	Exclude – this is not chronic wounds

iodine in clean-contaminated surgery." Br J Surg 97(11): 1614-1620.	
O'Meara, S., D. Al-Kurdi, et al. (2014) "Antibiotics and antiseptics for venous leg ulcers." Cochrane Database of Systematic Reviews DOI: 10.1002/14651858.CD003557.pub5.	Include
O'Meara, S., N. Cullum, et al. (2000) "Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration (Structured abstract)." Health Technology Assessment, 1-237.	Include
O'Meara, S. M., N. A. Cullum, et al. (2001). "Systematic review of antimicrobial agents used for chronic wounds." Br J Surg 88(1): 4-21.	Exclude – this is a publication from the HTA already included
Palfreyman, S. J., E. A. Nelson, et al. (2006). "Dressings for healing venous leg ulcers." Cochrane Database of Systematic Reviews(3).	Exclude – this is not about AWDs
Politano, A. D., K. T. Campbell, et al. (2013). "Use of Silver in the Prevention and Treatment of Infections: Silver Review." Surgical Infections 14(1): 8-20.	Exclude – this is not a systematic review
Reddy, M., S. S. Gill, et al. (2008). "Treatment of pressure ulcers: A systematic review." JAMA - Journal of the American Medical Association 300(22): 2647-2662.	Include
Reese A, Willoughby D, et al. (2012). "Revisiting the use of honey for treating chronic wounds." from http://coloradobeekeepers.org/wp-content/uploads/2012/07/Use-of-Honey-for-Chronic-Wounds.pdf .	Exclude – this is not a systematic review
Registered Nurses' Association of Ontario. (2013). "Assessment and management of foot ulcers for people with diabetes." 2nd. from http://rnao.ca/sites/rnao-ca/files/AssessmentManagementFootUlcerDiabetes.pdf .	Excluded – this is mostly an adaptation of other guidelines
Reinar, L. M., L. Forsetlund, et al. (2008). "Interventions for skin changes caused by nerve damage in leprosy." Cochrane Database of Systematic Reviews (3)(CD004833).	Exclude –this is not relevant to the Scottish context
Reinar, L. M., L. Forsetlund, et al. (2013). "Interventions for skin changes caused by nerve damage in leprosy." Sao Paulo Medical Journal 131(3): 210.	Exclude –this is not relevant to the Scottish context
Richmond, N. A., A. D. Maderal, et al. (2013). "Evidence-based management of common chronic lower extremity ulcers." Dermatol Ther 26(3): 187-196.	Exclude –this is not a systematic review
Royal College of Nursing and NICE. (2005). "The management of pressure ulcers in primary and secondary care: a clinical practice guideline." from http://www.nice.org.uk/nicemedia/live/10972/29885/29885.pdf .	Include
Ruttermann, M., A. Maier-Hasselmann, et al. (2013). "Local treatment of chronic wounds: in patients with peripheral vascular disease, chronic venous insufficiency, and diabetes." Dtsch Arztebl Int 110(3): 25-31.	Exclude – full guideline not available in English
Shaw, J., C. M. Hughes, et al. (2007). "The clinical effect of topical phenytoin on wound healing: A systematic review." British Journal of Dermatology 157(5): 997-1004.	Exclude – this is on topical phenytoin, the mechanism of action is 'subject to debate'. Therefore, it is not an antimicrobial
Shiao, C. and H. Liu (2009). "The effect on infected wound of topical silver and silver dressing: a view of evidence-based nursing PC6-37." World Council of Enterostomal Therapists Journal 29(4): 29-30.	Exclude – paper not obtainable
SIGN. (2010). "Management of chronic venous leg ulcers." from http://www.sign.ac.uk/pdf/sign120.pdf .	Include
Swedish Council on Technology Assessment in Healthcare. (2010). "Silver-releasing dressings in treating chronic wounds." from http://www.sbu.se/upload/Publikationer/Content0/3/SilverReleasing_Dressings_Chronic_Wounds_201002.pdf .	Exclude – only the summary and conclusions are available on the website in English
Thomas S. (2008). "Silverlon: a technical review." from http://www.euroband.com/Silverlon_Technical_Review.pdf .	Exclude – not a systematic review

Toy, L. W. and L. Macera (2011). "Evidence-based review of silver dressing use on chronic wounds." <i>J Am Acad Nurse Pract</i> 23(4): 183-192.	Exclude – not a systematic review
Ulbricht, C., J. Armstrong, et al. (2007). "An evidence-based systematic review of aloe vera by the natural standard research collaboration." <i>Journal of Herbal Pharmacotherapy</i> 7(3-4): 279-323.	Exclude – we are not including aloe vera
UpToDate. (2013). "Basic principles of wound management." from http://www.uptodate.com/contents/basic-principles-of-wound-management?detectedLanguage=en&source=search_result&search=dressing&selectedTitle=1%7E150&provider=noProvider#H369372661 .	Exclude – this is a point of care resource, not a systematic review
UpToDate. (2013). "Infectious complications of pressure ulcers." from http://www.uptodate.com/contents/infectious-complications-of-pressure-ulcers?source=search_result&search=antimicrobial+and+dressing&selectedTitle=10%7E150 .	Exclude – this is a point of care resource, not a systematic review
UpToDate. (2013). "Medical management of lower extremity chronic venous disease." from http://www.uptodate.com/contents/medical-management-of-lower-extremity-chronic-venous-disease?source=search_result&search=hydrocolloid+and+dressing&selectedTitle=6%7E132#H30 .	Exclude – this is a point of care resource, not a systematic review
VA Health Care. (2012). "Advanced wound care therapies for non-healing diabetic, venous, and arterial ulcers: a systematic review." from http://www.hsrd.research.va.gov/publications/esp/wound-care-EXEC.pdf .	Include
Vandamme, L., A. Heyneman, et al. (2013). "Honey in modern wound care: a systematic review." <i>Burns</i> 39(8): 1514-1525.	Exclude – the search is too limited, and there are not enough details on the included studies
Vermeulen H, van Hattem JM, et al. (2007). "Topical silver for treating infected wounds." from http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005486.pub2/pdf .	Include
Vermeulen, H., D. T. Ubbink, et al. (2005). "Systematic review of dressings and topical agents for surgical wounds healing by secondary intention." <i>British Journal of Surgery</i> 92(6): 665-672.	Exclude – superseded by Cochrane review by same authors
Vermeulen, H., D. T. Ubbink, et al. (2009). "Dressings and topical agents for surgical wounds healing by secondary intention." <i>Cochrane Database of Systematic Reviews</i> (4)(CD003554).	Include
Vermeulen, H., S. J. Westerbos, et al. (2010) "Benefit and harm of iodine in wound care: a systematic review." <i>Journal of Hospital Infection</i> , 191-199.	Include (the full paper – not the DARE abstract)
Vogler, B. K. and E. Ernst (1999). "Aloe vera: a systematic review of its clinical effectiveness." <i>British Journal of General Practice</i> 49(447): 823-828.	Exclude – we are not including aloe vera
Voigt, J. and V. R. Driver (2012). "Hyaluronic acid and wound healing." <i>Wound Repair and Regeneration</i> 20(3): 317-331.	Exclude – not relevant
Wang, X. T., Y. J. Teng, et al. (2013). "Effectiveness of aloe vera for acute and chronic wounds: A systematic review." <i>Chinese Journal of Evidence-Based Medicine</i> 13(4): 468-473.	Exclude – we are not including aloe vera
Wound Healing Society. (2007). "Wound care guideline of the Wound Healing Society." from http://onlinelibrary.wiley.com/doi/10.1111/wrr.2006.14.issue-6/issuetoc .	Exclude – not a systematic review
Wound Ostomy and Continence Nurses Society (WOCN). (2011). "Guideline for management of wounds inpatients with lower-extremity venous disease." from http://www.guideline.gov/content.aspx?id=38249#Section442 .	Exclude – not a systematic review
Wound Ostomy and Continence Nurses Society (WOCN). (2012). "Guideline for management of wounds in patients with lower-extremity neuropathic disease." from http://www.guideline.gov/content.aspx?id=38248#Section442 .	Exclude – not a systematic review
Yaghoobi R, Kazerouni A, et al. (2013). "Evidence for clinical use of honey in wound healing as an anti-bacterial, anti-inflammatory anti-oxidant and anti-viral agent: a review." <i>Jundishapur Journal of Natural</i>	Exclude – not a systematic review

The following systematic review was also included that was not picked up by the literature search. It was missed as the title is 'topical silver for preventing wound infection'. Studies concerned with the prevention of wound infection were excluded from this HTA. However, on reading the fulltext, it became apparent that other outcomes had been reported on, which are relevant to this HTA: wound healing; adverse events; pain; and health-related quality of life. Wound healing was listed as one of the primary outcomes.

Storm-Versloot MN, Vos CG, Ubbink DT, Vermeulen H. (2010) Topical silver for preventing wound infection. Cochrane database of systematic reviews.

Summary: 37 included systematic reviews, 99 excluded.

Several manufacturers submitted evidence, but only one study was highlighted that had not been picked up in the searches (as it was unpublished). Most of the evidence submitted did not meet the inclusion criteria.

Appendix 3: Quality of included systematic reviews

The quality of the included systematic reviews was graded using the SIGN methodology checklist for systematic reviews and meta-analyses. The following table is a summary of the agreements reached by two health services researchers (JK and SHM). To see the full checklists, completed independently by each researcher for each systematic review, please contact Healthcare Improvement Scotland.

Clinical effectiveness – full write-up

Reference
Clear Question?
2 people select and extract data?
Comprehensive literature search?
Authors state if review is limited by
Included and excluded studies listed?
Characteristics of included studies
Scientific quality of included studies
Quality of included studies assessed
Study results combined
Publication bias assessed?
Conflicts of interest declared?
Overall assessment (++) or + (studies

Clinical effectiveness – full write-up

AHRQ	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	++
Pan-Pacific guidelines (2012)	✓	✗	✓	✓	✓	✓	✓	✓	✓	✗	✓	++
Australian/New Zealand guidelines (2011)	✓	✗	✓	✓	✓	✓	✓	✓	✓	✗	✓	++
Bardy	✓	✓	✓	✓	✗	✓	✓	✓	✓	✗	✗	+
KCE	✓	✗	✓	✓	✗	✓	✓	✓	✓	CS	✓	+
Bergin	✓	✓	✓	✓	✓	CS	CS	CS	CS	CS	✓	++
Bradley	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	++
Carter	✓	✗	✗	✓	✗	✓	✓	✓	CS	✓	✓	+
Chaby	✓	✗	✓	✓	✗	✓	✓	✓	✓	✗	✓	+
Chambers	✓	✓	✓	✓	✗	✓	✓	✓	CS	✗	✗	+
NPUAP & EPUAP	✓	✓	✓	✓	✗	✓	✓	✓	✓	✗	✓	++
Dumville (2012a)	✓	✓	✓	✓	✓	✓	✓	✓	✓	CS	✓	++
Dumville (2012b)	✓	✓	✓	✓	✓	✓	✓	✓	✓	CS	✓	++
Game	✓	✓	✓	✓	✗	✓	✓	✓	✓	✗	✓	+
Ontario Health Technology	✓	CS	✓	✓	✗	✓	✓	✓	✓	✗	✓	++
Hinchliffe	✓	✗	✓	✓	✗	✓	✓	✓	✓	✗	✓	++
Jull	✓	✓	✓	✓	✓	✓	✓	✓	✓	CS	✓	++
Lo	✓	✓	✓	✓	✓	✓	✓	CS	✓	✓	✗	+
Mason	✓	✓	CS	✓	✗	✓	✓	✓	✓	CS	✓	+
Miller	✓	CS	✓	✓	✗	✓	✓	✓	✓	CS	✓	+
Moore	✓	✓	✓	✓	✗	✗	✓	✓	✓	CS	✗	+
Nelson	✓	✓	✓	✓	✓	✓	✓	✓	✓	CS	✓	++
NICE 2003	✓	✓	✓	✓	✓	✓	✓	✓	✓	CS	✓	++
NICE 2014	✓	✓	✓	✓	✓	✓	✓	✓	✓	CS	✓	++
O'Meara 2000	✓	✓	✓	✓	✓	✓	✓	✓	✓	CS	✓	++
O'Meara 2014	✓	✓	✓	✓	✓	✓	✓	✓	✓	CS	✓	++
Reddy	✓	✓	✓	✓	✗	✓	✓	✓	✓	CS	✓	++
RCON & NICE	✓	✓	✓	✓	✓	✓	✓	✓	✓	CS	✓	++
SIGN	✓	✓	✓	✓	✗	✓	✓	✓	✓	CS	✓	++
Storm-Versloot	✓	✓	✓	✓	✓	✓	✓	✓	✓	CS	✓	++
VA Health Care	✓	CS	CS	✓	✗	✓	✓	✓	✓	CS	✓	+
Vermeulen 2004	✓	✓	✓	✓	✓	✓	✓	✓	✓	CS	✓	++
Vermeulen 2007	✓	✓	✓	✓	✓	✓	✓	✓	✓	CS	✓	++
Vermeulen (2010)	✓	✓	✓	✓	✗	✓	✓	✓	CS	CS	✓	+

✓: yes ✗: no CS: cannot say ++: high quality +: acceptable quality

Appendix 4: Evidence tables

Evidence Table 1.1: Venous Ulcers – Iodine – Systematic Reviews and Meta-analyses

Reference	Study Objectives	Selection Criteria	Outcomes	Main results (of relevance)
O'Meara et al 2014¹¹ Quality score: ++	To determine the effects of systemic antibiotics and topical antibiotics and antiseptics on the healing of venous ulcers.	<p>RCTs recruiting people with venous leg ulceration, evaluating at least one systemic antibiotic, topical antibiotic or topical antiseptic that reported an objective assessment of wound healing (eg time to complete healing, frequency of complete healing, change in ulcer surface area).</p> <p>All definitions of venous ulcers were accepted. Selection was not restricted to those with a certain wound status at baseline (ie colonised or infected wounds).</p>	<p>The primary outcome was wound healing. All measures of wound healing were included, but the following were regarded as the best: Time to complete wound healing; proportion of ulcers healing during follow-up; change (or rate of change) in wound size. Secondary outcomes included: changes in signs and symptoms of clinical infection; changes in bacterial flora; development of bacterial resistance, ulcer recurrence rate, all adverse events; participant satisfaction; Health-related QoL; costs.</p>	<p>Authors' summary of results</p> <p>Cadexomer iodine: Eleven RCTs encompassing 962 participants (Skog 1983; Ormiston 1985; Harcup 1986; Lindsay 1986; Steele 1986; Kero 1987; Moss 1987; Laudanska 1988; Holloway 1989; Hansson 1998; Miller 2010). Comparisons were: standard care (7 RCTs); hydrocolloid dressing (1 RCT); paraffin gauze dressing (1 RCT); dextranomer (2 RCTs); and silver-impregnated dressings (1 RCT). All RCTs had either a high or unclear risk of bias. 1 RCT recruited only those with infected ulcers (comparator standard care), 1 recruited participants with infection or critical colonisation (comparator was silver-impregnated dressings) and one excluded participants with infected ulcers (comparators were hydrocolloid and paraffin gauze dressings). The other RCTs did not provide a clear report of baseline ulcer infection status (although the data suggests that those with ulcer infection would have been eligible for inclusion). Healing outcomes were better for cadexomer iodine when compared with standard care (RR 2.17; 95% CI 1.30 to 3.60; $I^2=0\%$; Fixed effect model used), however, the incidence of adverse effects was greater for those receiving cadexomer iodine (RR 4.59; 95% CI 1.40 to 15.05; Fixed effect model used). Other comparisons did not detect differences in terms of healing. The outcomes of bacterial growth and patient acceptability of treatment were similar for cadexomer iodine and silver impregnated dressings. Data on other outcomes (including those relating to wound infection) were limited¹¹.</p> <p>Povidone-iodine: Six RCTs encompassing 639 participants (Groenewald 1981; Smith 1992; Ishibashi 1996; Casoni 2002; Fumal 2002; Kuznetsov 2009). Comparisons were: dextranomer (1 RCT); growth factor (1 RCT); hydrocolloid dressing (3 RCTs); paraffin gauze dressing (1 RCT); and moist or foam dressing given according to ulcer status (1 RCT). All RCTs had either a high or unclear risk of bias. Participants with infected ulcers were excluded from 1 RCT, but ulcer infection status was unclear from the others. Overall, there was no evidence from healing data to suggest a difference between treatment groups (estimates either indicated no difference, or were</p>

Reference	Study Objectives	Selection Criteria	Outcomes	Main results (of relevance)
				<p>likely to be unreliable)¹¹.</p> <p>Authors' conclusions: 'In terms of topical preparations, some evidence supports the use of cadexomer iodine...Further good quality research is required before definitive conclusions can be drawn about the effectiveness of povidone-iodine...' These conclusions are reasonable, based on the evidence and analyses presented.</p>
<p>AHRQ 2014¹</p> <p>Quality score: ++</p>	<p>'For patients with chronic venous leg ulcers, what are the benefits and harms of using dressings that regulate wound moisture with or without active chemical, enzymatic, biologic, or antimicrobial component in conjunction with compression systems when compared with using solely compression systems?'</p>	<p>Included: human studies; patients with chronic venous leg ulcers defined as 'presence of an active ulcer for 6 weeks or more with evidence or earlier stages of venous disease such as varicose veins, edema, pigmentation, and venous eczema'; patients with or without comorbidities; at least 4-week follow-up. Excluded: arterial ulcers (and other chronic ulcer types); studies with mixed populations (ie not just venous ulcers); ulcers complicated by</p>	<p>Included studies that evaluated one of the following outcomes: Intermediate outcomes (wound healing rates for a minimum of 4 weeks time, pain, quality of wound bed, relationship of intermediate healing rates to complete healing); Final outcomes (time to achieve complete wound closure, proportion of ulcers healed at 16 weeks, rate of wound recurrence after 1 year, development of new wounds at different anatomical locations, QoL, mortality, functional status); Adverse events.</p>	<p>Included three RCTs on cadexomer iodine products (Ormiston 1985; Holloway 1989; Hansson 1998). Comparisons were: standard care (2 RCTs); hydrocolloid dressing/paraffin gauze dressing (1 RCT). All three of these were already reported on the O'Meara 2014 review. The results presented concur with the results presented by O'Meara 2014.</p> <p>The conclusions of the AHRQ report, in relation to the use of iodine in venous ulcers are: 'Antimicrobial dressings, such as those that contained cadexomer iodine, provided advantage in improved healing (moderate strength of evidence...' and 'Cochrane collaboration reviews have addressed the use of wound dressings and have found no data to support superiority of specific dressings. Our review of cadexomer iodine-containing dressings is consistent with that described in the Cochrane review, which indicated modest improvements in wound healing.' (NB The Cochrane review being referred to has since been removed from the Cochrane Library – as newer reviews, such as O'Meara 2014, are now available).</p>

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Reference	Study Objectives	Selection Criteria	Outcomes	Main results (of relevance)
		active infection (eg cellulitis, fasciitis).		
<p>Vermeulen et al 2010¹⁵</p> <p>Quality score: +</p>	<p>A systematic review of RCTs which investigated the possible beneficial and harmful clinical effects of iodine in the treatment of all kinds of (contaminated) wounds.</p>	<p>RCTs that reported on a local wound care product containing iodine in patients with any kind of (more or less contaminated) wound. Any concentration or manufacturer of iodine as well as any type of control treatment was allowed.</p>	<p>Primary outcomes were bacterial load or wound infection and wound healing. Secondary outcomes were adverse events, costs and length of hospital stay.</p>	<p>Included 8 RCTs of relevance (Skog 1983; Ormiston 1985; Laudanska 1988; Holloway 1989; Hansson 1998; Moss 1987; Groenewald 1981; Smith 1992). In 6, the intervention was cadexomer iodine products. Comparisons were: standard care (4 RCTs); hydrocolloid dressing/paraffin gauze dressing (1 RCT); Dextranomer (1 RCT). In 2, the intervention was povidone iodine products. Comparisons were: dextranomer (1 RCT); Hydrocolloid dressing/non-adherent paraffin gauze (1 RCT). All 8 RCTs were already reported on in the O'Meara 2014 review. The results presented concur with the results presented by O'Meara 2014. The authors conclusions relate to all wound types: 'Based on the available evidence from clinical trials, iodine is an effective antiseptic agent that shows neither the purported harmful effects nor a delay of the wound-healing process, particularly in chronic and burn wounds. The antiseptic effect of iodine is not inferior to that of other (antiseptic) agents and does impair wound healing.' and 'There is a need for high quality RCTs addressing the effectiveness of iodine to treat or prevent wound infection, in order to clearly determine the place of iodine in present-day wound care.' These conclusions do not contradict the more recent reviews (O'Meara 2014 and AHRQ 2014).</p>

Reference	Study Objectives	Selection Criteria	Outcomes	Main results (of relevance)
<p>O'Meara et al 2000¹²</p> <p>Quality score: ++</p>	<p>To assess the clinical- and cost-effectiveness of</p> <p>-i) Prevention and treatment strategies for diabetic foot ulcers and</p> <p>-ii) Systemic and topical antimicrobial agents in the prevention and healing of chronic wounds.</p>	<p>Included randomised and non-randomised trials with a concurrent treatment group; systemic or topical antimicrobials for chronic wounds;</p>	<p>Included studies had to report objective measures of outcome such as:</p> <ul style="list-style-type: none"> -any objective measure of wound healing -ulcer recurrence rate -side-effects <p>Studies reporting solely microbiological outcomes were excluded.</p>	<p>This included a CCT (n=21; Pierard-Franchimont 1997), which was methodologically flawed (small study and analysis not ITT). It compared venous leg ulcers treated with povidone iodine and hydrocolloid dressing to hydrocolloid dressing alone. It does not provide meaningful data, and so does not alter the conclusions of the more recent reviews.</p>
<p>Bradley et al 1999³</p> <p>Quality score: ++</p>	<p>This review evaluates the evidence for effectiveness and cost-effectiveness of dressings and topical preparations in pressure sores, leg ulcers and surgical wounds healing by secondary intention.</p>	<p>Included published or unpublished RCTs, which assessed the effectiveness of a dressing or topical agent in the treatment of pressure sores, leg ulcers, sinuses and surgical wounds healing by secondary intention. Where a particular dressings was not evaluated by an RCT, prospective controlled trials</p>	<p>Studies were only included if they reported either the proportion of the wounds healing within a time period or the percentage or absolute change in wound area.</p>	<p>Included one study of relevance, which compared cadexomer iodine to hydrocolloid dressings/paraffin gauze dressings (Hansson 1998). The RCT was already reported on in the O'Meara 2014 review, and the results presented concur.</p> <p>The authors did not present any conclusions specific to cadexomer iodine. They stated: 'There is little evidence to indicate which dressings or topical agents are the most effective in the treatment of chronic wounds...In the treatment of venous ulcers, low adherent dressing are as effective as hydrocolloid dressing beneath compression bandaging.'</p> <p>This does not alter the conclusions of the more recent reviews (eg O'Meara and AHRQ 2014).</p>

Reference	Study Objectives	Selection Criteria	Outcomes	Main results (of relevance)
		were included.		
<p>Additional information: Two guidelines (SIGN and Australian/New Zealand clinical practice guidelines) based on a systematic review were also identified, but did not include any data not already identified^{18, 19}. The SIGN guideline considered an earlier version of the O’Meara 2014 review (the 2010 version, which included largely the same body of evidence), and stated that: ‘There is insufficient consistent evidence on which to base a recommendation for either cadexomer iodine or povidone iodine.’ Based on the same version of the O’Meara review (the 2010 version), the Australian/New Zealand guidelines give a grade B recommendation: ‘Cadexomer iodine could be used to promote healing in VLU’s when there is known increased microbial burden.’ The Guidelines also detail the following caution and practice points: ‘Caution: Unless the patient has a hypersensitivity to iodine, cadexomer iodine is usually not associated with significant adverse events. Cadexomer iodine ointments and impregnated dressings should not be used in patients with a history of Hashimoto’s thyroiditis, Graves’ disease, lithium medications, non-toxic nodular goitre or thyroid disorders, or impaired renal function, in children or in pregnant or lactating women. Risk of systemic absorption increases when cadexomer iodine products are used on larger wounds or for prolonged periods. In some trials, patients treated with topical cadexomer iodine have experienced local burning sensations; however, this was not reported in the trials included in this review. Practice points: - Cadexomer iodine should not be used for longer than three months continuously. - Cadexomer iodine dressings should only be used when there is evidence of heavy bacterial load/local wound infection and these dressings should be stopped once local infection has been controlled. - Cadexomer iodine should not be covered with povidone iodine-soaked gauze/tulle gras as this practice results in the dumping of iodine, increasing toxicity.’ An additional practice point is detailed under a section on ‘other topical antimicrobials’: - <i>‘When using povidone iodine 10% solution it should be used at full concentration and rinsed off after two to five minutes.’</i></p>				

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Evidence table 1.2 Venous Ulcers – Honey – Systematic Reviews and Meta-analyses

Reference	Study Objectives	Selection Criteria	Outcomes	Main results (of relevance)
<p>O'Meara <i>et al</i> 2014¹¹</p> <p>Quality score: ++</p>	<p>To determine the effects of systemic antibiotics and topical antibiotics and antiseptics on the healing of venous ulcers.</p>	<p>RCTs recruiting people with venous leg ulceration, evaluating at least one systemic antibiotic, topical antibiotic or topical antiseptic that reported an objective assessment of wound healing (eg time to complete healing, frequency of complete healing, change in ulcer surface area).</p> <p>All definitions of venous ulcers were accepted. Selection was not restricted to those with a certain wound status at baseline (ie colonised or infected wounds).</p>	<p>The primary outcome was wound healing. All measures of wound healing were included, but the following were regarded as the best: Time to complete wound healing; proportion of ulcers healing during follow-up; change (or rate of change) in wound size. Secondary outcomes included: changes in signs and symptoms of clinical infection; changes in bacterial flora; development of bacterial resistance, ulcer recurrence rate, all adverse events; participant satisfaction, Health-related QoL; costs.</p>	<p>Two RCTs recruiting 476 participants evaluated honey-based preparations (Gethin 2009; Jull 2008). One RCT compared a honey-based topical application with hydrogel, and was rated as having a high risk of bias. The other compared a honey-impregnated dressing with non-honey dressings applied according to the clinician's choice (low risk of bias).</p> <p>Pooled data suggested no difference between groups for the outcomes of complete healing at 12 weeks (RR 1.15; 95% CI 0.96 to 1.38); and incidence of ulcer infection during the trial period (RR 0.71 95% CI 0.49 to 1.04).</p> <p>The RCT evaluating topical applications excluded participants with clinically infected wounds at baseline, but reported that some wounds were colonised with MRSA; no difference was detected between the groups for eradication of MRSA at 4 weeks. The RCT comparing honey-impregnated dressings with non-honey dressings reported no difference between groups for time to healing and change in health-related quality of life scores. However, the use of honey was associated with more adverse events. The same trial conducted a rigorous cost-effectiveness analysis in parallel with the RCT and concluded that honey was unlikely to be cost effective. This trial did not provide information about baseline ulcer infection status.</p> <p>The authors concluded that 'current evidence does not support the use of honey-based products.' This is a reasonable conclusion based on the evidence and analyses presented.</p>

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<p>AHRQ et al 2014¹</p> <p>Quality score: ++</p>	<p>‘For patients with chronic venous leg ulcers, what are the benefits and harms of using dressings that regulate wound moisture with or without active chemical, enzymatic, biologic, or antimicrobial component in conjunction with compression systems when compared with using solely compression systems?’</p>	<p>Included: human studies; patients with chronic venous leg ulcers defined as ‘presence of an active ulcer for 6 weeks or more with evidence or earlier stages of venous disease such as varicose veins, edema, pigmentation, and venous eczema’; patients with or without comorbidities; at least 4-week follow-up. Excluded: arterial ulcers (and other chronic ulcer types); studies with mixed populations (ie not just venous ulcers); ulcers complicated by active infection (eg cellulitis, fasciitis).</p>	<p>Included studies that evaluated one of the following outcomes: Intermediate outcomes (wound healing rates for a minimum of 4 weeks time, pain, quality of wound bed, relationship of intermediate healing rates to complete healing); Final outcomes (time to achieve complete wound closure, proportion of ulcers healed at 16 weeks, rate of wound recurrence after 1 year, development of new wounds at different anatomical locations, QoL, mortality, functional status); Adverse events.</p>	<p>Included one study of relevance (Gethin 2009), which was already included in the O’Meara 2014 review. The results presented concur with the results presented by O’Meara 2014.</p> <p>The conclusions are made for AWDs together, so it is not possible to draw out the conclusions relating to honey. However, it does not alter the conclusions of the O’Meara 2014 review.</p>
<p>Jull et al 2013⁷</p> <p>Quality score: ++</p>	<p>To determine whether honey increases the rate of healing in acute wounds (eg burns and lacerations)</p>	<p>Included RCTs and quasi-randomised trials that evaluated honey as a treatment for any</p>	<p>Primary outcomes: time to complete wound healing; proportion of participants with completely healed</p>	<p>For venous leg ulcers, the same data and analyses were presented as those in O’Meara 2014. The authors’ conclusion supports O’Meara 2014: ‘Honey dressings do not increase rates of healing significantly in venous leg ulcers when used as an adjuvant to compression.’</p>

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	and chronic wounds (eg skin ulcers, infected surgical wounds)	sort of acute or chronic wound.	wounds. Secondary outcomes: incidence of adverse events; length of hospital stay; change in wound size; incidence of infection; cost; quality of life.	
Bardy et al 2008² Quality score: +	To synthesise the evidence to assess whether honey has a role in health care; to identify if this evidence applies to cancer care; to make recommendations for practice.	Included: RCTs, CCTs, case studies, systematic reviews, any age group. Excluded: single patient case studies, biochemical studies, abstracts and trials in progress.	All outcomes reported in the literature appear to have been extracted.	Included two single-armed descriptive studies, and one non-randomised comparative study on the use of honey in venous ulcers. Methodologically, all studies were rated as having a 'low score'. They are of insufficient quality to add to the data from the more recent reviews.
<p>Two guidelines (SIGN and Australia/New Zealand clinical practice guidelines) based on a systematic review were also identified, but did not include any data not already identified^{18, 19}.</p> <p>The SIGN guideline considered the Jull 2013 review and gives a grade B recommendation:</p> <p>'Honey dressings are not recommended in the routine treatment of patients with venous leg ulcers'</p> <p>Based on the Jull 2013 review, the Australian and New Zealand guidelines give a grade A recommendation:</p> <p>'Honey offers no benefits over standard care in promoting healing in VLUs.'</p> <p>The Australian and New Zealand guideline also lists the following caution and good practice points:</p> <p>'Caution Treating VLUs with honey has been reported to lead to ulcer pain, deterioration of the ulcer and an increase in wound exudate. An SR found that adverse events (for example, ulcer pain, deterioration of the VLU and increased exudate) were more likely to occur in VLUs treated with honey compared with those</p>				

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treated with hydrogel or standard dressings and there was no difference in infection rates.

Practice points

For trained health professionals or patients who choose to use honey despite the current lack of evidence for an effect in healing VLUs:

- Use honey products according to the manufacturer's instructions
- The honey should be specifically indicated for application to wounds
- Manuka honey should be rated UMF (Unique Manuka Factor)+12 or above for topical dressing products
- Use gamma-irradiated honey as other sterilising processes will destroy the UMF in the honey.

Honey may increase exudates levels thus warranting more frequent dressing changes.'

Evidence table 1.3 Venous Ulcers – Silver – systematic reviews and meta-analyses

Reference	Study Objectives	Selection criteria	Outcomes	Main Results (of relevance)
<p>O'Meara et al 2014¹¹</p> <p>Quality score: ++</p>	<p>To determine the effects of systemic antibiotics and topical antibiotics and antiseptics on the healing of venous ulcers.</p>	<p>RCTs recruiting people with venous leg ulceration, evaluating at least one systemic antibiotic, topical antibiotic or topical antiseptic that reported an objective assessment of wound healing (eg time to complete healing, frequency of complete healing, change in ulcer surface area).</p> <p>All definitions of venous ulcers were accepted. Selection was not restricted to those with a certain wound status at baseline (ie colonised or infected wounds).</p>	<p>The primary outcome was wound healing. All measures of wound healing were included, but the following were regarded as the best: Time to complete wound healing; proportion of ulcers healing during follow-up; change (or rate of change) in wound size. Secondary outcomes: changes in signs and symptoms of clinical infection; changes in bacterial flora;</p>	<p>Included 12 RCTs (Chaloner 2004; Bishop 1992; Blair 1988; Fumal 2002; Wunderlich 1991; Jorgensen 2005; Meaume 2005; Munter 2006; Lazareth 2008; Dimakakos 2009; Michaels 2009; Kerihuel 2010) that evaluated silver products for the treatment of venous ulcers. Also included an additional RCT (Miller 2010) that compared cadexomer iodine to a silver impregnated dressing (this is summarised in the venous ulcers – iodine section of the report).</p> <p>Authors' summary of results: 'Twelve RCTs recruiting 1514 participants evaluated the effects of silver-based preparations. Silver sulphadiazine cream was compared with: usual care (one RCT); placebo (one RCT); growth factor (one RCT); and non-adherent dressing (one RCT). Silver impregnated dressings were compared with alternative silver dressings (one RCT) and non-antimicrobial dressings (eight RCTs). There was no difference between treatment groups for most healing outcomes; some short-term surrogate measures of healing suggested benefit of silver dressing compared with non-antimicrobial dressing, whilst others suggested no between-group difference. Data on secondary outcomes suggested no difference between silver-impregnated dressing and non-antimicrobial dressing for adverse effects and changes in health-related quality of life scores. A rigorous cost-effectiveness analysis conducted alongside one RCT concluded that silver-impregnated dressings were unlikely to be cost-effective when compared with non-antimicrobial dressings. Two RCTs were large; one had low risk of bias and the other was unclear. The remainder were small with mostly unclear risk of bias. The ulcer infection status at baseline varied across trials.'</p> <p>Authors' conclusion: 'Current evidence does not support the use of honey- or silver-based products.' This is a reasonable conclusion based on the evidence and analyses presented.</p>

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Reference	Study Objectives	Selection criteria	Outcomes	Main Results (of relevance)
			development of bacterial resistance, ulcer recurrence rate, all adverse events; participant satisfaction, Health-related QoL; costs.	
<p>AHRQ 2014¹ Quality score: ++</p>	<p>'For patients with chronic venous leg ulcers, what are the benefits and harms of using dressings that regulate wound moisture with or without active chemical, enzymatic, biologic, or antimicrobial component in conjunction with</p>	<p>Included: human studies; patients with chronic venous leg ulcers defined as 'presence of an active ulcer for 6 weeks or more with evidence or earlier stages of venous disease such as varicose veins, edema, pigmentation, and venous eczema'; patients with or without comorbidities; at least 4-week follow-up.</p>	<p>Included studies that evaluated one of the following outcomes: Intermediate outcomes (wound healing rates for a minimum of 4 weeks time, pain, quality of wound bed, relationship of intermediate healing rates to complete healing); Final</p>	<p>Included two RCTs of relevance to this section of the HTA (Harding 2012; Michaels 2009).</p> <p>The Michaels 2009 RCT was included in the O'Meara 2014 review, but the study by Harding 2012 was not. It compared an ionic silver dressing to a lipidocolloid silver dressing. Reported no significant difference in healing rates between groups (38.24% SD 40.63 versus 32.47% SD 48.93).</p> <p>The other RCTs included by O'Meara 2014 were excluded by the AHRQ 2014. However, the overall conclusions of the reviews concur: '...silver dressings did not improve wound healing as compared with nonsilver dressings. One RCT comparing silver dressings with non-silver dressings did not show any improvement in terms of the wound healing rate.'</p>

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Reference	Study Objectives	Selection criteria	Outcomes	Main Results (of relevance)
	compression systems when compared with using solely compression systems?’	Excluded: arterial ulcers (and other chronic ulcer types); studies with mixed populations (ie not just venous ulcers); ulcers complicated by active infection (eg cellulitis, fasciitis).	outcomes (time to achieve complete wound closure, proportion of ulcers healed at 16 weeks, rate of wound recurrence after 1 year, development of new wounds at different anatomical locations, QoL, mortality, functional status); Adverse events.	
Miller et al 2012⁹ Quality score: +	In patients with either partial-thickness burns or venous stasis ulcers, does the use of topical silver sulfadiazine (SSD)	Included: any age; patients with partial thickness burns or venous stasis ulcers; randomised to either SSD or placebo/saline-soaked gauze/paraffin	Mortality, wound healing, re-epithelialisation, infection rates, or pain scores.	Included one RCT (Bishop 1992), that was also reported in O’Meara 2014. The results presented concur with the results presented by O’Meara 2014. The authors also reported on two prospective non-randomised studies, which assessed venous stasis ulcer healing and infection rates among patients treated with topical SSD: <ul style="list-style-type: none"> - Bender 1982: 64 ambulatory patients were treated with weekly administration of topical SSD and monitored for 6 weeks. After 6 weeks, 52 ulcers were completely healed, seven showed incomplete epithelialisation, three showed no change and two worsened. The two participants whose ulcers worsened were noted to be noncompliant with the treatment regimen. No infections were noted. - Ouvry 1989: Assessed ulcer healing and infection rates in 71 ambulatory

Reference	Study Objectives	Selection criteria	Outcomes	Main Results (of relevance)
	<p>compared with nonantibiotic dressings improve mortality, wound healing, re-epithelialisation, infection rates, or pain scores?</p>	<p>gauze/ sterile dry dressing/nonantibiotic moist dressing. Excluded: studies in which patients received both intervention and control; studies comparing SSD with other interventions known to have antimicrobial properties; studies assessing chronic ulceration not caused by venous insufficiency.</p>		<p>patients with venous stasis ulcers. SSD was applied once a week. By day 45, 64 patients (70 ulcers) were followed. The authors found that by day 45, 40 ulcers had completely healed, 25 remained but were healing favourably, 4 were unchanged, and 1 worsened. Whereas 29 ulcers showed evidence of infection on day 0, only two ulcers showed evidence of infection by day 45. Two patients were intolerant to treatment, and 7 required treatment modification.</p> <p>The authors concluded that ‘There is limited evidence assessing the role of topical treatment of stasis dermatitis ulcers with SSD cream. The available evidence shows no clear benefit in wound healing.’ This supports the conclusion of the more recent reviews (O’Meara 2014 and AHRQ 2014).</p>
<p>VA Health Care 2012¹³ Quality score: +</p>	<p>KQ2: ‘What are the efficacy and harms of therapies for venous ulcers? Is efficacy dependent on ancillary therapies? Does efficacy</p>	<p>Search was limited to: RCTs from 1995-2012; human subjects over 18 years old; and published in English. Several advanced wound care therapies were included, but the only one of relevance to this</p>	<p>Primary outcome was the percentage of ulcers healed at study completion. Secondary outcomes included ulcer infected during treatment,</p>	<p>Included six RCTs on the use of silver products in treating venous ulcers, encompassing 771 patients (Harding 2012; Bishop 1992; Blair 1988; Dimakakos 2009; Michaels 2009; Belcaro 2010).</p> <p>Results summarised by the authors as follows: ‘One good quality and one fair quality study compared silver cream/ointment to standard care. One fair quality study compared silver cream to copper cream or to placebo copper cream. Overall, no statistically significant difference in ulcer healing was observed with silver therapy (range 21% to 63%) versus standard care or placebo (range 3% to 80%) with evidence of large heterogeneity (RR 1.65; 95% CI 0.54 to 5.03; I²=84%). Compared to copper-based cream, the silver-based cream significantly improved healed ulcers (21% versus 0%, p=0.01 with fisher’s exact test).</p>

Reference	Study Objectives	Selection criteria	Outcomes	Main Results (of relevance)
	<p>differ according to patient demographics, comorbid conditions, treatment compliance, or activity level?</p>	<p>HTA was 'silver products'.</p>	<p>ulcer recurrence, time to recurrence, pain and adverse events.</p>	<p>Results were mixed for two studies, both fair quality, that compared a silver dressing to a similar non-silver dressing. One of the trials (n=42) found a higher rate of healing in the silver dressing group compared to the control dressing at 9 weeks (81% versus 48%; ARD 33%; 95% CI 6% to 61%); a larger trial (n=204) found no difference (60% versus 57%).</p> <p>One study (n=281) comparing two silver dressings also found no difference (17% versus 15%).</p> <p>Pooled data from two studies of silver versus non-silver dressings show a non-significant outcome and evidence of heterogeneity (RR 1.27; 95% CI 0.80 to 2.01; I²=67%).</p> <p>Two studies, of fair quality, reported time to ulcer healing when a silver dressing was compared to a non-silver dressing. One found no significant difference; one did not report significance.</p> <p>No differences were observed between silver-based therapies and other treatments or standard care for other outcomes or adverse events. In one study, female gender (p=0.01), and smaller ulcer size (up to 3cm diameter, p=0.008) were significantly related to ulcer healing. In another study, a significant difference in healing between treatment and control was observed for shallow ulcers (p=0.04) but not for deep ulcers (p=0.29).'</p> <p>Four of these six studies were included in O'Meara 2014; and two were included in AHRQ 2014. One additional RCT was identified, which was not included in either the AHRQ 2014 or O'Meara 2014 review (it was not mentioned in O'Meara, and listed as an exclusion by AHRQ as the intervention was not considered relevant). It compared silver ointment to standard wound care, but did not alter the overall conclusions.</p> <p>Authors' conclusion: 'silver creams improved healing in two studies (one comparing silver cream to standard care and one comparing silver cream to copper-based cream), while three studies of silver dressings found mixed results (significant benefit in one study of silver dressing compared to non-silver dressing and no differences in two studies with non-silver or alternative silver dressings as the comparators). Strength of evidence was low for these outcomes...' These conclusions are reasonable based on the evidence presented, and support the conclusions of O'Meara 2014 and AHRQ 2014.</p>

Reference	Study Objectives	Selection criteria	Outcomes	Main Results (of relevance)
				This review included three further studies under the heading of 'mixed ulcer types' (Fumal 2002; Jorgensen 2005; Miller 2010). All of these studies were included in the O'Meara 2014 review.
Moore et al 2011 ¹⁰ Quality score: +	A systematic review of the literature examining the effectiveness of silver in wound care treatment	Inclusions: At least one group must have received a topical solution, cream, foam or impregnated dressing containing silver; various types of wounds (including venous leg ulcers); any age; RCTs.	Authors stated that studies should measure at least one of the following outcomes: wound healing; resolution of exudate, odour and inflammation; pain and comfort; cost-effectiveness; safety; patients' quality of life.	This review included one RCT (Jorgensen 2005), which was already considered by O'Meara 2014. The scope of this review included all wound types, and the conclusions for venous ulcers cannot be pulled out. However, the results do not add to what has already been reported on by the more recent reviews (O'Meara 2014 and AHRQ 2014). The overall conclusions are more positive than O'Meara 2014 and AHRQ 2014: 'Although the effectiveness and safety of silver implemented in wound care treatment appears to be promising, the small sample size of research articles and RCTs on this population and treatment method support the need for additional research to further investigate the effectiveness of silver dressings and topical agents in wound care treatment.'
Carter et al 2010 ⁴ Quality score: +	To conduct a systematic review of silver dressings and treatments in wounds focusing on healing outcome parameters; to	Included any type of leg ulcer or wound (but those focusing on burns or other parts of the body were excluded). Did not include studies that compared one type of silver	Studies eligible for inclusion had to report at least one outcome related to wound healing. Studies that	Includes eight studies that consider use of silver products in venous ulcers (Bishop 1992; Blair 1998; Fumal 2002; Wunderlich 1991; Jorgensen 2005; Meaume 2005; Munter 2006; Lazareth 2008). All were included in the O'Meara 2014 review. The results presented concur with the results presented by O'Meara 2014. The review included meta-analyses, but the data is not applicable to this HTA, as studies evaluating different wound types were combined together. The scope of this review included all wound types, and the conclusions for venous ulcers cannot be pulled out. However, the results do not add to what is already presented in

Reference	Study Objectives	Selection criteria	Outcomes	Main Results (of relevance)
	attempt meta-analyses for these parameters.	dressing to another. Limited to RCTs.	focused solely on safety, diagnostics or infection were excluded.	more recent reviews (O'Meara 2014 and AHRQ 2014). The conclusion relates to all wound types: 'Our results strengthen the proposition that silver-impregnated dressings improve the short-term healing of wounds and ulcers. However, because of lack of trial data with longer follow-up times there is no evidence that silver-impregnated dressings are effective using complete wound-healing criteria.'
Storm-Versloot et al 2010¹⁶ Quality score: ++	To establish the effects of silver-containing wound dressings and topical agents in preventing wound infection and healing of wounds.	Included: RCTs (published and unpublished); adults aged over 18 years; any care setting; uninfected wounds of any aetiology.	Primary outcomes: wound infection rate; wound healing. Secondary outcomes: included adverse events, pain, HRQoL, and patient satisfaction.	This review was not picked up in the initial search for this HTA. This is because the title is 'topical silver for preventing wound infection' – and prevention of infection is excluded from this review. However, the primary outcomes included wound healing, and so this review meets the inclusion criteria. It included one study of relevance to this section of the HTA, which was already included in the O'Meara 2014 review (Wunderlich 1991). The results presented concur with the results presented in O'Meara 2014. The overall conclusions are not specific to venous ulcers, but do not contradict the conclusions of O'Meara 2014 or AHRQ 2014.
Lo et al 2009⁸ Quality score: +	To examine the efficacy of silver-releasing dressings in the management of non-healing chronic wounds	Limited to English or Chinese RCTs. Included studies in which participants all had wounds that exhibited delayed healing, or were critically colonised or infected. Acute wounds (eg burns) were	Reported outcomes were classified as physical, psychological or economic.	Included three RCTs (Jogensen 2005; Meaume 2005; Munter 2006) already identified by O'Meara (2014), and a further RCT that was not eligible for inclusion in O'Meara (2014): Romanelli 2005: This was a non-blinded RCT (n=109), which compared a foam dressing to a silver-impregnated foam dressing in people with critically colonised (but not clinically infected) chronic venous or mixed arterial/venous ulcers. This trial was not eligible for inclusion in the O'Meara 2014 review as the primary outcome did not relate to wound healing, but was on health-related quality of life (measured using odour, leakage, comfort during wear and pain). Lo 2009 stated that the RCT did not include a sample size estimation and that the analysis was not intention-to-treat. Lo 2009 reported that the results of the study favour treatment with silver. However, the detail presented is insufficient, and so no conclusions can be drawn from this.

Reference	Study Objectives	Selection criteria	Outcomes	Main Results (of relevance)
		excluded.		<p>Lo 2009 reported on some meta-analyses, however, it is not clear what studies were included in these. As the scope included all wound types – and the meta-analyses potentially include a mixture of wound types – these are not relevant to this HTA.</p> <p>Lo (2009) concluded that silver dressings were effective in promoting wound healing and improving patients' quality of life, but stated that more RCTs were needed. This conclusion is more positive than the other reviews, probably because Lo (2009) scored the included RCTs more generously than the other reviews.</p>
<p>Chaby et al 2007⁵</p> <p>Quality score: +</p>	To critically review the literature on the efficacy of modern dressings in healing chronic wounds and acute wounds by secondary intention	<p>Inclusions: studies that assessed one of the outcomes listed in the next column; publications in English or French; acute and chronic wounds.</p> <p>Exclusions: case reports and case series; studies on deep partial- and full-thickness burns.</p>	The endpoints for selecting studies were the rate of complete healing, time to complete healing, rate of change in wound area, and general performance criteria (eg pain, ease of use).	<p>This included two RCTs already identified by the O'Meara 2014 review (Jorgensen 2005; Meaume 2005).</p> <p>The scope of this review includes all wound types, and the conclusions for venous ulcers cannot be pulled out. However, the results do not add to what is already presented in more recent reviews (O'Meara 2014 and AHRQ 2014).</p>
<p>Chambers et al 2007⁶</p> <p>Quality score: +</p>	A systematic review of RCTs looking at the effects of silver-based dressings and topical agents	Inclusions: RCTs (published or unpublished); any language; patients with venous, arterial or mixed etiology leg	Included RCTs that reported on ulcer healing.	<p>Included nine studies, eight of which were included in the O'Meara 2014 review (Chaloner 2004; Bishop 1992; Blair 1988; Fumal 2002; Wunderlich 1991; Jorgensen 2005; Meaume 2005; Munter 2006). The results presented concur with the results presented by O'Meara 2014.</p> <p>One additional study was included (Ivins, 2005). This was excluded by the O'Meara 2014 review as it is not an RCT (random allocation of only some patients from one treatment</p>

Reference	Study Objectives	Selection criteria	Outcomes	Main Results (of relevance)
	on leg ulcer healing	ulcers; and reporting on ulcer healing. Studies that included patients with an infection before and after recruitment were eligible		<p>group of a previously reported trial to receive either the treatment or the comparator for a further 4 weeks). This study reported no significant difference between treatments (a silver foam dressing and a hydrocellular foam dressing) in mean relative reduction in ulcer area, nor in proportion of ulcers healed. This does not add to the evidence already presented.</p> <p>Chambers 2007 included meta-analyses:</p> <ul style="list-style-type: none"> - Pooled data from two studies (Bishop 1992; Blair 1988), which reported the proportion of participants completely healed. This did not detect a statistically significant difference in healing between leg ulcers treated with silver sulfadiazine and placebo/non-adherent dressing (RR 1.8; 95% CI 0.19 to 17.11; p=0.63) - Two studies were pooled that compared the effects of silver-based dressings with dressings not containing silver on the proportion of ulcers healed during the study period (Wunderlich 1991; Jorgensen 2005). The results indicated no statistically significant difference in healing with silver (RR 1.66; 95% CI 0.68 to 4.05; p=0.27). <p>The authors' conclusions support the conclusions of more recent reviews (O'Meara 2014 and AHRQ 2014): 'the current evidence base on the use of these silver-based products on leg ulcers is limited, both in terms of the quantity available and the quality of the evidence. This review highlights the need for further, more rigorous research to be carried out...'</p>
<p>Vermeulen et al 2007¹⁴</p> <p>Quality score: ++</p>	To evaluate the effects on wound healing of topical silver and silver dressings in the treatment of contaminated	Included: RCTs; trial authors definitions of infection were all accepted; any contaminated or infected wound of any aetiology.	Primary outcomes of interest: An objective measure of healing rate (eg time to complete healing, rate of	<p>Included three studies in total, all of which were included in the O'Meara 2014 review (Jorgensen 2005; Meaume 2005; Munter 2006). The results presented concur with the results presented by O'Meara 2014.</p> <p>The studies could not be combined in a meta-analysis.</p> <p>The results are summarised as follows: 'The data from these trials show that silver-containing foam dressings did not significantly increase complete ulcer healing as compared with standard foam dressings or best local practice after up to four weeks of</p>

Reference	Study Objectives	Selection criteria	Outcomes	Main Results (of relevance)
	and infected acute or chronic wounds		healing). Trials were to be included only if the primary outcome was reported. Secondary outcomes included: days of wound infection, adverse effects, pain and quality of life.	<p>follow-up, although a greater reduction of ulcer size was observed with the silver containing foam. The use of antibiotics was assessed in two trials, but no significant differences were found. Data on pain, patient satisfaction, length of hospital stay, and costs were limited and showed no differences. Leakage occurred significantly less frequently in patients with leg ulcers and chronic wounds treated with a silver dressing than with a standard foam dressing or best local practice in one trial.'</p> <p>The authors conclude that: 'There is insufficient evidence to recommend the use of silver-containing dressing or topical agents for treatment of infected or chronic wounds.' This concurs with the conclusions of the more recent reviews (O'Meara 2014; AHRQ 2014).</p>
<p>O'Meara et al 2000¹²</p> <p>Quality score: ++</p>	<p>To assess the clinical- and cost-effectiveness of</p> <ul style="list-style-type: none"> -Prevention and treatment strategies for diabetic foot ulcers and -Systemic and topical antimicrobial agents in the prevention and healing of 	<p>Included randomised and non-randomised trials with a concurrent treatment group; systemic or topical antimicrobials for chronic wounds;</p>	<p>Included studies reporting on objective measures of outcome such as:</p> <ul style="list-style-type: none"> -any objective measure of wound healing -ulcer recurrence rate -side-effects <p>Studies reporting</p>	<p>Included three RCTs of relevance to this section of the HTA (Bishop 1992; Blair 1988; Wunderlich 1991). These were all included in the O'Meara 2014 review. The results presented concur with the results presented by O'Meara 2014.</p> <p>The authors conclude for venous leg ulcers that 'results were conflicting for silver-based products (silver sulphadiazine and silver-impregnated activated charcoal dressing).' This supports the conclusions of more recent reviews (O'Meara 2014 and AHRQ 2014).</p>

Reference	Study Objectives	Selection criteria	Outcomes	Main Results (of relevance)
	chronic wounds.		solely microbiological outcomes were excluded.	
Bradley et al 1999³ Quality score: ++	This review evaluates the evidence for effectiveness and cost-effectiveness of dressings and topical preparations in pressure sores, leg ulcers and surgical wounds healing by secondary intention.	Included published or unpublished RCTs, which assessed the effectiveness of a dressing or topical agent in the treatment of pressure sores, leg ulcers, sinuses and surgical wounds healing by secondary intention. Where a particular dressings was not evaluated by an RCT, prospective controlled trials were included.	Studies were only included if they reported either the proportion of the wounds healing within a time period or the percentage or absolute change in wound area.	Included two RCTs of relevance to this section of the HTA (Bishop 1992; Wunderlich 1991). The authors did not present any conclusions specific to silver. They stated: ‘There is little evidence to indicate which dressings or topical agents are the most effective in the treatment of chronic wounds...In the treatment of venous ulcers, low adherent dressing are as effective as hydrocolloid dressing beneath compression bandaging.’ This does not alter the conclusions of the more recent reviews (O’Meara 2014 and AHRQ 2014).
<p>Additional Information Two guidelines (SIGN and Australia/New Zealand clinical practice guidelines) based on a systematic review were also identified, but did not include any data not already identified^{18, 19}. The SIGN guideline considered the Vermeulen 2007 review, and the trial by Michaels 2009 (included in several of the reviews, including O’Meara 2014) and gives a grade A recommendation:</p>				

Reference	Study Objectives	Selection criteria	Outcomes	Main Results (of relevance)
<p>'Silver dressings are not recommended in the routine treatment of patients with venous leg ulcers.'</p> <p>Based on the Chambers (2007) and O'Meara (2000) review, and two primary studies (Dimakakos 2009; Miller 2010 – included in some of the reviews described above) The Australian and New Zealand guidelines give a grade C recommendation:</p> <p>'Silver products offer no benefit over standard care in reducing the healing time of VLUs.'</p> <p>The Australian and New Zealand guidelines also list the following caution and practice points:</p> <p>'Caution Potential renal toxicity should be considered when using topical silver agents for extended periods (for example, greater than four weeks) on large wound beds. The risk appears to be low but caution is warranted. As with other antimicrobial therapies there is a risk of bacterial resistance with extended use of silver products.</p> <p>Practice point For trained health professionals of patients who chose to use silver, despite the current lack of high-level evidence for an effect in healing VLUs</p> <ul style="list-style-type: none"> - Use silver products as directed by the manufacturer - There is insufficient evidence to indicate any one specific silver product is superior to others <p>Colloidal silver, either internally or topically, is not recommended.'</p> <p>A low quality RCT was also identified (Kucharzewski 2013; n=58)¹⁷.</p> <p>Paatients: had chronic venous ulceration, who had previously been treated with no positive result for at least 2 years in regional dermatological and surgical ambulatory care clinics. The authors stated that no treatment of superficial reflux had been done before application of the dressings.</p> <p>Intervention: a membranous dressing with silver ions (Textus Bioactiv® by Biocell GmbH Germany)</p> <p>Comparison: a hydrocolloid dressing Unna's boot. Dressings were changed every 7 days.</p> <p><i>All patients received compression therapy, but the silver group received elastic compression therapy and the hydrocolloid group non-elastic compression.</i></p> <p>Results: The authors reported that all ulcers healed after seven weeks in the group treated with Textus Bioactiv® dressings; and in the group treated with the hydrocolloid dressing Unna's boot it took 16 weeks before all ulcers healed.</p>				

Evidence table 1.4: Venous Ulcers – ‘other’ AWDs – Systematic Reviews and Meta-analyses

Reference	Study Objectives	Selection Criteria	Outcomes	Main results (of relevance)
<p>O’Meara et al 2014¹¹</p> <p>Quality score: ++</p>	<p>To determine the effects of systemic antibiotics and topical antibiotics and antiseptics on the healing of venous ulcers.</p>	<p>RCTs recruiting people with venous leg ulceration, evaluating at least one systemic antibiotic, topical antibiotic or topical antiseptic that reported an objective assessment of wound healing (eg time to complete healing, frequency of complete healing, change in ulcer surface area).</p> <p>All definitions of venous ulcers were accepted. Selection was not restricted to those with a certain wound status at baseline (ie colonised or infected wounds).</p>	<p>The primary outcome was wound healing. All measures of wound healing were included, but the following were regarded as the best: Time to complete wound healing; proportion of ulcers healing during follow-up; change (or rate of change) in wound size. Secondary outcomes included: changes in signs and symptoms of clinical infection; changes in bacterial flora; development of bacterial resistance, ulcer recurrence rate, all adverse events; participant satisfaction, Health-related</p>	<p>Included nine RCTs on ‘other’ AWDs. Only one of these related to an AWD that is listed in section A5.3 of the BNF:</p> <ul style="list-style-type: none"> - ‘One RCT was identified, which recruited 17 participants, each with two leg ulcers, who acted as his or her own controls; the ulcer was the unit of randomisation (Fumal 2002c). Application of 5% chlorhexidine digluconate solution in addition to usual care was compared with usual care alone (defined as hydrocolloid dressing and a ‘compressive bandage’ – no further details were provided). Treatment duration was six weeks. Ulcers were not clinically infected at baseline. The overall risk of bias was unclear. Median time to healing was reported as 14 weeks (range 7 to 17 weeks) for the group receiving chlorhexidine plus usual care, and 15 weeks (range 7 to 19 weeks) for those allocated to usual care alone. The trial authors described the between-group difference as not statistically significant, but the p value was not presented.’ <p>For the remaining RCTs on AWDs not listed in section A5.3 of the BNF, the following summaries have been taken from the O’Meara review:</p> <p><u>Summary of evidence for peroxide-based preparations</u> Four RCTs (Beitner 1985a, Beitner 1985b, Belcaro 2003, Belcaro 2007) recruiting 72 participants evaluated the effects of peroxide-based topical preparations. Comparator interventions included saline dressing (two RCTs) and placebo (two RCTs). Healing estimates were based on surrogate measures (change in wound area). The data suggested that benzoyl peroxide in both 10% and 20% concentrations were more effective than saline dressing. The 10% preparation was associated with adverse effects (versus none for saline). No adverse effects were reported in either group for the comparison of 20% benzoyl peroxide versus saline. The baseline ulcer infection status was not described for either of the benzoyl peroxide RCTs. Hydrogen peroxide 1% cream resulted in greater wound area reduction when compared with a placebo cream; there were no data on</p>

			QoL; costs.	<p>secondary outcomes. For both benozyl peroxide RCTs it is likely that patients with infected ulcers were excluded. All of the RCTs were small and had either high or unclear risk of bias.</p> <p><u>Summary of evidence for miscellaneous topical preparations (this included the trial on chlorhexidine)</u></p> <p>Five RCTs recruiting 590 participants evaluated the effect of topical applications: topical antibiotics (three RCTs) and topical antiseptics (two RCTs). All had unclear risk of bias.</p> <p>The comparisons involving topical antibiotics were: chloramphenicol-containing ointment versus enzymatic wound cleanser (one RCT); framycetin sulphate-containing ointment versus enzymatic wound cleanser (one RCT); chloramphenicol-containing ointment versus framycetin sulphate-containing ointment (one RCT); mupirocin versus vehicle (one RCT); and topical antibiotics according to cultures and sensitivities versus herbal ointment (one RCT). More participants healed at four weeks using an enzymatic wound cleanser when compared with a chloramphenicol-containing ointment. No other between-group differences were found in terms of healing, or for secondary outcomes (adverse effects, bacterial eradication). Two RCTs were small. One trial excluded patients with baseline ulcer infection, but in the other two there was no information about baseline ulcer infection status. No difference was found in terms of time to healing for chlorhexidine added to usual care versus usual care alone (one small RCT); patients with infected ulcers were excluded. Another trial reported that the number of responsive ulcers (defined as >20% reduction in ulcer surface area) was greater, and also that patient-reported satisfaction was greater, with ethacridine lactate treatment when compared with placebo. For the same trial, adverse effects were reported as similar between groups. There was no information about baseline ulcer infection status.</p> <p><u>Authors' conclusions:</u> 'Current evidence does not support the routine use of honey- and silver-based preparations. Further good quality research is required before definitive conclusions can be made about the effectiveness of systemic antibiotics and topical preparations such as povidone-iodine, peroxide-based preparations, chloramphenicol, framycetin sulphate, mupirocin, topical antibiotics given according to antibiogram, ethacridine lactate, and chlorhexidine in healing venous leg ulceration.'</p>
AHRQ 2014¹	'For patients with chronic venous leg	Included: human studies; patients with chronic	Included studies that evaluated one of the	Included no studies on 'other' AWDs that are listed in section A5.3 of BNF67.

Clinical effectiveness – full write-up

<p>Quality score: ++</p>	<p>ulcers, what are the benefits and harms of using dressings that regulate wound moisture with or without active chemical, enzymatic, biologic, or antimicrobial component in conjunction with compression systems when compared with using solely compression systems?’</p>	<p>venous leg ulcers defined as ‘presence of an active ulcer for 6 weeks or more with evidence or earlier stages of venous disease such as varicose veins, edema, pigmentation, and venous eczema’; patients with or without comorbidities; at least 4-week follow-up. Excluded: arterial ulcers (and other chronic ulcer types); studies with mixed populations (ie not just venous ulcers); ulcers complicated by active infection (eg cellulitis, fasciitis).</p>	<p>following outcomes: Intermediate outcomes (wound healing rates for a minimum of 4 weeks time, pain, quality of wound bed, relationship of intermediate healing rates to complete healing); Final outcomes (time to achieve complete wound closure, proportion of ulcers healed at 16 weeks, rate of wound recurrence after 1 year, development of new wounds at different anatomical locations, QoL, mortality, functional status); Adverse events.</p>	
<p>Additional information: The SIGN guidelines on ‘Management of chronic venous leg ulcers’¹⁹ state that there is insufficient evidence on which to base a recommendation for mupirocin and peroxide. This is based on the evidence presented in the O’Meara 2014 review, described above (although the SIGN guidelines report on an earlier version of the review). Australian and New Zealand guidelines¹⁸ report that other topical antimicrobials include: benzoyl peroxide, chlorhexidine, dimethyl sulphoxide powder, ethacridine lactate, hydrogen peroxide and mupirocin. The evidence they report on comes largely from an earlier version of the O’Meara 2014 review. They make the following recommendations:</p> <ul style="list-style-type: none"> - <i>‘Topical antimicrobial agents should not be used in the standard care of VLU healing with no signs of infection (Grade B)’</i> - <i>‘There may be a role for judicious use of topical antimicrobials when there is known or suspected increased microbial burden (consensus based recommendation)’</i> 				

They detail the following cautions:

- *'The Expert Working Committee does not recommend the use of hydrogen peroxide in wound management. Deaths have been reported as a result of irrigation of closed cavity wounds with hydrogen peroxide.'*
- *'Skin sensitivity may result when products are used for extended periods.'*
- *'Toxic effects of antimicrobial/antiseptic solutions on fibroblasts and macrophages in vitro are well documented.'*
- *'Acetic acid has been associated with pain at the ulcer site and skin irritation at higher concentrations. There is a risk of acidosis when use for extended periods over very large wound surfaces. It has been demonstrated that there is no dilution of acetic acid that is toxic to bacteria without being toxic to fibroblasts.'*

They detail the following practice points:

- *'Topical antiseptic solutions should generally only be used for treatment of topical contamination or minor skin infections and should be avoided on clean, healing ulcers.'*
- *'The length of treatment with topical antimicrobials should be determined by the response of the VLU and the patient.'*
- *'Acetic acid at 3% concentration may be considered for treatment as a topical wash to reduce the burden of pseudomonas where other topical interventions and unavailable or have been ineffective.'*

Another section of the Australian and New Zealand guideline relates to topical antibiotics. The guideline authors report that they did not identify any systematic reviews or RCTs on the effectiveness of topical antibiotics for treating VLUs. They make the following consensus-based recommendation:

- *'Use topical antibiotics judiciously in managing VLUs as there is a concern that their use is associated with antibiotic resistance and sensitivities.'*

They give the following caution: *'Skin sensitivity may result from topical products used for extended periods.'*

They give the following practice point: *'Topical metronidazole may be used for a short period to reduce odour related to anaerobes.'*

A search of the primary evidence highlighted one additional RCT by Vanscheidt 2012²¹. The study is of lower quality, with the randomisation process not being clearly described, no blinding and an analysis that is not intention to treat. The main elements of the study are described below using the PICO framework:

Participants: 126 people with a locally infected chronic venous ulcer at any location below the knee joint; male or female; aged 18 and over. Had to meet any of the following criteria: confirmed diagnosis of CVI; duration of the target ulcer of more than 4 weeks and less than 2 years; surface area of more than 2 and less than 20 cm²; presence of at least two of nine infection criteria.

Intervention: Topical antiseptic agent OHP that is established under the trade name octenisept® (Mayr & Schuelke GmbH, Norderstedt, Germany) (n=60); treatment was for up to 12 weeks.

Comparison: Ringer solution as the standard wound cleansing (n=66); treatment was for up to 12 weeks.

Outcomes: Primary endpoint was time to complete wound closure.

Results: 'The median time to complete ulcer healing was comparable between the OHP and Ringer solution groups (92 days versus 87 days; p=0.952), without being influenced by wound size or duration of the target ulcer (p-values 0.947/0.978). In patients treated with OHP, fewer adverse events (AEs) were observed compared with the Ringer group (17% versus 29% of patients reported 20 versus 30 AEs).'

Evidence table 2.1: Arterial Ulcers – Systematic Reviews and Meta-analyses

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
<p>VA Health Care¹³</p> <p>Quality score: +</p>	<p>What are the efficacy and harms of therapies for arterial ulcers? Is efficacy dependent on ancillary therapies? Does efficacy differ according to patient demographic, comorbid conditions, treatment compliance, or activity level?</p>	<p>Search was limited to: RCTs from 1995-2012; human subjects over 18 years old; and published in English. Several advanced wound care therapies were included, but the only one of relevance to this HTA was 'silver products'.</p>	<p>Primary outcome was the percentage of ulcers healed at study completion. Secondary outcomes included ulcer infected during treatment, ulcer recurrence, time to recurrence, pain and adverse events.</p>	<p>Did not identify any RCTs solely on arterial ulcers. Included three RCTs on patients with mixed ulcer types (Fumal 2002; Jorgensen 2005; Miller 2010). These were all included in the O'Meara 2014 review included in the venous ulcer section.</p> <p>Results summarised as follows: 'Three fair quality studies reported on the use of silver products for patients with mixed ulcer types. One included 129 patients with chronic venous or mixed venous/arterial ulcers of at least 2cm² (with no decrease in area of greater than 0.5cm in the past 4 weeks), ABI of 0.65 or higher, and signs of infection...Patients were treated with a silver-releasing foam dressing or a similar dressing without silver. The second study included 281 patients with venous and mixed ulcers with a diameter of 15cm or less. All patients had clinical signs of infection and an ABI of 0.6 or higher...One group received a silver-based dressing and the other group received an iodine-based dressing...The third study enrolled 17 patients with at least 2 chronic leg ulcers. Patients with infection, diabetes, or arterial occlusion were excluded...Two similar looking ulcers on each patient were randomly assigned to treatment with silver sulfadiazine cream or standard care for 6 weeks.</p> <p>The two studies reporting healed ulcers found no significant difference between a silver-releasing foam dressing and a similar dressing without silver (9.6% versus 8.8% at 4 weeks) or a silver dressing and an iodine dressing (64% versus 63% at 12 weeks). The study comparing silver and iodine dressings also reported no difference in days to healing. The third study did not report healed ulcers but did report a non-significant difference in time to healing (15 weeks for silver-treated ulcers, 16 weeks for standard care). One study looked at subgroups. There was no difference in the number of ulcers healed with silver or iodine dressings for 'young' ulcers (less than 12 weeks), 'old' ulcers (more than 12 weeks), 'small' ulcers (3.6cm² or smaller), or 'large' ulcers (greater than 3.6 cm²). Decrease in pain during the treatment period and quality of life were found to be similar in patients treated with silver-releasing foam dressing compared to non-silver foam dressing. Two studies reported adverse events. The percentages of patients with adverse events (silver dressing versus iodine dressing) or device-related adverse events (silver-releasing foam dressing versus non-silver foam dressing) did not differ.'</p>

Evidence table 3.1 Foot ulcers in people with diabetes – Iodine – systematic reviews and meta-analyses

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
<p>Jull <i>et al</i> 2013⁷</p> <p>Quality score: ++</p>	<p>To determine whether honey increases the rate of healing in acute wounds (eg burns, lacerations) and chronic wounds (eg skin ulcers, infected surgical wounds).</p>	<p>Included: RCTs; quasi-randomised trials; participants of any age; any type of acute or chronic wound; topical application of honey applied by any means alone or in combination with other dressings or components</p>	<p>Primary outcomes: time to complete healing; proportion of participants with completely healed wounds. Secondary outcomes: incidence of adverse events; length of hospital stay; change in wound size; incidence of infection; cost; quality of life.</p>	<p>This review evaluated the use of honey in the treatment of wounds, but included one study of relevance to this section, as it compared honey to povidone-iodine:</p> <p>Shukrimi 2008: This RCT (n=30) from Malaysia was rated as having an unclear risk of bias by Jull 2013. It included people with non-insulin dependent diabetes mellitus with Wagner grade 2 ulcers who were admitted for surgery and met the following parameters: age 35-65; transcutaneous oxygen tension >30mmHg and serum albumin level of >35g/dl. One group were randomised to treatment with honey applied daily, and the other to povidone-iodine soaked gauze applied daily. Treatment followed from surgical debridement and treatment with antibiotics. Treatment was continued until the wound closed. The mean time to heal in days was not significantly different between the groups (14.4 for the honey group versus 15.4 in the povidone-iodine group; standard deviations not given).</p> <p>The conclusions of Jull 2013 relate to the use of honey in all wound types – not iodine. Therefore, the conclusions are not relevant to this section of the review.</p>
<p>Dumville <i>et al</i> 2012b²²</p> <p>Quality score: ++</p>	<p>To compare the effects of hydrocolloid wound dressings with no dressing or alternative dressings on the healing of foot ulcers in people with diabetes</p>	<p>Included: published or unpublished RCTs irrespective of publication status or language; people with type 1 or 2 diabetes with an open foot ulcer; any definition of</p>	<p>Primary outcomes: time to ulcer healing and number of ulcers healed within a specific time period. Secondary outcomes: HRQoL; amputations; adverse events; cost; ulcer</p>	<p>This review evaluated the use of hydrocolloid dressings in the treatment of foot ulcers in people with diabetes, but included one study of relevance to this section:</p> <p>Jeffcoate 2009: This RCT (n=317) from the UK was rated as having a low risk of bias by Dumville 2012. It had three arms, comparing an iodine-impregnated dressing (Inadine[®], Johnson & Johnson) and fibrous-hydrocolloid dressings (Aquacel[®], ConvaTec) with a non-adherent dressing, viscose filament gauze (Johnson & Johnson). It included adults with type 1 or 2 diabetes who had a foot ulcer present for at least 6 weeks. The exclusion criteria included patients with infection of the bone or soft tissue infection requiring systemic antibiotics, or patients living more than 10 miles from the clinic. Dressings were changed daily, on alternate days, or three times a week according to the need and/or availability of professional staff. Ulcers, once healed, were following bi-weekly</p>

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		<p>diabetic foot ulcer; studies in which the primary intervention was any type of hydrocolloid wound dressing.</p> <p>Excluded: trials which included people with a number of different wound aetiologies.</p>	<p>recurrence; change in ulcer area.</p>	<p>for 4 weeks. Ulcers that recurred within the 4 weeks were classed as unhealed. All healed ulcers assessed at 12 weeks. Patients with persistent ulcers were assessed by 24 weeks, and withdrawn from the intervention.</p> <p>There was quite large losses to follow-up (withdrawals; n=88).</p> <p>Main results (only presented for Aquacel versus Inadine):</p> <p>Aquacel versus Inadine</p> <p>primary outcome: ulcer healing</p> <ul style="list-style-type: none"> - No statistically significant difference in the number of ulcers healed in Inadine group (48/108; 44%) compared with Aquacel group (46/103; 45%); RR 1.00 (95% CI 0.74 to 1.34) - Mean time to healing was reported as 127.8 days (SD 54.2) for Inadine group and 125.8 days (SD 55.9) for Aquacel group. <p>Secondary outcomes: HRQoL, amputations, adverse events, cost, ulcer recurrence</p> <ul style="list-style-type: none"> - 1 amputation in Inadine group versus 4 in Aquacel group - The cost of healing an additional ulcer was £848 for Inadine group - Both groups had similar numbers of serious (37 in Inadine group vs 28 in Aquacel group) and non-serious (239 in Inadine group vs 227 in Aquacel group) adverse events. - No difference in quality of life or in recurrence rates - No evidence to suggest that iodine reduces incidence of secondary infection (Aquacel group n=54; Inadine group n=71) <p>Dumville 2012 excluded the RCT by Apelqvist 1996 (included in some other reviews) as 'no single, identifiable dressing type evaluated'.</p> <p>The conclusions of Dumville 2012 relate to the use of hydrocolloid dressings for foot ulcers in people with diabetes – not iodine dressings. Therefore, the conclusions are not relevant to this section of the review.</p>
<p>Game et al 2012²³</p> <p>Quality score: +</p>	<p>A systematic review of interventions to enhance healing of chronic ulcers of the foot in diabetes.</p>	<p>Included prospective and retrospective controlled studies published in any language, that evaluated the interventions for</p>	<p>Primary outcomes used were: healing, time to healing, reduction in ulcer area or amputation.</p>	<p>Included the RCTs by Jeffcoate 2009 and Shukrimi 2008.</p> <p>The results reported from these primary studies concur with the results reported by Jull 2013 and Dumville 2012.</p> <p>The conclusions of Game 2012 are: 'with the exception of HBOT and, possibly, negative pressure wound therapy, there is little published evidence to justify the use of newer therapies.'</p>

Clinical effectiveness – full write-up

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
		the treatment of chronic foot ulcers in adults with type 1 or 2 diabetes. Studies were included “if they concerned agents or interventions that may accelerate the healing process.”		
Vermeulen et al 2010¹⁵ Quality score: +	A systematic review of RCTs which investigated the possible beneficial and harmful clinical effects of iodine in the treatment of all kinds of (contaminated) wound.	RCTs that reported on a local wound care product containing iodine in patients with any kind of (more or less contaminated) wounds. Any concentration or manufacturer of iodine as well as any type of control treatment was allowed.	Primary endpoints were bacterial load or wound infection and wound healing. Secondary endpoints were adverse events, costs and length of hospital stay.	Included one RCT of relevance (Apelqvist 1996). This was described most completely in the review by Nelson 2006 (see below). The results reported by Vermeulen 2010 concur with the results presented in Nelson 2006. The authors conclusions relate to all wound types: 'Based on the available evidence from clinical trials, iodine is an effective antiseptic agent that shows neither the purported harmful effects nor a delay of the wound-healing process, particularly in chronic and burn wounds. The antiseptic effect of iodine is not inferior to that of other (antiseptic) agents and does impair wound healing.' and 'There is a need for high quality RCTs addressing the effectiveness of iodine to treat or prevent wound infection, in order to clearly determine the place of iodine in present-day wound care.'
Hinchliffe et al 2008²⁴ Quality	To identify effectiveness of interventions to enhance	Included: prospective and retrospective controlled studies; any	Included studies that assessed the effect of interventions on healing, time to	Included one RCT of relevance (Apelqvist 1996). This was described most completely in the review by Nelson 2006 (see below). The results reported by Hinchliffe 2008 concur with the results presented in Nelson 2006. The authors' conclusions relate to a variety of interventions. With regards to AWDs, they

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
score: ++	healing of chronic foot ulcers in diabetes.	language; adults with type 1 or 2 diabetes with foot ulcers;	healing, reduction in ulcer area or amputation.	say: 'No data were found to justify the use of any other topically applied product or dressing, including those with antiseptic properties.'
Nelson et al 2006²⁶ Quality score: ++	-to review systematically the evidence on the performance of diagnostic tests used to identify infection in DFUs and of interventions to treat infected DFUs. -to use estimates derived from the systematic reviews to create a decision analytic model in order to identify the most effective method of diagnosing and treating infection and	RCTs or CCTs of the effect of microbiological analysis or antimicrobial agents in people with DFUs.	The authors listed several outcome measures that studies must report on to be eligible for inclusion. They state that the most important relate to mortality, amputation and wound healing. Others included: pain, ulcer recurrence, bacterial profile of ulcer, acquisition of resistant organisms, relationship between ulcer healing and bacteriology.	Included one lower-quality RCT of relevance. Apelqvist 1996: This is an open RCT from Sweden (n=41), conducted over a 12-week period. It included people with Wagner grade 1 or 2 diabetic foot ulcers. The study compared topically applied cadexomer iodine ointment (Iodosorb)(G1) with a standard topical treatment consisting of gentamicin, streptokinase or dry saline gauze (G2). All patients were offered oral antibiotics if necessary, along with saline dressing, a paraffin gauze and special footwear where appropriate. Main results: Withdrawals: G1: 4/22 (18%); G2: 2/19 (11%) The analysis was based on treatment completers only (ie not ITT). <ul style="list-style-type: none"> • Surgical revision performed: G1 3/17 (18%) G2 5/18 (28%) RR 0.64; 95% CI 0.19 to 2.07 • Complete healing G1 5/17 (29%) G2 2/18 (11%) RR 2.65; 95% CI 0.68 to 10.89 • Wound area reduction of at least >50% or improvement in Wagner grade G1 12/17 (71%) G2 13/18 (72%) RR 0.98; 95% CI 0.64 to 1.49 Adverse effects: the authors reported that none were documented. Authors' conclusions: These are not limited to topical iodine and iodine impregnated dressings, but are for any topical preparation: 'There is no strong evidence for recommending any particular antimicrobial agents for the prevention of amputation, resolution of infection or ulcer healing. Results suggest that growth factor (G-CSF) was less costly than standard care, cadexomer iodine dressings may be less costly than standard care (daily dressings) and A/S was less costly than A/C. These results are from small, single trials and need replication. Topical pexiganan cream

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
	to identify areas of research that would lead to large reductions in clinical uncertainty.			may be as effective as oral antibiotic treatment with ofloxacin.'
Mason et al 1999²⁵ Quality score: +	To assess the value of treatments for foot ulcers in patients with type 2 diabetes mellitus	“Studies were examined if they specifically addressed an intervention for patients with diabetic foot ulcers. In each area considered, the best available evidence was used and where randomised, controlled trials were available, studies of lesser design were excluded unless they added a further dimension to the understanding.”	Not specifically stated, but all outcomes reported in the studies seem to have been included.	<p>Included one RCT of relevance (Apelqvist 1996). This was described most completely in the review by Nelson 2006 (see above). The results reported by Mason 1999 concur with the results presented in Nelson 2006.</p> <p>The authors' conclusions relate to all treatments: 'Given the prevalence, morbidity and healthcare costs of diabetic foot disease, it is surprising that available trials provide inadequate evidence to improve upon current empirically based treatment approaches. Substantial effort and resources should be deployed in order to investigate both new and existing treatments in a co-ordinated, systematic and consistent manner, so that a proper evidence base can be established for this important disease area.'</p>
<p>Additional Information One NICE guideline²⁷ was identified, which included the RCT by Apelqvist (1996). This included two D grade recommendations:</p> <p>'In the absence of strong evidence of clinical and cost effectiveness, health care professionals should use wound dressings that best match clinical experience, patient preference, and the site of the wound and consider the cost of the dressings.'</p>				

Clinical effectiveness – full write-up

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
<p>and 'Wounds should be closely monitored and dressings changed regularly.'</p> <p>This is based on the following evidence statement: 'There is insufficient evidence to support the effectiveness of any type of protective dressing, or topical application, over any other for treating diabetic foot ulcers (1b).'</p>				

Evidence table 3.2 Foot ulcers in people with diabetes – Honey – systematic reviews and meta-analyses

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
<p>Jull et al 2013⁷</p> <p>Quality score: ++</p>	<p>To determine whether honey increases the rate of healing in acute wounds (eg burns, lacerations) and chronic wounds (eg skin ulcers, infected surgical wounds).</p>	<p>Included: RCTs; quasi-randomised trials; participants of any age; any type of acute or chronic wound; topical application of honey by any means alone or in combination with other dressings or components</p>	<p>Primary outcomes: time to complete healing; proportion of participants with completely healed wounds. Secondary outcomes: incidence of adverse events; length of hospital stay; change in wound size; incidence of infection; cost; quality of life.</p>	<p>This review evaluated the use of honey in the treatment of all wounds, but included one article of relevance to foot ulcers in people with diabetes.</p> <p>Shukrimi 2008: This RCT (n=30) from Malaysia was rated as having an unclear risk of bias by Jull 2013. It included people with non-insulin dependent diabetes mellitus with Wagner grade II ulcers who were admitted for surgery and met the following parameters: age 35-65; transcutaneous oxygen tension >30mmHg and serum albumin level of >35g/dl. One group were randomised to treatment with honey applied daily, and the other to povidone-iodine soaked gauze applied daily. Treatment followed from surgical debridement and treatment with antibiotics. Treatment was continued until the wound closed. The mean time to heal in days was not significantly different between the groups (14.4 for the honey group versus 15.4 in the povidone-iodine group; standard deviations not given).</p> <p>The conclusions of Jull 2013, specific to foot ulcers in people with diabetes: 'The effect of honey on diabetic foot ulcers cannot be determined. The included trial lacked sufficient detail to determine risk of bias for most domains accurately. Further trials are justified.'</p>
<p>Game et al 2012²³</p> <p>Quality score: +</p>	<p>A systematic review of interventions to enhance healing of chronic ulcers of the foot in diabetes.</p>	<p>Included prospective and retrospective controlled studies published in any language, that evaluated the interventions for the treatment of chronic foot ulcers in adults with type 1 or 2 diabetes. Studies were included if they concerned agents or interventions that</p>	<p>Primary outcomes were: healing, time to healing, reduction in ulcer area or amputation.</p>	<p>Included one RCT of relevance (Shukrimi 2008), which was already included in the Jull 2013 review.</p> <p>The results presented concur with the results presented by Jull 2013. Some additional detail was available in Game 2012 (ranges for healing time endpoints):</p> <p>The mean time to heal in days was not significantly different between the groups: 14.4 for the honey group (<i>range 7 to 26</i>) versus 15.4 in the povidone-iodine group (<i>range 9 to 36</i>)</p> <p>The conclusions of Game 2012 are: 'with the exception of HBOT and, possibly, negative pressure wound therapy, there is little published evidence to justify the</p>

		may accelerate the healing process.		use of newer therapies.'
<p>Additional Information:</p> <p>The primary literature search for this HTA highlighted one study, which was reported as an RCT (Kamaratos 2014)²⁸. This included 63 patients who had neuropathic diabetic foot ulcers being treated in the outpatient setting in Greece. Patients had Wanger classification grade 1 or 2 lower limb neuropathic ulcers. The study compared manuka honey-impregnated dressings with conventional dressings (saline-soaked dressings), following patients up on a weekly basis for 16 weeks.</p> <p>The study has a high risk of bias. Patients were enrolled into the treatment groups in an alternating fashion. This is not random, and prevents allocation to treatment groups being concealed. In addition, the study is described as 'double blinded', but it is not clear if anyone involved in the trial was truly unaware of which treatment each participant was getting. The main results are:</p> <ul style="list-style-type: none"> - 97% (31/32) of NDFU in the MIHD group healed during the follow up compared with 90% (28/31) in the group treated with conventional dressings, p=0.4. - Mean duration of healing was 31 ± 4 days in the honey group versus 43 ± 3 days in the conventional dressing group (95% CI -10.7 TO -8.7), p<0.05 - In the honey group 78.13% of ulcers became sterile in the first week compared with 35.5% in the conventional dressing group. 				

Evidence table 3.3 Foot ulcers in people with diabetes – silver – systematic reviews and meta-analyses

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
<p>Dumville et al 2012a³⁰</p> <p>Quality score: ++</p>	<p>To compare the effects of alginate wound dressings with no wound dressing or alternative dressing on the healing of foot ulcers in people with diabetes</p>	<p>Included: published and unpublished RCTs that evaluated the effects of any alginate wound dressing in foot ulcers in people with diabetes; type 1 or 2 diabetes; any age.</p> <p>Excluded: studies on patients with wounds of a variety of aetiologies, unless the results were reported separately.</p>	<p>Primary outcomes: time to ulcer healing; and number of ulcers completely healed within a specific time period.</p> <p>Secondary outcomes: HRQoL; amputations; adverse events; cost; ulcer recurrence; change in ulcer area.</p>	<p>Included one RCT of relevance (Jude 2007), rated as having an unclear risk of bias (n=134). This compared a silver fibrous-hydrocolloid dressing with a calcium alginate dressing. Included patients with type 1 or 2 diabetes. 22 had clinically infected ulcers at baseline. Follow-up was 8 weeks.</p> <ul style="list-style-type: none"> - There was no statistically significant difference in the number of ulcers healed in the silver fibrous-hydrocolloid-dressed group (21/67; 31%) compared with the alginate-dressed group (15/67; 22%). A RR was calculated by Dumville 2012a: RR 1.40; 95% CI 0.79 to 2.47). - The mean time to healing was reported as 52.6 days (SD 1.8) in the silver-fibrous-hydrocolloid-dressed group compared with 57.7 days (SD 1.7) in the alginate-dressed group. - 25 participants experienced one or more adverse events in the silver fibrous-hydrocolloid-dressed group compared with 26 participants in the alginate-dressed group. There was one death in each treatment group. - The mean number of dressing changes during the study was similar for both groups (21.9 for the silver fibrous-hydrocolloid-dressed group and 20.8 for the alginate dressed group). <p>Authors' conclusion (relating to silver, not the conclusion of the whole review): 'There was no statistically significant difference in the number of ulcers healed between antimicrobial (silver) hydrocolloid dressings and standard alginate dressings.'</p>
<p>Dumville et al 2012b²²</p> <p>Quality score: ++</p>	<p>To compare the effects of hydrocolloid wound dressings with no dressing or alternative dressings on the healing of foot ulcers in people with</p>	<p>Included: published or unpublished RCTs irrespective of publication status or language; people with type 1 or 2 diabetes with an open foot ulcer; any definition of diabetic foot ulcer; studies in which the primary</p>	<p>Primary outcomes: time to ulcer healing and number of ulcers healed within a specific time period. Secondary outcomes: HRQoL; amputations; adverse events; cost; ulcer</p>	<p>Included one RCT of relevance (Jude 2007), already reported on in Dumville 2012a.</p> <p>The same results from Dumville 2012a are presented.</p> <p>Authors' conclusion: 'There was no statistically significant difference in the number of ulcers healed between antimicrobial (silver) hydrocolloid dressings and standard alginate dressings.'</p>

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
	diabetes	intervention was any type of hydrocolloid wound dressing. Excluded: trials which included people with a number of different wound aetiologies.	recurrence; change in ulcer area.	
Game et al 2012²³ Quality score: +	A systematic review of interventions to enhance healing of chronic ulcers of the foot in diabetes.	Included prospective and retrospective controlled studies published in any language, that evaluated the interventions for the treatment of chronic foot ulcers in adults with type 1 or 2 diabetes. Studies were included if they concerned agents or interventions that may accelerate the healing process.	The primary outcomes used were clinical: healing, time to healing, reduction in ulcer area or amputation.	<p>Included the RCT by Jude 2007, and reported on some additional outcomes:</p> <ul style="list-style-type: none"> - Healing velocity: calcium alginate group 0.26 (SD 0.9) cm²/week ; silver group 0.29 (SD 0.33) cm²/week (difference not significant). - % reduction in area over 8 weeks: silver group 58.1±53.1%; calcium alginate group 60.5±42.7% (difference not significant) - Change in ulcer depth: silver group 0.25 (0.49)cm; calcium alginate group=0.13 (0.37) cm (p=0.042) <p>The other results presented (number of ulcers healed and time to healing) concur with the results presented in both reviews by Dumville <i>et al.</i></p> <p>Also included an RCT from the USA by Jacobs 2008 (methodological rating 3/9). It included people with diabetic foot ulcers at least 3cm in diameter (n=40). It excluded people with clinical evidence of local infection. Silver sulfadiazine cream was used in the control group, with the intervention group being treated with oak bark extract. Treatment was given for 6 weeks. The outcome reported on was reduction in diameter: Silver sulfadiazine group: 54.7% Oak bark extract group: 72.5% P=0.059</p> <p>The conclusions of Game 2012 are: ‘with the exception of HBOT and, possibly, negative pressure wound therapy, there is little published evidence to justify the use of newer therapies.’</p>
VA Health Care 2012¹³ Quality score: +	KQ1: ‘What are the efficacy and harms of therapies for diabetic	Search was limited to: RCTs from 1995-2012; human subjects over 18 years old; and published in English.	Primary outcome was the percentage of ulcers healed at study completion. Secondary outcomes included	<p>Included both RCTs by Jude 2007 and Jacobs 2008. Reported on some additional outcomes for both trials:</p> <p>Jude 2007:</p> <ul style="list-style-type: none"> - Global assessment of healing: 88% of ulcers healed or improved in the silver dressing group compared to 71% in the calcium dressing group

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
	<p>ulcers? Is efficacy dependent on ancillary therapies? Does efficacy differ according to patient demographics, comorbid conditions, treatment compliance, or activity level?</p>	<p>Several advanced wound care therapies were included, but the only one of relevance to this HTA was 'silver products'.</p>	<p>ulcer infected during treatment, ulcer recurrence, time to recurrence, pain and adverse events.</p>	<p>(non-significant difference). Subgroup analysis based on location (plantar vs non-plantar) and type of ulcer (neuropathic, neuroischaemic) also were non-significant. The only significant finding was a greater percentage of ulcers healed or improved (92% versus 50%) in the silver group among patients taking systemic antibiotics at baseline.</p> <p>Jacobs 2008 Healed Diabetic Ulcers n/N (%)</p> <ul style="list-style-type: none"> - Silver sulfadiazine group: 6/20 (30%) - Oak bark extract group: 8/20 (40%) - ARD: -10 (95% CI -39 to 19) - RR: 0.75 (95% CI 0.32 to 1.77) <p>No patients experienced adverse events</p> <p>The other results presented concur with the results presented in both reviews by Dumville <i>et al.</i></p> <p>Included two further RCTs (Belcaro 2010; Viswanathan 2011).</p> <ul style="list-style-type: none"> - Belcaro 2010: RCT conducted in Italy. Rated as 'fair quality', but the authors note that allocation concealment and blinding were unclear. Included people with both diabetic foot ulcers and venous ulcers. The results presented are for 66 foot ulcers in people diabetes. It compared standard care to treatment with silver ointment twice daily. The authors noted that infection was the cause of some of the ulcers, but antibiotic use was not reported. Treatment duration was 4 weeks. Healed diabetic ulcers n/N (%) Silver oxide ointment: 13/34 (39%) Standard care: 5/32 (16%) ARD: 23 (95% CI 2 to 43); p<0.05 RR: 2.45 (95% CI 0.98 to 6.09) mean time to ulcer healing not reported; no patients experienced adverse events. - Viswanathan 2011: RCT conducted in India (n=40). Rated as 'fair quality', but the authors note that the allocation method and blinding was unclear, and that the analysis was not intention to treat. The study excluded people with clinical signs of severe infection. The control group were treated with silver sulfadiazine cream, while the treatment

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
				<p>group were treated with a 'polyherbal treatment'. Time to healing: no difference between polyherbal and silver group (43 days versus 44 days). No difference in ulcer recurrence between polyherbal and silver group (42% versus 47%). No difference in ulcers infected during treatment. No patients experienced adverse events. Reported all-cause mortality. Overall value was low; maximum of 1 patient per group, with no differences between polyherbal and silver group.</p> <p>Authors' conclusions (p53): 'We found no benefit in time to ulcer healing for collagen, biological dressings, or silver products...One study of a silver dressing versus a calcium dressing reported a global outcome of healed or improved ulcers with no difference between groups.'</p>
<p>Moore et al 2011¹⁰</p> <p>Quality score: +</p>	To examine the effectiveness of silver in wound care treatment.	Included: studies in which at least one group received silver in their wound care treatment; any wound type; any gender or age; clinical trials (including RCTs). Excluded: letters, abstracts, unpublished articles, literature reviews, animal studies and laboratory studies. Also excluded studies not in English, or not available in fulltext.	At least one of the following outcome measures were used in order for each study to be included in this literature review: wound healing; resolution of exudate, odour or inflammation; pain and overall comfort; cost-effectiveness; safety; influence of treatment on patient's quality of life.	Included a small single-armed study (Rayman 2005). It evaluated the use of a sustained silver releasing dressing, Contreet Foam, for 4 weeks. It included 27 people, of which 18 completed the study. Of these 18 people, mean ulcer area reduction was 56%, and in four people the wounds healed completely. As this is just a small single-armed study, no conclusions can be drawn. The authors conclusions are more positive, but relate to all wound types: 'Although the effectiveness and safety of silver implemented in wound care treatment appears to be promising, the small sample size of research articles and RCTs on this population and treatment method support the need for additional research to further investigate the effectiveness of silver dressings and topical agents in wound care treatment.' The review also seems to have missed some RCTs that were picked up by the other reviews.
<p>Carter et al 2010⁴</p> <p>Quality</p>	To conduct a systematic review of silver	Included any type of leg ulcer or wound (but those focusing on burns or other	Studies eligible for inclusion had to report at least one outcome related to	This included the RCT by Jude 2007, and does not add to the data already presented. The review includes meta-analyses, but the data is not applicable to this HTA,

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
score: +	dressings and treatments in wounds focusing on healing outcome parameters; to attempt meta-analyses for these parameters.	parts of the body were excluded). Did not include studies that compared one type of silver dressing to another. Limited to RCTs.	wound healing. Studies that focused solely on safety, diagnostics or infection were excluded.	as studies evaluating different wound types were combined together. The scope of this review includes all wound types, and the conclusions for foot ulcers in people with diabetes cannot be pulled out. However, the results do not add to what is already presented in more recent reviews. The conclusion, which relates to all wound types: 'Our results strengthen the proposition that silver-impregnated dressings improve the short-term healing of wounds and ulcers. However, because of lack of trial data with longer follow-up times there is no evidence that silver-impregnated dressings are effective using complete wound-healing criteria.'
Storm-Versloot et al 2010¹⁶ Quality score: ++	To establish the effects of silver-containing wound dressings and topical agents in preventing wound infection and healing of wounds.	Included: RCTs (published and unpublished); adults aged over 18 years; any care setting; uninfected wounds of any aetiology.	Primary outcomes: wound infection rate; wound healing. Secondary outcomes: included adverse events, pain, HRQoL, and patient satisfaction.	This review was not picked up in the initial search for this HTA. This is because the title is 'topical silver for preventing wound infection' – and prevention of infection is excluded from this review. However, the primary outcomes include wound healing, and so this review meets the inclusion criteria. It included two studies (Jacobs 2008; Jude 2007) of relevance to this section of the HTA, which were already picked up in the other reviews. Reported an additional outcome for Jude 2007: No statistically significant difference in the number of patients who developed wound infection (11/67 in the silver group; 8/67 in the calcium alginate group) RD 0.04; 95% CI -0.07 to 0.16. The overall conclusions are not specific to foot ulcers in people with diabetes: 'There is insufficient evidence to establish whether silver-containing dressings or topical agents promote wound healing or prevent wound infection.'
Lo et al 2009⁸ Quality score: +	To examine the efficacy of silver-releasing dressings in the management of non-healing chronic wounds	Limited to English or Chinese RCTs. Included studies in which participants all had wounds that exhibited delayed healing, or were critically colonised or infected. Acute wounds (eg burns) were excluded.	Reported outcomes were classified as physical, psychological or economic.	Included one RCTs (Jude 2007) already identified by the other reviews. Lo 2009 report on some meta-analyses, however, it is not clear what studies were included in these. As the scope included all wound types – and the meta-analyses potentially include a mixture of wound types – these are not relevant to this HTA. Lo (2009) concluded that silver dressings were effective in promoting wound healing and improving patients' quality of life, but stated that more RCTs were needed. This conclusion is more positive than the other reviews, probably because Lo (2009) scored the included RCTs more generously than the other

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
				reviews.
Bergin et al 2006²⁹ Quality score: ++	To evaluate the effects of silver-containing dressings and topical agents on infection rates and healing of diabetes related foot ulcers	RCTs and non-RCTs were considered for inclusion. Studies were included if they involved patients with type 1 or 2 diabetes and related foot ulcers, and compared the intervention with a placebo or sham dressing, an alternative non-silver based dressing or no dressing.	Primary outcomes: proportion of ulcers completely healed; change in total ulcer area; time to complete healing or reduced size; signs and symptoms of clinical infection. Secondary outcomes: ulcer re-occurrence rates; adverse effects of treatment; quality of life; costs; hospital admissions, amputation; death.	The review was well conducted, but identified no studies that met with the inclusion criteria.
<p>Additional Information</p> <p>One guideline⁴⁷ was identified, which made the following recommendation:</p> <p>'We do not advocate using topical antimicrobials for treatment most clinically infected wounds (strong recommendation, low quality evidence)'</p> <p>This recommendation is based on the following evidence statement:</p> <p>'The controversial concept of excess wound bioburden has led to increasing use of antimicrobials, particularly topical antiseptics (eg, cadexomer-iodine) and silver-based dressings, despite little evidence substantiating any benefit of these dressings over conventional therapy. In addition to their expense and potential for causing local adverse effects, use of these antimicrobials may further promote the emergence of bacterial resistance. With these theoretical risks, and a lack of evidence of any advantages, we do not advocate using topical antimicrobials for most clinically infected wounds. Furthermore, the available evidence does not support any benefit to using silver-based dressings for clinically infected wounds.'</p> <p>A primary literature search highlighted one additional Danish RCT (Gottrup 2013)³². The authors describe how randomisation was achieved, and allocation concealment was ensured. However, the study is small (n=39) and the analysis was not intention to treat. The study lasted 14 weeks:</p> <p><i>Patients:</i> Diabetic foot ulcers of at least 30 days duration with no local or systemic signs of infection. Exclusion criteria included known allergies to intervention, peripheral arterial disease or toe pressure ≤ 45 mm, and concomitant conditions or treatments that may have interfered with wound healing.</p> <p><i>Intervention:</i> Promogran Prisma (Systagenix). A dressing consisting of collagen/oxidised regenerated cellulose (ORC)/silver therapy. 24 patients were randomised to this group.</p> <p><i>Comparison:</i> standard treatment (n=15). The same type of dressings were used in the test and control group and consisted of a foam dressing for moderately exuding wounds and a more absorbent dressing for highly secreting wounds. Patients in both groups were treated with standard wound treatment protocol</p>				

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
<p>including debridement and off-loading based on specialist clinical evaluation.</p> <p><i>Results:</i></p> <ul style="list-style-type: none"> - More wounds in the collagen/ORC/silver group reached 50% wound closure by week 4 compared with the control group (79% [19/24] versus 43% [6/14], p=0.035). - “At the end of the study, 91% of wounds treated with collagen/ORC/silver treatment group compared with 69% of wounds in the control group either healed or showed a reduction in wound size of at least 50% (no p-value given)”. - “At each week throughout the 14 week study, the proportion of healed wounds in the collagen/ORC/silver group was higher than that in the control group (not significant p>0.05). At week 14, 52% (12/23) of wounds in the collagen/ORC/silver group had healed compared with 31% (4/13) in the control group”. - “In the control group, 31% (4/13) of patients were withdrawn from the study due to the development of wound infection. This was significantly different from the collagen/ORC/silver group, in which 0% (0/23) of patients were withdrawn because of infection (p=0.012)”. - “There were no reported adverse events in relation to the use of collagen/ORC/ silver. Five adverse events were reported in the control group. There were four cases of withdrawal from the study because of infection. One adverse event was filed as the wound showed clinical signs of infection; this patient was administered antibiotic treatment and went on to complete the study”. - “The authors also reported that the sum of matrix metalloproteinase-9 and elastase concentration was higher in nonresponders (people whose wound had not reduced by at least 50%) compared with responders (people whose wound had reduced in size by at least 50%) at baseline (p=0.0705; not statistically significant) and week 4 (p=0.012)”. <p>The authors conclude: ‘...collagen/ORC/ silver treatment significantly increased healing rates and decreased levels of infection compared with standard therapy. In addition, the study showed that a combination of protease levels can be used as a biomarker for healing status. An excessive level of proteases would indicate that the wound in not healing, and it may be appropriate to use a protease-codulating dressing such as collagen/ORC/silver.’</p>				

Evidence table 3.4 Foot ulcers in people who have diabetes – other AWDs – systematic reviews and meta-analyses

Reference	Study Objectives	Selection Criteria	Outcomes	Main Results (of relevance)
<p>Game et al 2012²³</p> <p>Quality score: +</p>	<p>A systematic review of interventions to enhance healing of chronic ulcers of the foot in diabetes.</p>	<p>Included prospective and retrospective controlled studies published in any language, that evaluated the interventions for the treatment of chronic foot ulcers in adults with type 1 or 2 diabetes. Studies were included if they concerned agents or interventions that may accelerate the healing process,</p>	<p>The primary outcomes used were clinical: healing, time to healing, reduction in ulcer area or amputation.</p>	<p>Included no studies on ‘other’ AWDs that are listed in section A5.3 of BNF67.</p> <p>Included one non-randomised cohort study on the use of surface antimicrobials (tobramycin beads) on the wound at the time of forefoot amputation (Krause 2009). The comparator group received no local antibiotics. The results suggested a weak significant effect on the need for later surgical revision. However, the review authors state that little can be drawn from this study, as the apparent effect could have resulted from confounding influences. Results:</p> <ul style="list-style-type: none"> - Time to healing: intervention 10.5 weeks (SD 4.5); control 14.5 weeks (SD 3.8); difference not significant (no other details given). - Rate of surgical revision: intervention 8.2%; control 25%; p<0.05 - Transtibial amputation at an average follow-up of 28.8 months: intervention 27%; control 25%
<p>Hinchliffe et al 2008²⁴</p> <p>Quality score: ++</p>	<p>To identify interventions for which there is evidence of effectiveness.</p>	<p>Included: prospective and retrospective controlled studies; any language; adults with type 1 or 2 diabetes with foot ulcers;</p>	<p>Included studies that assessed the effect of interventions on healing, time to healing, reduction in ulcer area or amputation.</p>	<p>Included no studies on ‘other’ AWDs that are listed in section A5.3 of BNF67.</p> <p>Included one lower quality RCT (Apelqvist 1990), that included 44 patients with necrotic ulcers. The authors compared 22 people treated with adhesive zinc oxide to 22 people treated with hydrocolloid. Follow-up was 5 weeks, and the outcome was ‘necrotic ulcer are reduction greater than 50%’. The outcome was achieved in 14/21 of those treated with zinc oxide, and 6/21 treated with hydrocolloid (p<0.025).</p>
<p>Chaby et al 2007⁵</p> <p>Quality score: +</p>	<p>To critically review the literature on the efficacy of modern</p>	<p>Limited to publications in English or French. Wounds were considered chronic if</p>	<p>The endpoints for selecting studies were the rate of complete</p>	<p>Included no studies on ‘other’ AWDs that are listed in section A5.3 of BNF67.</p>

Reference	Study Objectives	Selection Criteria	Outcomes	Main Results (of relevance)
	dressings in healing chronic wounds and acute wounds by secondary intention	time to healing was delayed as a result of impaired tissue repair due to poor oxygenation, malnutrition, or infection. Case reports and case series were excluded. In addition, studies on deep partial and full-thickness burns were excluded.	healing, time to complete healing, rate of change in wound area, and general performance criteria (eg pain, ease of use).	
<p>Nelson et al 2006²⁶</p> <p>Quality score: ++</p>	<p>-to review systematically the evidence on the performance of diagnostic tests used to identify infection in DFUs and of interventions to treat infected DFUs.</p> <p>-to use estimates derived from the systematic reviews to create a decision analytic model in order to identify the most effective method of diagnosing and</p>	<p>RCTs or CCTs of the effect of microbiological analysis or antimicrobial agents in people with DFUs.</p>	<p>The authors listed several outcome measures that studies must report on to eligible for inclusion. They state that the most important relate to mortality, amputation and wound healing. Others include: pain, ulcer recurrence, bacterial profile of ulcer, acquisition of resistant</p>	<p>Included one RCT which compared a hydrogel with dry gauze irrigated with chlorhexidine.</p> <p>Vandeputte (1996): An RCT (n=29) comparing a hydrogel dressing with dry gauze irrigated with chlorhexidine. Participants had foot ulcers associated with diabetes, and the RCT was conducted over a 3-month period. Systemic antibiotics and topical treatments/antiseptics were available to all patients if required. The control group received various topical treatments, including povidone iodine cream, in addition to the chlorhexidine:</p> <ul style="list-style-type: none"> - The necessity for amputation (one or more toes) was slightly higher in the chlorohexidine group, but this difference was not statistically significant [5/14 (36%) versus 1/15 (7%); RR for amputation 5.4 (95% CI 0.98 to 32.7)] - Complete healing data (verified by photographic measure) at the end of treatment showed fewer ulcers healed in the chlorhexidine group compared with the hydrogel group [5/14 (36%) versus 14/15 (93%); RR 2.61 (95% CI 1.45 to 5.76)]. - There was a lower incidence of infection amongst patients in the hydrogel group [1/15 (7%) versus 7/14 (50%); RR 7.5 (95% CI 1.47 to 44.1). - There was a reduced requirement for systemic/local antibiotics/topical treatment in the hydrogel group compared with the chlorhexidine group [14/14 (100%) versus 1/15 (7%); RR 0.067, 95% CI 0.01 to 0.31].

Reference	Study Objectives	Selection Criteria	Outcomes	Main Results (of relevance)
	treating infection and to identify areas of research that would lead to large reductions in clinical uncertainty.		organisms, relationship between ulcer healing and bacteriology.	<p>The authors concluded (p47): ‘The trial was sufficiently powered on the complete healing outcome and infection incidence outcome to detect clinically important differences as statistically significant, but was underpowered to detect other differences in outcomes as statistically significant.’</p> <p>Also included an RCT which compared an antiseptic spray (content not described) with a 2% eosin and 0.3% chloroxylenol spray in 40 people, of whom 21 had foot ulcers caused by diabetes (Marchina 1997). At 15 days, 82% of the people in the eosin/chloroxylenol group were completely healed, compared with 50% in the antiseptic spray group. This trial was too small to detect clinically important differences in healing rates.</p>
<p>NICE 2003²⁷</p> <p>Quality score: ++</p>	To produce a guideline to cover the foot care and management of people diagnosed with Type 2 diabetes.	Searches were limited to 1996-2002/3 and to English language papers. No study or publication type restrictions were applied.	Not specifically stated, but it seems that all outcomes reported in the literature were included.	<p>Included no studies on ‘other’ AWDs that are listed in section A5.3 of BNF67.</p> <p>The following D-grade recommendations are made:</p> <ul style="list-style-type: none"> • ‘In the absence of strong evidence of clinical and cost effectiveness, health care professionals should use wound dressings that best match clinical experience, patient preference, and the site of the wound and consider the cost of dressings.’ • ‘Wounds should be closely monitored and dressings changed regularly.’ <p>These are based on the following evidence statement: ‘There is insufficient evidence to support the effectiveness of any type of protective dressing, or topical application, over any other for treating diabetic foot ulcers.’</p>
<p>O’Meara et al 2000¹²</p> <p>Quality score: ++</p>	To assess the clinical- and cost-effectiveness of -Prevention and treatment strategies for diabetic foot ulcers and -Systemic and topical antimicrobial agents in the	Included randomised and non-randomised trials with a concurrent control group; systemic or topical antimicrobials for chronic wounds;	Included studies had to report objective measures of outcome such as: -any objective measure of wound healing -ulcer recurrence rate	Included the RCT by Vandeputte (1996), which has already been summarised.

Clinical effectiveness – full write-up

Reference	Study Objectives	Selection Criteria	Outcomes	Main Results (of relevance)
	prevention and healing of chronic wounds.		-side-effects Studies reporting solely microbiological outcomes were excluded.	
Mason <i>et al</i> 1999²⁵ Quality score: +	To assess the value of treatments for foot ulcers in patients with type 2 diabetes mellitus	“Studies were examined if they specifically addressed an intervention for patients with diabetic foot ulcers. In each area considered, the best available evidence was used and where randomised, controlled trials were available, studies of lesser design were excluded unless they added a further dimension to the understanding.”	Not specifically stated, but all outcomes reported in the studies seem to have been included.	Included no studies on ‘other’ AWDs that are listed in section A5.3 of BNF67.

Evidence table 4.1 Pressure ulcers – iodine – systematic reviews and meta-analyses

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
<p>NICE 2014³⁷</p> <p>Quality score: ++</p>	<p>This is a guideline that rationalises the approaches used for the prevention and management of pressure ulcers. Recommendations are based on a systematic review of the best available evidence. This guideline has been included in the main evidence table as it included a comprehensive review of the primary studies, including detailed evidence tables.</p>	<p>The guideline considers several clinical questions. The one of relevance to this section is:</p> <p>- What are the most clinically and cost effective topical agents for the treatment of pressure ulcers?</p> <p>The authors only included RCTs.</p>	<p>All outcomes reported in the primary studies appear to have been extracted.</p>	<p>What are the most clinically and cost effective topical agents for the treatment of pressure ulcers?</p> <p>Included 36 RCTs in total, 3 of which evaluated iodine products:</p> <p>Kaya 2005: Rated as ‘very low’ quality (n=49). Included hospitalised patients with a spinal cord injury and at least one pressure ulcer (grade 1 to 3). It compared a hydrogel dressing to povidone-iodine soaked gauze. The study reported that there is potentially no clinical difference between hydrogel and povidone-iodine dressings for mean rate of healing of pressure ulcers, and the direction of the estimate of effect favours hydrogel:</p> <p>Mean healing rate (SD) cm²/day <i>Hydrogel group: 0.12 (0.16)</i> <i>Povidone-iodine group: 0.09 (0.05) p=0.97</i></p> <p>Kim 1996: Rated as ‘very low’ quality (n=44). It included people with a grade 1 or 2 pressure ulcer, and compared treatment with povidone-iodine to hydrocolloid dressings.</p> <p>Proportion of patients with complete healing <i>Hydrocolloid group: 21/26 ; 80.8%</i> <i>Povidone-iodine group: 14/18; 77.8% ; p>0.05</i> <i>RR 0.96; (95% CI 0.71 to 1.31); NS</i></p> <p>Mean healing speed (SD) mm²/day <i>Hydrocolloid group: 9.1 (5.4)</i> <i>Povidone-iodine group: 7.9 (4.7); p>0.05: NS</i></p> <p>Proportion of people with hypergranulation <i>Hydrocolloid group: 3/26 (11.5%)</i> <i>Povidone-iodine group: 0/18 (0%)</i> <i>OR 0.17; (95% CI 0.02 to 1.79); NS</i></p> <p>All cause mortality: 0% in both groups.</p> <p>Moberg 1983: Rated as ‘low’ quality (n=34). This included hospitalised adults with a deep or superficial pressure ulcer. It compared treatment for 3</p>

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
				<p>weeks with cadexomer iodine or standard treatment.</p> <p>Proportion of ulcers reduced with 50% after 3 weeks <i>Cadexomer iodine group: 8/16 (50%)</i> <i>Standard treatment group: 1/18 (5.6%)</i> <i>RR 9 (95% CI 1.26 to 64.33)</i></p> <p>Mean cm² (SD) decrease in ulcer area after 3 weeks <i>Cadexomer iodine group: 2.9 (5.2)</i> <i>Standard treatment group: 2.5 (4.67); NS</i></p> <p>Mean percentage (SD) reduction in ulcer area after 3 weeks <i>Cadexomer iodine group: 30.9 (46)</i> <i>Standard treatment group: 19.6 (83.16); NS</i></p> <p>All cause mortality: 0% in both groups.</p> <p>Conclusions (for iodine only): “There was no strong evidence to favour iodine solutions (povidone-iodine and cadexomer iodine solutions). Povidone-iodine solution was not as beneficial as hydrocolloid dressing. There was no clinical benefit of povidone-iodine when compared to hydrogel dressings and cadexomer iodine showed unclear results when compared to standard treatment (which was a range of different comparators including saline dressings, enzyme-based debriding agents, and nonadhesive dressing). There was no clinical benefit for hydrocolloid dressing compared to povidone-iodine for people completely healed and no clinical benefit of povidone-iodine for mean speed of healing. There was a clinical benefit for the proportion of pressure ulcers reduced by 50 percent, which is an uncommon outcome. There was also a mean percentage reduction in pressure ulcer area but there was no clinical benefit for the mean cm² reduction in pressure ulcer area for cadexomer iodine compared to standard treatment. Standard treatment was individualised to each person and included saline dressings, enzyme-based debriding agents, and non-adhesive dressings. Povidone-iodine had no clinical benefit when compared to hydrogel dressings.”</p> <p>Based on the evidence from all 36 RCTs, looking at a variety of topical agents, NICE makes the following recommendation: “Do not routinely use topical antiseptics or antimicrobials to treat a pressure ulcer in adults.”</p>
KCE	The guideline	<i>Patient:</i> people of	<i>Critical Outcomes:</i>	Included four RCTs on the use of iodine products in the treatment of

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
<p>(2013)³⁴</p> <p>Quality score: +</p>	<p>includes 12 clinical questions, and the two of relevance are:</p> <p>'What are the most clinically effective topical agents for the treatment of pressure ulcers?'</p> <p>'What are the most clinically effective dressings for the treatment of pressure ulcers?'</p>	<p>any ages with existing pressure ulcers in any care setting.</p> <p><i>Intervention:</i> topical agents (including antiseptics); dressings.</p> <p><i>Comparison:</i> no topical agent; comparison between topical agents; placebo; other pressure ulcer therapy</p>	<p>time to complete healing; rate of complete healing; rate of change in size and volume of ulcer; reduction in size and volume of ulcer; proportion of patients completely healed within trial period.</p> <p><i>Important outcomes:</i> wound-related pain; time in hospital; patient acceptability; side effects and HRQoL.</p>	<p>pressure ulcers. Three of these were included in the NICE guideline (Kaya 2005; Kim 1996; Moberg 1983), and the following evidence statements are made:</p> <p>Kim 1996: One study (n=44) (general populations):</p> <ul style="list-style-type: none"> - showed that there may be no difference between povidone-iodine and hydrocolloid to reduce the proportion of stage 1 and 2 pressure ulcers, the direction of the estimate of the effect favoured the hydrocolloid (VERY LOW QUALITY); - reported percentage healing rate for povidone-iodine and hydrocolloid. The healing rate for povidone-iodine was 77.8% and 80.8% for hydrocolloid dressing. No estimate of effect or precision could be derived (VERY LOW QUALITY); - showed that hydrocolloid may be more effective compared to povidone-iodine for mean speed of healing (stage 1 and 2 pressure ulcers) (VERY LOW QUALITY); - showed that povidone-iodine may be more effective compared to a hydrocolloid to reduce the incidence of hypergranulation (Stage I and II PUs) (VERY LOW QUALITY). <p>Kaya 2005: One study (n=49) (general population) showed that hydrogel is potentially more effective compared to povidone-iodine for mean speed of healing (Stage 1 to 3 pressure ulcers) (VERY LOW QUALITY).</p> <p>Moberg 1983: One study (n=34) (general populations) showed that cadexomer iodine is:</p> <ul style="list-style-type: none"> -clinically more effective compared to standard treatment to reduce the proportion of deep and superficial PUs healed for 50% (LOW QUALITY) - clinically more effective compared to standard treatment for the mean cm² reduction in ulcer area (LOW QUALITY) - clinically more effective compared to standard treatment for mean percentage reduction in ulcer area (LOW QUALITY). <p>KCE 2013 include a further RCT:</p> <p>Kucan 1981: this RCT included 45 hospitalised patients with a pressure ulcer. Study limitations include no report of allocation concealment or blinding, and an analysis that was not intention-to-treat. Participants were randomised to one of three treatments: silver sulfazidine cream (1%), povidone-iodine solution, or physiologic saline. Results reported were:</p> <ul style="list-style-type: none"> - proportion of patients clinically responding within 3 weeks: comparing silver sulfazidine group and povidone iodine group, the p-value in favour of

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
				<p>silver sulfazidine was reported ($p \leq 0.022$);</p> <ul style="list-style-type: none"> - the number of patients who reached a bacterial count of $<10^5$ per gram of tissue during the 3 week treatment: Silver group 15/15; povidone-iodine group 7/11; saline group 11/14. <p>Based on the evidence for all topical agents and dressings (not just iodine), the authors make the following recommendation: “consider improving wound healing environment by using modern dressings and topical agents (eg hydrocolloids, hydrogels, hydrofibres, foams, alginates, silver dressings) instead of basic dressing types (eg gauze, paraffin gauze and simple dressing pads).</p> <p>As clinical studies did not demonstrate the superiority of one type of modern dressing and topical agent over another, decisions about which type of modern dressing/topical agent to use should be based on:</p> <ul style="list-style-type: none"> - Ulcer assessment (condition of wound, tissue, exudate, depth, degree of infection, odor, pain, wound edges and wound environment); - General skin assessment; - Treatment objective; - Dressing characteristics; - Previous positive effect of particular dressing/topical agent; - Manufacturer’s indications for use and contraindications; - Risk of adverse events; - Patient preferences (lifestyle, abilities and comfort).” <p>The strength of this recommendation is ‘weak’, and the level of evidence is ‘very low’.</p>
<p>Vermeulen et al 2010¹⁵</p> <p>Quality score: +</p>	<p>A systematic review of RCTs which investigated the possible beneficial and harmful clinical effects of iodine in the treatment of all kinds of (contaminated)</p>	<p>RCTs that reported on a local wound care product containing iodine in patients with any kind of (more or less contaminated) wound. Any concentration or manufacturer of</p>	<p>Primary outcomes were bacterial load or wound infection and wound healing. Secondary outcomes were adverse events, costs and length of hospital stay.</p>	<p>Included three RCTs of relevance to this section, all of which were included in the NICE 2014 or KCE 2013 reviews (Kaya 1996; Kucan 1981; Moberg 1983). The data presented concurs with what is presented in NICE 2014 and KCE 2013. The review does not add to the data already presented.</p> <p>The authors conclusions relate to all wound types: ‘Based on the available evidence from clinical trials, iodine is an effective antiseptic agent that shows neither the purported harmful effects nor a delay of the wound-healing process, particularly in chronic and burn wounds. The antiseptic effect of iodine is not inferior to that of other</p>

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
	wound.	iodine as well as any type of control treatment was allowed.		(antiseptic) agents and does impair wound healing.’ and ‘There is a need for high quality RCTs addressing the effectiveness of iodine to treat or prevent wound infection, in order to clearly determine the place of iodine in present-day wound care.’
<p>NPUAP & EPUAP 2009³⁵</p> <p>Quality score: ++</p>	<p>This guideline provides evidence-based recommendations for the prevention and treatment of pressure ulcers.</p>	<p>Inclusions: studies focused on pressure ulcer prevention, risk assessment and treatment; published in a peer reviewed journal; with an abstract; all study designs (excluding series with less than 10 participants); any language. Excluded: economic evaluations.</p>	<p>The authors appear to have extracted all outcomes identified in the literature.</p>	<p>The review includes one RCT of relevance to this section (Kaya 2005), which was already picked up in NICE (2014), KCE (2013) and Vermuelen (2010). The results presented concur with the other reviews, however the authors state that the statistics in the Kaya (2005) study are incorrect.</p> <p>They make the following C-grade recommendations (they state that C-grade recommendations are based on indirect evidence and/or expert opinion):</p> <ul style="list-style-type: none"> - Consider use of cadexomer iodine dressings in moderately to highly exudating pressure ulcers - Avoid use of cadexomer iodine in individuals with iodine sensitivity and in those with thyroid disease. - Avoid use of cadexomer iodine in large-cavity ulcers that require frequent (daily) dressing changes. <p>Under the section on the assessment and treatment of infection, they make the further C-grade recommendations:</p> <ul style="list-style-type: none"> - Consider the use of topical antiseptics that are properly diluted and appropriate for pressure ulcers. Antiseptics should be used for a limited time period to control the bacterial bioburden, clean the ulcer, and reduce surrounding inflammation. The professional should be knowledgeable about proper dilutions, as well as risks of toxicity and adverse reactions. - Consider the use of topical antiseptics for pressure ulcers that are not expected to heal and are critically colonised. - Consider the use of topical antimicrobial silver or medical-grade honey dressings for pressure ulcers infected with multiple organisms, because these dressings offer broad antimicrobial coverage. However, before applying honey dressing, make sure that the individual is not allergic to honey, bee products, or bee stings. - Limit the use of topical antibiotics on infected pressure ulcers, except in special situations.

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
<p>Ontario Health Technology 2009³⁶</p> <p>Quality Score: ++</p>	<p>A systematic review on interventions used to treat pressure ulcers to answer: -Do currently available interventions for the treatment of pressure ulcers increase the healing rate of pressure ulcers compared with standard care, a placebo, or other similar interventions? - Within each category of intervention, which one is most effective in promoting the healing of existing pressure ulcers?</p>	<p>Included: Patients in any setting with one or more pressure ulcers; nondrug and nonsurgical treatments of pressure ulcers; compared to a placebo, a sham treatment or another intervention; Clinical controlled trials or other observational studies only if RCTs are not available; sample ≥ 10 ulcers. Exclusion: other ulcer types; studies with subjective outcomes; non-systematic reviews and case reports; opinion articles, letters etc; articles not in English.</p>	<p>Proportion of ulcers that healed completely (closed); percent change in surface area/volume, rate of change in surface area (cm^2/day or week); mean time to achieve complete healing; change in the amount of exudate; granulation; PSST score, PUSH score; treatment-related adverse events; absorbency and ease of removal (for dressings).</p>	<p>Included two RCTs (Kim 1996; Barrois 1992), one of which was included in the more recent reviews (eg NICE 2014, KCE 2013).</p> <p>Barrois 1992, randomised 76 people with pressure ulcers to treatment with a hydrocolloid dressing or a tulle dressing impregnated with povidone-iodine. Treatment was for 8 weeks. The study reported no difference in the number of ulcers healed between groups (10/38 in the hydrocolloid group; 9/38 in the povidone-iodine group).</p> <p>The review authors combined the results from Barrios 1992 and Kim 1996 for the outcome of 'ulcers healed'. No statistically significant difference was reported in the proportions of ulcers healed between the two treatments (RR 0.99; 95% CI 0.71 to 1.37; $p=0.94$) The test of heterogeneity was not significant ($I^2 = 0\%$; $p=0.56$).</p>
<p>Reddy 2008³⁸</p> <p>Quality score: ++</p>	<p>To systematically review published RCTs evaluating therapies for pressure ulcers.</p>	<p>Included: RCTs published in English.</p> <p>Excluded: studies that evaluated wounds other than pressure ulcers; studies that assessed only adverse events or secondary outcomes</p>	<p>Only studies that calculated wound size with wound volume and/or surface area, used evaluation tools that incorporated these measurements, or used complete healing as</p>	<p>Included three studies of relevance to this section, all of which were included in the more recent reviews (Kim 1996; Kaya 2005; Moberg 1983).</p> <p>Authors' conclusions: 'Two of the RCTs we examined compared antiseptics with moist dressings. Neither of these trials met any CLEAR NPT* criteria. Antiseptics are inexpensive and non-RCT evidence supports their continued use in maintenance or nonhealable wounds to help prevent wound deterioration.'</p> <p>* : CLEAR NPT = 'a checklist to evaluate a report of a nonpharmacological trial'</p>

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
		(eg pain).	endpoints were included.	
<p>RCON & NICE 2005³⁹</p> <p>Quality score: ++</p>	<p>The guidelines included a number of clinical questions. The objective of the section of relevance to this HTA was: 'To systematically assess the evidence for the clinical effectiveness of systemic and topical antimicrobial agents in the treatment of existing pressure ulcers.</p>	<p>Inclusions: prospective controlled trials, published and unpublished RCTs; people with existing pressure ulcers, of any grade or severity; any setting; trials in which a dressing or topical agent was compared with another dressing or topical agent, or compared with a placebo, usual care, or no treatment.</p> <p>Exclusions: studies which focus on microbiological outcomes eg wound cultures, bacterial counts and bacterial eradication.</p>	<p>The primary outcome was wound healing. To be eligible for inclusion, studies had to incorporate at least one objective assessment of wound healing (eg change in ulcer size, rate of healing, frequency of complete healing or time to complete healing).</p> <p>Where studies reported both wound healing and microbiological outcomes, only the former were incorporated in the review.</p>	<p>Included three lower quality RCTs of relevance to this section of the HTA, which were not included in the more recent reviews (Toba 1997; Worsley 1991; Huchon 1992).</p> <p>The main results are summarised:</p> <p>“Two trials (Huchon n=76; Worsley n=27) compared the use of a hydrocolloid dressing with one impregnated with povidone iodine. Neither trial individually, or when their results were combined in a meta-analysis, demonstrated a significant difference between the two treatments in terms of the number of pressure ulcers assessed as completely or partially healed at follow up between eight and 12 weeks (RR 1.19; 95% CI 0.92 to 1.54). Worsley 1991 drew attention to the fact that fewer dressing changes per week were needed in the hydrocolloid group compared with the povidone iodine group (mean ± SD: 3 ± 1.38 versus 4.9 ± 1.69, respectively, p<0.005)”</p> <p>“A small trial (n=19) by Toba (1997) assessed the effects of GVcAMP ointment (gentian violet 0.1% blended with dibutyl cAMP) in elderly women with pressure ulcers contaminated with MRSA. There was no statistically significant difference (mean difference -11.1%; 95% CI -27.86 to 5.66) between the two groups in change in wound area at 14 weeks. The authors hypothesised that the lack of difference seen might be due to the fact that the two largest wounds (area greater than 50cm²) were in the experimental group. However, an absence of power calculations makes assessment of this comment difficult.’ (NB the comparison in this study was povidone iodine and sugar ointment applied to pressure ulcers every day).”</p> <p>“Considering all the evidence for antimicrobials (not just iodine), the evidence summary is: ‘there is insufficient evidence to indicate whether antimicrobials are effective in the treatment of pressure ulcers.’”</p>
<p>O’Meara et al 2000¹²</p> <p>Quality score: ++</p>	<p>To assess the clinical- and cost-effectiveness of -Prevention and treatment</p>	<p>Included randomised and non-randomised trials with a concurrent control</p>	<p>Included studies had to report objective measures of outcome such as:</p>	<p>Includes three RCTs of relevance to this section of the HTA, which were already reported on in the RCON & NICE 2005 guideline (Toba 1997; Worsley 1991; Huchon 1992).</p> <p>The conclusions of relevance to this section are: ‘No significant difference</p>

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
	strategies for diabetic foot ulcers and -Systemic and topical antimicrobial agents in the prevention and healing of chronic wounds.	group; systemic or topical antimicrobials for chronic wounds;	-any objective measure of wound healing -ulcer recurrence rate -side-effects Studies reporting solely microbiological outcomes were excluded.	was detected between a hydrocolloid dressing and povidone iodine ointment, or between a gentian violet preparation and povidone iodine/sugar ointment.'
<p>Additional information:</p> <p>Pan Pacific Guideline³³ (quality score ++): Based on the systematic reviews by Vermeulen 2010¹⁵ and Reddy 2008³⁸ (described above), this guideline makes the following C-grade recommendation: 'Cadexomer iodine could be used to promote healing in pressure injuries when there is a known increased microbial burden. Caution: cadexomer iodine ointments and impregnated dressings should not be used in patients with iodine sensitivity, taking lithium, history of Hashimoto's thyroiditis, Graves disease, non-toxic nodular goitre or thyroid disorders, or impaired renal function, in children or in pregnant or lactating women. Risk of systemic absorption increased when cadexomer iodine products are used on larger or deeper wounds or for prolonged periods. Practice points: - Cadexomer iodine should not be used for longer than three months continuously. - Cadexomer iodine should not be covered with povidone-iodine soaked gauze/tulle gras as this practice results in the increased release of iodine, increasing toxicity.'</p>				

Evidence table 4.2: Pressure ulcers – honey – systematic reviews and meta-analyses

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
<p>NICE 2014³⁷</p> <p>Quality score: ++</p>	<p>This is a guideline that rationalises the approaches used for the prevention and management of pressure ulcers. Recommendations are based on a systematic review of the best available evidence. This guideline has been included in the main evidence table as it included a comprehensive review of the primary studies, including detailed evidence tables.</p>	<p>The guideline considers several clinical questions. The one of relevance to this section is:</p> <p>- What are the most clinically and cost effective topical agents for the treatment of pressure ulcers?</p> <p>The authors only included RCTs.</p>	<p>All outcomes reported in the primary studies appear to have been extracted.</p>	<p>What are the most clinically and cost effective topical agents for the treatment of pressure ulcers?</p> <p>Included 36 RCTs in total, one of which evaluated a honey dressing:</p> <p>Günes 2007: NICE reported several limitations with this RCT: it did not report on sequence allocation or allocation concealment, the analysis was not intention-to-treat, and it was not blinded. It randomised 27 people with 50 pressure ulcers to treatment with either a gauze dressing impregnated with honey (3.8% concentration), or ethoxydiaminoacridine and nitrofurazone (E and N) dressings. The patients were aged 18 and older, were hospitalised and had grade II or III pressure ulcers. Treatment continued until the wounds healed, or for up to 5 weeks. Results:</p> <p><i>Mean percentage decrease in PUSH score</i> Honey group: 56.3 R and N group: 12.9 P<0.001</p> <p><i>Mean percentage reduction in ulcer size</i> Honey group: 56% R and N group: 13% P<0.001</p> <p><i>Proportion of ulcers completely healed</i> Honey group: 5/25 R and N group: 0/25 P<0.001</p> <p><i>Proportion of patients with adverse events attributed to the treatment</i> Honey group: 0/15 R and N group: 0/11</p> <p>NICE reported that the guideline development group informed them that E and N dressings were not used in clinical practice in the UK and could not be found in the BNF. Therefore, there are no conclusions that can be drawn from this study. The recommendation given by NICE, which relates to all topical antimicrobials (not just honey), is: 'Do not routinely use topical</p>

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
				antiseptics or antimicrobials to treat pressure ulcer in adults’.
KCE (2013)³⁴ Quality score: +	The guideline includes 12 clinical questions, and the two of relevance are: ‘What are the most clinically effective topical agents for the treatment of pressure ulcers?’ ‘What are the most clinically effective dressings for the treatment of pressure ulcers?’	<i>Patient:</i> people of any ages with existing pressure ulcers in any care setting. <i>Intervention:</i> topical agents (including antiseptics); dressings. <i>Comparison:</i> no topical agent; comparison between topical agents; placebo; other pressure ulcer therapy	<i>Critical Outcomes:</i> time to complete healing; rate of complete healing; rate of change in size and volume of ulcer; reduction in size and volume of ulcer; proportion of patients completely healed within trial period. <i>Important outcomes:</i> wound-related pain; time in hospital; patient acceptability; side effects and HRQoL.	This included one RCT, which was also included in NICE 2014 (Günes 2007). Does not add to the data already presented.
Jull et al 2013⁷ Quality score: ++	To determine whether honey increases the rate of healing in acute wounds (eg burns and lacerations) and chronic wounds (eg skin ulcers, infected surgical wounds)	Included RCTs and quasi-randomised trials that evaluated honey as a treatment for any sort of acute or chronic wound.	Primary outcomes: time to complete wound healing; proportion of participants with completely healed wounds. Secondary outcomes: incidence of adverse events; length of hospital	Jull 2013 included one RCT, rated as having an ‘unclear risk of bias’, which compared honey and saline-soaked gauze dressings (Weheida 1991). Randomly allocated 40 people with uninfected grade I or II pressure injuries greater than 2 cm in diameter. There was very limited information on baseline comparability and no indication of the duration of treatment or length of follow-up. Mean time to healing favoured the honey-treated group (8.2 days versus 9.93 days; MD -1.73; 95% CI -1.09 to -2.37). Jull 2013 conclusions for honey and pressure ulcers are: ‘The effect of honey on pressure ulcers cannot be determined. The included trial was small and lacked sufficient detail to determine risk of bias accurately for most domains....Further trials are justified.’

Clinical effectiveness – full write-up

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
			stay; change in wound size; incidence of infection; cost; quality of life.	
NPUAP & EPUAP 2009³⁵ Quality score: ++	This guideline provides evidence-based recommendations for the prevention and treatment of pressure ulcers.	Inclusions: studies focused on pressure ulcer prevention, risk assessment and treatment; published in a peer reviewed journal; with an abstract; all study designs (excluding series with less than 10 participants); any language. Excluded: economic evaluations.	The authors appear to have extracted all outcomes identified in the literature.	This included one RCT, which was also included in NICE 2014 (Günes 2007). Does not add to the data already presented. They make the following C-grade recommendation (they state that C-grade recommendations are based on indirect evidence and/or expert opinion): <ul style="list-style-type: none"> - “Consider use of dressings impregnated with medical-grade honey for the treatment of category/stage II and III pressure ulcers.” Under the section on the assessment and treatment of infection, they make the further C-grade recommendations: <ul style="list-style-type: none"> - “Consider the use of topical antiseptics that are properly diluted and appropriate for pressure ulcers. Antiseptics should be used for a limited time period to control the bacterial bioburden, clean the ulcer, and reduce surrounding inflammation. The professional should be knowledgeable about proper dilutions, as well as risks of toxicity and adverse reactions. - Consider the use of topical antiseptics for pressure ulcers that are not expected to heal and are critically colonised. - Consider the use of topical antimicrobial silver or medical-grade honey dressings for pressure ulcers infected with multiple organisms, because these dressings offer broad antimicrobial coverage. However, before applying honey dressing, make sure that the individual is not allergic to honey, bee products, or bee stings. - Limit the use of topical antibiotics on infected pressure ulcers, except in special situations.”
Ontario Health Technology 2009³⁶ Quality Score: ++	A systematic review on interventions used to treat pressure ulcers to answer: -Do currently available interventions for	Included: Patients in any setting with one or more pressure ulcers; nondrug and nonsurgical treatments of pressure ulcers;	Proportion of ulcers that healed completely (closed); percent change in surface area/volume, rate of change in surface area	This included one RCT, which was also included in NICE 2014 (Günes 2007). Does not add to the data already presented.

Clinical effectiveness – full write-up

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
	the treatment of pressure ulcers increase the healing rate of pressure ulcers compared with standard care, a placebo, or other similar interventions? - Within each category of intervention, which one is most effective in promoting the healing of existing pressure ulcers?	compared to a placebo, a sham treatment or another intervention; Clinical controlled trials or other observational studies only if RCTs are not available; sample ≥ 10 ulcers. Exclusion: other ulcer types; studies with subjective outcomes; non-systematic reviews and case reports; opinion articles, letters etc; articles not in English.	(cm ² /day or week); mean time to achieve complete healing; change in the amount of exudate; granulation; PSST score, PUSH score; treatment-related adverse events; absorbency and ease of removal (for dressings).	
Reddy 2008³⁸ Quality score: ++	To systematically review published RCTs evaluating therapies for pressure ulcers.	Included: RCTs published in English. Excluded: studies that evaluated wounds other than pressure ulcers; studies that assessed only adverse events or secondary outcomes (eg pain).	Only studies that calculated wound size with wound volume and/or surface area, used evaluation tools that incorporated these measurements, or used complete healing as endpoints were included.	This included one RCT, which was also included in NICE 2014 (Günes 2007). Does not add to the data already presented.
<p>Additional information: A Pan-Pacific guideline included the systematic reviews by Jull 2013⁷ (an earlier version than the one detailed above) and Reddy 2008³⁸. Based on the two RCTs, which they acknowledge are at high risk of bias, and on a consensus recommendation from an evidence-based guideline, they give the following D-grade recommendation: 'Consider using topical medical grade honey to promote healing in pressure injuries. Caution: Treating PIs with honey has been reported to lead to pain, deterioration of the wound area and an increase in wound exudate. A SR found that</p>				

Clinical effectiveness – full write-up

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
<p>adverse events (eg pain, deterioration and increased exudate) were more likely to occur in other types of chronic wounds treated with honey compared with those treated with hydrogel or standard dressings and there was no difference in infection rates.</p> <p>Practice points for honey: The honey should be specifically indicated for application to wounds (ie medical grade). Manuka honey should be rated UMF (Unique Manuka Factor) +12 or above for topical dressing products. Use gamma irradiated honey as other sterilising processed with destroy the UMF in the honey.³³</p>				

Evidence table 4.3: Pressure ulcers – silver – systematic reviews and meta-analyses

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
<p>NICE 2014³⁷</p> <p>Quality score: ++</p>	<p>This is a guideline that rationalises the approaches used for the prevention and management of pressure ulcers. Recommendations are based on a systematic review of the best available evidence. This guideline has been included in the main evidence table as it included a comprehensive review of the primary studies, including detailed evidence tables.</p>	<p>The guideline considers several clinical questions. The two of relevance to this section is:</p> <ul style="list-style-type: none"> - What are the most clinically and cost effective topical agents for the treatment of pressure ulcers? - What are the most clinically and cost effective dressings for the treatment of pressure ulcers? <p>The authors only included RCTs.</p>	<p>All outcomes reported in the primary studies appear to have been extracted.</p>	<p>What are the most clinically and cost effective topical agents for the treatment of pressure ulcers?</p> <p>Included 36 RCTs in total, one of which evaluated silver products: Chuangsuwanich 2011: This is a low quality RCT. Limitations noted by NICE included a small sample size, inadequate reporting of allocation concealment and no blinding. It included 40 inpatients and outpatients with a grade III or IV pressure ulcer. It compared treatment with a silver mesh dressing with silver sulfadiazine cream. Dressings were changed twice a day. Results: <i>Mean healing rate (%) at 8 weeks</i> Silver mesh dressing group: 36.95 Silver sulfadiazine cream: 25.06 p=0.507 <i>Percentage reduction in PUSH score at 8 weeks</i> Silver mesh dressing group: 28.15 Silver sulfadiazine cream: 34.51 p=0.473 <i>Complications</i> Silver mesh dressing group: 0/20 Silver sulfadiazine cream: 0/20 NICE reported that they felt the comparison in this study was irrelevant, as both products contained silver. Authors' conclusions: 'There was no strong evidence to recommend silver sulfazidine cream over silver dressing.'</p> <p>What are the most clinically and cost effective dressings for the treatment of pressure ulcers?</p> <p>Included 62 RCTs in total, four of which evaluated silver products: Chuansuwanich 2011: described above Münter 2006: This is a low quality RCT. Limitations noted by NICE included: no report of blinding; it is unclear how many patients had pressure ulcers; little information on ulcer assessment. It included 619 patients. Within this there was 43 pressure ulcers in ? patients. Included adults (≥18 years) with a grade II or III pressure ulcer. It compared treatment with a</p>

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
				<p>silver-releasing foam dressing (changed weekly or dependent on exudate) with local best practice (eg foams/alginate, hydrocolloids, silver dressings and other AWDs). Treatment duration was 4 weeks. Results:</p> <p><i>Mean percentage reduction in ulcer area</i> Silver- releasing foam dressings: 58.5% Local best practice: 33.3% No estimate of precision could be derived.</p> <p>Meaume 2005: This is a low quality RCT. Limitations noted by NICE included: inadequate allocation concealment; no blinding; unclear setting. It included 28 patients, aged over 65 years, with stage 3 or 4 pressure ulcers (the whole study included 99 patients in total with different wound types). Wounds were not infected at baseline. It compared treatment with a silver hydroalginate dressing to a standard alginate dressing. Treatment was for 4 weeks. Results:</p> <p><i>Absolute decrease in ulcer area (cm²)</i> Silver group: -7.2 (9.0); alginate group: -0.8 (10.0) <i>Percentage reduction in ulcer area at week 4</i> Silver group: 31.6 (38.1); alginate group: 13.9 (50.3) <i>Healing rate (cm²/day)</i> Silver group: 0.26 (0.32); alginate group: 0.03 (0.36) <i>Mean mASEPSIS index at week 4</i> <i>ITT analysis</i> Silver group: 81.8 (45.1); alginate group: 115.3 (80.2) <i>PP analysis</i> Silver group: 87.3 (42.2); alginate group: 111.3 (74.2) <i>Proportion of patients with ulcer infection</i> Silver group: 1/13; alginate group: 2/15 <i>Proportion of patients with ulcer aggravation</i> Silver group: 2/13; alginate group: 4/15 <i>Proportion of patients with poor local acceptability and/or tolerability</i> Silver group: 1/13; alginate group: 0/15</p> <p>Trial 2010: This is a low quality RCT. Limitations noted by NICE included: no report of sequence generation or blinding; sample size lower than calculated; and pressure ulcers not classified. Included 24 people aged ≥18 years with a pressure ulcer and one or more signs of local infection. It compared treatment with a silver alginate dressing to an alginate dressing. Treatment duration was 2 weeks. The percentage decrease in infection</p>

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
				<p>score was 52.2% in the silver alginate group and 50% in the alginate group. Authors conclusions: “More pressure ulcers worsened with an alginate dressing than with a silver alginate dressing and there was a clinical benefit for silver alginate dressing for reduction in pressure ulcer area. There were no clinical differences for rate of healing of pressure ulcers, poor acceptability and/or tolerability, infection and mortality between alginate and silver alginate dressings....The GDG did not feel that the evidence allowed for a recommendation to be made about the use of a specific type of dressing.”</p> <p>For dressing types – NICE makes two recommendations, which are based on all dressings, not just AWDs: <i>‘Consider using a dressing for adults that promotes a warm, moist wound healing environment to treat grade 2, 3 and 4 pressure ulcers.’</i> <i>‘Discuss with adults with a pressure ulcer and, if appropriate, their family or carers, what type of dressing should be used, taking into account:</i></p> <ul style="list-style-type: none"> - <i>Pain and tolerance</i> - <i>Position of the ulcer</i> - <i>Amount of exudate</i> - <i>Frequency of dressing change’</i>
<p>KCE (2013)³⁴</p> <p>Quality score: +</p>	<p>The guideline includes 12 clinical questions, and the two of relevance are: ‘What are the most clinically effective topical agents for the treatment of pressure ulcers?’ ‘What are the most clinically effective dressings for the treatment of pressure ulcers?’</p>	<p><i>Patient:</i> people of any ages with existing pressure ulcers in any care setting. <i>Intervention:</i> topical agents (including antiseptics); dressings. <i>Comparison:</i> no topical agent; comparison between topical agents; placebo; other pressure ulcer therapy</p>	<p><i>Critical Outcomes:</i> time to complete healing; rate of complete healing; rate of change in size and volume of ulcer; reduction in size and volume of ulcer; proportion of patients completely healed within trial period. <i>Important outcomes:</i> wound-related</p>	<p>Included five RCTs that evaluated the use of silver products in the treatment of pressure ulcers (Meaume 2005; Münter 2006; Trial 2010; Chuangsuwanich 2011; Kucan 1981). Four of these were included in the NICE guideline. The additional RCT is summarised as follows:</p> <p>Kucan 1981: this RCT included 45 hospitalised patients with a pressure ulcer. Study limitations include no report of allocation concealment or blinding, and an analysis that was not intention-to-treat. Participants were randomised to one of three treatments: silver sulfazidine cream (1%), povidone-iodine solution, or physiologic saline. Results reported were:</p> <ul style="list-style-type: none"> - proportion of patients clinically responding within 3 weeks: comparing silver sulfazidine group and povidone iodine group, the p-value in favour of silver sulfazidine was reported (p≤0.022); - the number of patients who reached a bacterial count of <10⁵ per gram of tissue during the 3 week treatment: Silver group 15/15; povidone-iodine group 7/11; saline group 11/14.

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
			pain; time in hospital; patient acceptability; side effects and HRQoL.	<p>Based on the evidence for all topical agents and dressings (not just iodine), the authors make the following recommendation: ‘consider improving wound healing environment by using modern dressings and topical agents (eg hydrocolloids, hydrogels, hydrofibres, foams, alginates, silver dressings) instead of basic dressing types (eg gauze, paraffin gauze and simple dressing pads).</p> <p>As clinical studies did not demonstrate the superiority of one type of modern dressing and topical agent over another, decisions about which type of modern dressing/topical agent to use should be based on:</p> <ul style="list-style-type: none"> - Ulcer assessment (condition of wound, tissue, exudate, depth, degree of infection, odor, pain, wound edges and wound environment); - General skin assessment; - Treatment objective; - Dressing characteristics; - Previous positive effect of particular dressing/topical agent; - Manufacturer’s indications for use and contraindications; - Risk of adverse events; - Patient preferences (lifestyle, abilities and comfort).’ <p>The strength of this recommendation is ‘weak’, and the level of evidence ‘very low’.</p>
Carter <i>et al</i> 2010⁴ Quality score: +	To conduct a systematic review of silver dressings and treatments in wounds focusing on healing outcome parameters; to attempt meta-analyses for these parameters.	Included any type of leg ulcer or wound (but those focusing on burns or other parts of the body were excluded). Did not include studies that compared one type of silver dressing to another. Limited to RCTs	Studies eligible for inclusion had to report at least one outcome related to wound healing. Studies that focused solely on safety, diagnostics or infection were excluded.	Included two RCTs that evaluated the use of silver products in the treatment of pressure ulcers (Meaume 2005; Münter 2006). These have already been described in the NICE 2014 and KCE 2013 guidelines.
NPUAP & EPUAP 2009³⁵	This guideline provides evidence-based	Inclusions: studies focused on pressure ulcer prevention, risk	The authors appear to have extracted all	This included one RCT, which was also included in NICE 2014 and KCE 2013 (Meaume 2005). Does not add to the data already presented.

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
Quality score: ++	recommendations for the prevention and treatment of pressure ulcers.	assessment and treatment; published in a peer reviewed journal; with an abstract; all study designs (excluding series with less than 10 participants); any language. Excluded: economic evaluations.	outcomes identified in the literature.	<p>They make the following B- and C-grade recommendations (they state that B-grade recommendations are supported by direct scientific evidence, and C-grade recommendations are based on indirect evidence and/or expert opinion):</p> <ul style="list-style-type: none"> - “Consider use of silver dressings for pressure ulcers that are infected or heavily colonized (B-grade) - Consider use of silver dressings for ulcers at high risk of infection (B-grade) - Avoid prolonged use of silver dressings; discontinue when the infection is controlled (C-grade) - Consider use of silver sulfadiazine (Silvadene®) in heavily contaminated or infected pressure ulcers until definitive debridement is accomplished (C-grade).” <p>Under the section on the assessment and treatment of infection, they make the further C-grade recommendations:</p> <ul style="list-style-type: none"> - “Consider the use of topical antiseptics that are properly diluted and appropriate for pressure ulcers. Antiseptics should be used for a limited time period to control the bacterial bioburden, clean the ulcer, and reduce surrounding inflammation. The professional should be knowledgeable about proper dilutions, as well as risks of toxicity and adverse reactions. - Consider the use of topical antiseptics for pressure ulcers that are not expected to heal and are critically colonised. - Consider the use of topical antimicrobial silver or medical-grade honey dressings for pressure ulcers infected with multiple organisms, because these dressings offer broad antimicrobial coverage. However, before applying honey dressing, make sure that the individual is not allergic to honey, bee products, or bee stings. - Limit the use of topical antibiotics on infected pressure ulcers, except in special situations.”
Ontario Health Technology	A systematic review on interventions used	Included: Patients in any setting with one or	Proportion of ulcers that healed completely	Included two RCTs that evaluated the use of silver products in the treatment of pressure ulcers. These were also included in NICE 2014 and KCE 2013 (Meaume 2005; Münter 2006). Summarised as follows:

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
2009³⁶ Quality Score: ++	to treat pressure ulcers to answer: -Do currently available interventions for the treatment of pressure ulcers increase the healing rate of pressure ulcers compared with standard care, a placebo, or other similar interventions? - Within each category of intervention, which one is most effective in promoting the healing of existing pressure ulcers?	more pressure ulcers; nondrug and nonsurgical treatments of pressure ulcers; compared to a placebo, a sham treatment or another intervention; Clinical controlled trials or other observational studies only if RCTs are not available; sample ≥ 10 ulcers. Exclusion: other ulcer types; studies with subjective outcomes; non-systematic reviews and case reports; opinion articles, letters etc; articles not in English.	(closed); percent change in surface area/volume, rate of change in surface area (cm ² /day or week); mean time to achieve complete healing; change in the amount of exudate; granulation; PSST score, PUSH score; treatment-related adverse events; absorbency and ease of removal (for dressings).	'Meaume et al. reported that pressure ulcers treated with a silver-releasing alginate dressing appear to have a greater wound reduction after 4 weeks (31.6% vs. 13.9%) and greater reduction in wound severity score (30.7% vs. 17.5%) compared with ulcers treated with an alginate dressing. No statistical analysis can be performed, however, because of the small sample sizes (statistical significance is, therefore, also unknown). Munter et al. found that at the end of 4 weeks of treatment, the silver-releasing foam dressing had greater reduction in ulcer area (58.5% vs. 33.3%), less maceration, better exudate handling, and faster reduction of malodour compared with dressings in standard practice. However, the sample was too small to perform statistical analysis. The mean wear time was significantly longer for silver-releasing foam dressing (3.1 days vs. 2.1 days, $P < .0001$).'
Lo et al 2009⁸ Quality score: +	To examine the efficacy of silver-releasing dressings in the management of non-healing chronic wounds	Limited to English or Chinese RCTs. Included studies in which participants all had wounds that exhibited delayed healing, or were critically colonised or infected. Acute wounds (eg burns) were excluded.	Reported outcomes were classified as physical, psychological or economic.	Included two RCTs that evaluated the use of silver products in the treatment of pressure ulcers (Meaume 2005; Münter 2006). There were included in NICE 2014 and KCE 2013.
Chaby et al 2007⁵	To critically review the literature on the efficacy of	Limited to publications in English or French.	The endpoints for selecting studies were the rate of	Included one RCT that evaluated the use of silver products in the treatment of pressure ulcers (Meaume 2005). This was included in NICE 2014 and KCE 2013, and so the review does not add to the data already presented.

Clinical effectiveness – full write-up

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
<p>Quality score: +</p>	<p>modern dressings in healing chronic wounds and acute wounds by secondary intention</p>	<p>Wounds were considered chronic if time to healing was delayed as a result of impaired tissue repair due to poor oxygenation, malnutrition, or infection. Case reports and case series were excluded. In addition, studies on deep partial and full-thickness burns were excluded.</p>	<p>complete healing, time to complete healing, rate of change in wound area, and general performance criteria (eg pain, ease of use).</p>	
<p>Additional information: A Pan Pacific guideline³³, published in 2012, did not identify any systematic reviews investigating the role of topical silver preparations for treating pressure ulcers. They give a consensus based recommendation: 'Consider using topical silver to promote healing in pressure injuries.'</p>				

Evidence table 4.4: Pressure ulcers – other AWDs – systematic reviews and meta-analyses

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
<p>NICE 2014³⁷</p> <p>Quality score: ++</p>	<p>This is a guideline that rationalises the approaches used for the prevention and management of pressure ulcers. Recommendations are based on a systematic review of the best available evidence.</p>	<p>The guideline considers several clinical questions. The two of relevance to this section:</p> <ol style="list-style-type: none"> 1. What are the most clinically and cost effective topical agents for the treatment of pressure ulcers? 2. What are the most clinically and cost effective dressings for the treatment of pressure ulcers? <p>The authors only included RCTs.</p>	<p>All outcomes reported on in the primary studies appear to have been extracted.</p>	<p>Question 1: For this question, the NICE guideline identified 36 RCTs. Five of these have been described in the other sections of this HTA as they were on iodine, silver or honey. Of the remaining 31 RCTs – none evaluated treatment with any of the antimicrobial dressings detailed in section A5.3 of BNF68. The comparisons were: zinc oxide versus streptokinase-streptodornase ointment; saline-soaked gauze versus hydrocolloid (4); aloe vera, silver chloride and decyl glucoside versus isotonic saline; oxyquinoline versus A&D ointment; growth factors versus placebo (2); phenytoin cream versus saline-soaked gauze versus hydrocolloid; dialysate versus placebo; saline-soaked gauze versus foam dressing; ointment (Resurflix®) versus petrolatum; nerve growth factor versus placebo; saline-soaked gauze versus dextranomer; chlorinated lime solution and paraffin versus dextranomer; saline-soaked gauze versus polyurethane dressing; growth factors versus placebo; phenytoin versus triple antibiotics versus hydrocolloid; resin salve versus hydrofibre; phenytoin versus saline-soaked gauze; saline-soaked gauze versus hydrogel; Insulin versus standard treatment; antibiotic ointment versus foam dressing.</p> <p>The authors summarise the results as follows: “The GDG felt that there was no convincing evidence to support a recommendation to suggest the use of 1 topical agent over another or against placebo. The evidence was not strong enough to suggest the effectiveness of topical agents and therefore the choice of agent would be down to local resources and cost. There was no conclusive evidence towards saline-soaked gauze or hydrocolloid dressing. There is some crossover to the dressings review but the topical agents review focuses on the topical agent that is applied or in gauze. In addition the GDG recognised that there were many confounders and biases. The GDG noted that phenytoin cream is used topically for venous leg ulcers, and although it is not routinely used for pressure ulcers, it could be effective.</p> <p>The GDG felt that there was limited evidence available across the broad</p>

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
				<p>range of products and as such, it was not appropriate to develop a recommendation in favour of using 1 product. Furthermore, the GDG did not feel that topical agents were likely to be significant additional benefits to the use of topical agents compared to the use of dressings, which were likely to have further benefits, for example, promoting autolytic debridement. Additionally, it is likely that topical agents would need to be used in combination with a dressing. The GDG did not think that the addition of a topical agent to a dressing would provide any further clinical benefit.</p> <p>The GDG therefore developed a recommendation that topical antiseptics and antibiotics should not be routinely used to treat pressure ulcers, acknowledging that there may be specific situations in which the use of these agents may be beneficial.'</p> <p>The recommendation given is not specific to a particular AWD: "Do not routinely use topical antiseptics and antimicrobials to treat a pressure ulcer in adults."</p> <p>Question 2: The review for this question consisted of RCTs for numerous types of dressings, including 'antibacterial dressings'. In total, 62 RCTs were included. However, none of the comparisons related to the AWDs as described in section A5.3 of the BNF. Two RCTs evaluated antibiotic ointment (compared to hydrocolloid dressings and phenytoin ointment in one study; and to foam dressings in another). The NICE guideline concluded that : "There was no clinical benefit of hydrocolloid dressing for time to healing or for adverse events when compared to antibiotic ointment" Considering all the evidence together for this question, they state: "The GDG did not feel that the evidence allowed for a recommendations to be made about the use of a specific type of dressing. This was due to the lack and quality of evidence, as well as the importance of considering the function of the dressing and specific patient factors. The GDG emphasised that the effectiveness of each dressing would be dependent upon the type of pressure ulcer. The GDG therefore chose to recommend a dressing which promotes the optimum healing environment, rather than a specific type of dressing"</p>
KCE 2013 ³⁴	The guideline	<i>Patients:</i> people of	<i>Critical outcomes:</i>	Question 1:

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
<p>Quality score: +</p>	<p>includes 12 clinical questions, and the two of relevance are: Q1: 'What are the most clinically effective topical agents for the treatment of pressure ulcers?' Q2: 'What are the most clinically effective dressings for the treatment of pressure ulcers?'</p>	<p>any ages with existing pressure ulcers in any care setting. <i>Intervention:</i> topical agents (including antiseptics); dressings. <i>Comparison:</i> no topical agent; comparison between topical agents; placebo; other pressure ulcer therapy</p>	<p>time to complete healing; rate of complete healing; rate of change in size and volume of ulcer; proportion of patients completely healed within trial period. <i>Important outcomes:</i> wound-related pain; time in hospital; patient acceptability; side effects and HRQoL.</p>	<p>The review for this question included 47 RCTs. However, no studies (other than on silver, honey or iodine products) were identified that evaluated AWDs as described in A5.3 of the BNF.</p> <p>Question 2: The review for this question included 61 RCTs. One of these evaluated a polyhexadine dressing:</p> <p>Wild 2012: Included 30 people with grade II, III or IV pressure ulcers and MRSA. It compared a polyhexadine containing cellulose dressing to polyhexadine swabs. All patients had long-term intractable MRSA colonization in which disinfection had not been achieved despite several attempts, such as the use of iodine, silver, and so on, during a 2-week washout period. The authors of the KCE report note limitations with this study (eg no a priori sample size calculation; and no measure of statistical difference between the groups). The results were as follows: <i>Percentage reduction in pain score:</i> Polyhexadine dressing: 82.4% Polyhexadine swab: 52.6% <i>Proportion of patients MRSA eradicated</i> Polyhexadine dressing: 15/15 Polyhexadine swab: 10/15</p> <p>The KCE guidance considers the evidence for all dressing types and topical agents together: "Consider improving wound healing environment by using modern dressings and topical agents (eg hydrocolloids, hydrogels, hydrofibres, foams, alginates, silver dressings) instead of basic dressing types (eg gauze, paraffin gauze and simple dressing pads). As clinical studies did not demonstrate the superiority of one type of modern dressing and topical agent over another, decisions about which type of modern dressing/topical agent to use should be based on:</p> <ul style="list-style-type: none"> - Ulcer assessment (condition of wound: tissue, exudates, depth, degree of infection, odor, pain, wound edges and wound environment); - General skin assessment; - Treatment objective;

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
				<ul style="list-style-type: none"> - Dressing characteristics; - Previous positive effect of particular dressing/topical agent; - Manufacturer's indications for use and contraindications; - Risk of adverse events; - Patient preferences (lifestyle, abilities and comfort)."
<p>NPUAP & EPUAP 2009³⁵</p> <p>Quality score: ++</p>	<p>This guideline provides evidence-based recommendations for the prevention and treatment of pressure ulcers.</p>	<p>Inclusions: studies focused on pressure ulcer prevention, risk assessment and treatment; published in a peer reviewed journal; with an abstract; all study designs (excluding series with less than 10 participants); any language.</p> <p>Excluded: economic evaluations</p>	<p>The authors appear to have extracted all outcomes reported in the literature.</p>	<p>This did not include any studies that considered the use of any of the AWDs listed in section A5.3 of the BNF (other than silver, honey and iodine). It makes the following C-grade recommendations (In this guideline, C-grade recommendations are based on indirect evidence or expert opinion):</p> <ul style="list-style-type: none"> - "Consider the use of topical antiseptics that are properly diluted and appropriate for pressure ulcers. Antiseptics should be used for a limited time period to control the bacterial bioburden, clean the ulcer, and reduce surrounding inflammation. The professional should be knowledgeable about proper dilutions, as well as risks of toxicity and adverse reactions." - "Consider the use of topical antiseptics for pressure ulcers that are not expected to heal and are critically colonised." - "Consider the use of topical antimicrobial silver or medical-grade honey dressings for pressure ulcers infected with multiple organisms, because these dressings offer broad antimicrobial coverage. However, before applying a honey dressing, make sure that the individual is not allergic to honey, bee products, or bee stings." - "Limit the use of topical antibiotics on infected pressure ulcers, except in special situations"
<p>Reddy 2008³⁸</p> <p>Quality score: ++</p>	<p>To systematically review published RCTs evaluating therapies for pressure ulcers</p>	<p>Included: RCTs published in English.</p> <p>Excluded: studies that evaluated wounds other than pressure ulcers; studies that assessed only adverse events or secondary outcomes (eg pain)</p>	<p>Only studies that calculated wound size with wound volume and/or surface area, used evaluation tools that incorporated these measurements, or used complete healing as</p>	<p>This did not include any studies that considered the use of any of the AWDs listed in section A5.3 of the BNF (other than silver, honey and iodine). It included three RCTs that evaluated 'other' antimicrobials. Comparisons were: polymeric membrane dressing versus antibiotic ointment (Yastrub 2004); phenytoin suspension versus hydrocolloid versus triple antibiotic ointment (Rhodes 2001); and oxyquinoline versus lanolin or petrolatum (Gerding 1992).</p> <p>Based on this data, the only summarising statement in the text is: "Gerding and Browning found oxyquinoline improved wound healing compared with lanolin or petrolatum. However, lanolin may cause allergic contact dermatitis and has fallen out of favour in chronic wound treatment."</p> <p>Based on all the results on antiseptics, the authors make the following</p>

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
			endpoints were included	conclusion: “Standard local wound care for a maintenance or nonhealable pressure ulcer may require antiseptics. Controversy persists in the literature regarding the efficacy and safety of antiseptics (such as povidone-iodine solution). Two of the RCTs we examined compared antiseptics with moist dressings. Neither of these trials met any CLEAR NPT criteria. Antiseptics are inexpensive and non-RCT evidence support their continued use in maintenance or nonhealable wounds to help prevent wound deterioration.”
RCO & NICE 2005 ³⁹ Quality score: ++	The guidelines included a number of clinical questions. The objective of the section of relevance to this HTA was: ‘To systematically assess the evidence for the clinical effectiveness of systemic and topical antimicrobial agents in the treatment of existing pressure ulcers.	Inclusions: published and unpublished RCTs; people with existing pressure ulcers, of any grade or severity; any setting; trials in which a dressing or topical agent was compared with another dressing or topical agent, or compared with a placebo, usual care, or no treatment. Exclusions: studies which focus on microbiological outcomes eg wound cultures, bacterial counts and bacterial eradication.	The primary outcome was wound healing. To be eligible for inclusion, studies had to incorporate at least one objective assessment of wound healing (eg change in ulcer size, rate of healing, frequency of complete healing or time to complete healing). Where studies reported both wound healing and microbiological outcomes, only the former were incorporated in the review.	This did not include any studies that considered the use of any of the AWDs listed in section A5.3 of the BNF (other than silver, honey and iodine). Included two RCTs that considered ‘other’ antimicrobials. Comparisons were: gentian violet-based ointment versus a povidone iodine ointment (Toba 1997) (already picked up in other reviews); and oxyquinoline versus lanolin or petrolatum (Gerding 1992). Based on the evidence for all antimicrobials, the following summary is given: “There is insufficient evidence to indicate whether antimicrobials are effective in the treatment of pressure ulcers.”
O’Meara et al 2000 ¹²	To assess the clinical- and cost-	Included randomised and non-randomised	Included studies had to report	This did not include any studies that considered the use of any of the AWDs listed in section A5.3 of the BNF (other than silver, honey and iodine).

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
Quality score: ++	effectiveness of -Prevention and treatment strategies for diabetic foot ulcers and -Systemic and topical antimicrobial agents in the prevention and healing of chronic wounds.	trials with a concurrent treatment group; systemic or topical antimicrobials for chronic wounds;	objective measures of outcome such as: -any objective measure of wound healing -ulcer recurrence rate -side-effects Studies reporting solely microbiological outcomes were excluded.	Included one RCT that considered ‘other’ antimicrobials (already picked up in other reviews). Comparison was: gentian violet-based ointment versus a povidone iodine ointment (Toba 1997).
<p>Additional information: A Pan Pacific guideline³³ states that their ‘literature search did not identify any SRs investigating the role of topical antimicrobials in promoting healing of PIs.’ The topical antimicrobials they were referring to were: chlorhexidine; hydrogen peroxide; sodium hypochlorite; polyhexadine and betaine; povidone-iodine; and acetic acid. They make the following consensus-based recommendation: ‘Toxic topical antiseptic agents should not be used in the standard care of pressure injuries. Antiseptic solutions with no demonstrated toxicity should be considered in the treatment of pressure injuries with clinical evidence of infection or critical colonisation. Caution: The guideline development group does not recommend the use of hydrogen peroxide in wound management. Deaths have been reported as a result of irrigation of closed cavity wounds with hydrogen peroxide. Toxic effects of most antiseptic solutions on fibroblasts and macrophages in vitro are well documented. Acetic acid at concentrations greater than 3% has been associated with pain at the wound site and skin irritation. There is a risk of acidosis when used for extended periods over very large wound surfaces. It has been demonstrated that there is no dilution of acetic acid that is toxic to bacteria without being toxic to fibroblasts.’ The guideline also states that their literature search did not identify any SRs investigating the role of topical antibiotics in promoting healing of PIs. They give the following consensus-based recommendation: ‘Topical antibiotics are best avoided in the management of pressure injuries as there is a concern that their use if associated with antibiotic resistance and sensitivities.’</p>				

Evidence table 5.1 Dehisced surgical wounds and wounds healing by secondary intention – all AWDs – systematic reviews and meta-analyses

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
<p>Jull <i>et al</i> 2013⁷</p> <p>Quality score: ++</p>	<p>To determine whether honey increases the rate of healing in acute wounds (eg burns and lacerations) and chronic wounds (eg skin ulcers, infected surgical wounds)</p>	<p>Included RCTs and quasi-randomised trials that evaluated honey as a treatment for any sort of acute or chronic wound.</p>	<p>Primary outcomes: time to complete wound healing; proportion of participants with completely healed wounds.</p> <p>Secondary outcomes: incidence of adverse events; length of hospital stay; change in wound size; incidence of infection; cost; quality of life.</p>	<p>Did not identify any RCTs of relevance to this section of the HTA (ie AWDs in people with dehisced surgical wounds, or wounds healing by secondary intention).</p>
<p>Moore <i>et al</i> 2011¹⁰</p> <p>Quality score: +</p>	<p>A systematic review of the literature examining the effectiveness of silver in wound care treatment</p>	<p>Inclusions: At least one group must have received a topical solution, cream, foam or impregnated dressing containing silver; various types of wounds (including venous leg ulcers); any age; RCTs.</p>	<p>Authors stated that studies should measure at least one of the following outcomes: wound healing; resolution of exudate, odour and inflammation; pain and comfort; cost-effectiveness; safety; patients' quality of life.</p>	<p>Included five RCTs in total, of which one (Jurczak 2007; N=67) included participants with open surgical or traumatic wounds left to heal by secondary intention. Open surgical wounds included dehisced wounds, surgically reopened wounds, and incised and draining abscesses. The authors described these as acute wounds, but this HTA is including dehisced wounds – so the results have been presented. Patients were randomised to treatment with Hydrofiber Ag or povidone-iodine gauze. Dressing changes were completed as clinically indicated (at least once every 7 days) and were used until complete healing or for up to 2 weeks. Results summarised as follows: “fifty-one patients completed the study: 11 wounds healed prior to the completion of the study (eight in the Hydrofiber group and three in the povidone-iodine gauze group); one patient was lost to follow-up, one had an adverse event and three did not complete due to unclassified reasons. Hydrofiber Ag dressing was significantly better than povidone-iodine gauze for ability to manage pain, overall comfort, wound trauma on dressing removal,</p>

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
				<p>exudates handling and ease of use.” (no figures etc presented). The review authors gave this RCT 7/10 (PEDro score). The results presented for the same RCT by Carter <i>et al</i> (see below) are not consistent. Moore <i>et al</i> have not really mentioned the wound healing result, which was not statistically significant.</p> <p>Another (Kammerlander 2008) included people with mixed aetiology ulcers, including surgical wounds. However, the results were not presented separately for each wound type.</p>
<p>Carter <i>et al</i> 2010⁴</p> <p>Quality score: +</p>	<p>To conduct a systematic review of silver dressings and treatments in wounds focusing on healing outcome parameters; to attempt meta-analyses for these parameters.</p>	<p>Included any type of leg ulcer or wound (but those focusing on burns or other parts of the body were excluded). Did not include studies that compared one type of silver dressing to another. Limited to RCTs.</p>	<p>Studies eligible for inclusion had to report at least one outcome related to wound healing. Studies that focused solely on safety, diagnostics or infection were excluded.</p>	<p>Included 10 studies, of which one was relevant to this section of the HTA (Jurczak 2007). This RCT was already picked up by the Moore 2011 review, however, the main results that are presented are different. Carter <i>et al</i> state: ‘In a relatively small RCT that was part of a phase III study (N=67), Jurczak <i>et al</i> also tested the effect of Aquacel Ag in their experimental group although the control group received a povidone-iodine (PI) gauze dressing. The target wounds were open surgical or traumatic wounds that required an antimicrobial dressing. None of the healing parameters (complete wound healing, mean time to heal, wound size reduction, or adjusted wound depth) were statistically significant between the groups at 2 weeks, although there were slight advantages for the silver-impregnated dressing group over the control group. Mean time to heal in both groups was approximately 14 days.’ The present the following results;</p> <ul style="list-style-type: none"> - Complete healing: Aquacel Ag 8/35; PI 3/32 (2 weeks); 95% CI -0.04 to 0.31; not significant - Mean time to heal (days): Aquacel Ag 14.1; PI 13.9 (2 weeks) - Wound size reduction: Aquacel Ag 5.51; PI 4.01 (2 weeks) - Adjusted change wound depth (cm): Aquacel Ag 0.9; PI 1.0 (2 weeks)
<p>Vermeulen <i>et al</i> 2010¹⁵</p> <p>Quality score: +</p>	<p>A systematic review of RCTs which investigated the possible beneficial and harmful clinical effects of iodine in the treatment of all kinds of (contaminated)</p>	<p>RCTs that reported on a local wound care product containing iodine in patients with any kind of (more or less contaminated) wound. Any concentration or manufacturer of iodine as well as</p>	<p>Primary endpoints were bacterial load or wound infection and wound healing. Secondary endpoints were adverse events, costs and length of hospital stay.</p>	<p>Included 29 studies, of which one was relevant to this section of the HTA (Jurczak 2007). This was picked up by the systematic reviews already summarised.</p>

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
	wound.	any type of control treatment was allowed.		
Vermeulen et al 2004⁴⁰ Quality score ++	To assess the effectiveness of dressings and topical agents on surgical wounds healing by secondary intention.	Included: all RCTs evaluating the effects of dressings or topical agents for wounds healing by secondary intention (whether or not the secondary intention was planned or unplanned); men and women aged 18+ years; comparisons between any dressing or topical agent; had to report at least one of the primary outcomes	Primary outcomes: wound healing objectively measured by: (a) time to complete wound healing/proportion of wounds completely healed in a specified time period; (b) change in wound area surface over time/proportion of wounds partly healed in a specified time period. Secondary outcomes: Pain; exudates; complications and morbidity; patient satisfaction; quality of life; costs of the dressings and topical agents; cost-effectiveness or cost-benefit analysis; hospitalisation period.	Included 13 RCTs, of which three are relevant to this section of the HTA: Williams 1981: This RCT randomised 80 patients with excision of a pilonidal sinus to either silastic foam cavity dressing or gauze soaked in 0.5% aqueous solution of chlorhexidine. The study was rated as having an unclear risk of bias in relation to allocation concealment and blinding of the outcome assessor. <ul style="list-style-type: none"> - Time to healing: did not show a statistically significant difference (66.2 days versus 57.7; mean difference 8.5; 95% CI -1.52 to 18.52). - Discomfort experienced when the dressing was changed during the first week. The degree of discomfort was obtained by dividing the total score for that week by the number of dressing changes undertaken: extreme (3), moderate (2), mild (1), none (0). The average discomfort experienced was significantly lower in the foam group (1.4 ± 0.6 versus 2.9 ± 2.6 in the gauze group; WMD 1.5, 95% CI 0.63 to 2.37). The clinical relevance of the 1.5 change in the discomfort score is not clear. - Time lost for work: 38.6 days for foam versus 45.4 days for gauze, with fewer home nursing visits for foam (4.6 visits versus 35.1 for gauze; WMD -30.50, 95% CI -37.71 to -23.39). - Duration of hospital stay (8.5 days for foam compared to 7.3 for gauze, WMD 1.2, 95% CI -2.96 to 5.36). Guillotreau 1996: This RCT compared calcium alginate rope with povidone iodine packing soaked gauze in patients with incision and draining of pilonidal abscess. Most domains of the Cochrane risk of bias tool were rated as having an unclear risk of bias. <ul style="list-style-type: none"> - “Healing was reported as proportion of wounds completely healed during a 3-week follow-up period, 13 out of 37 wounds in the alginate group (35%) compared with 6 of 33 (18%) wounds in the gauze group were healed at 3 weeks, the difference was not statistically significant (RR 1.93; 95% CI 0.83 to 4.50). The trial was small and therefore underpowered to detect clinically important differences. - Used a visual analogue scale and reported that alginate rope was painless (p=0.0001) compared to gauze, but no group data were

Reference	Study Objective	Selection Criteria	Outcomes	Main Results (of relevance)
				<p>given.”</p> <ul style="list-style-type: none"> - Mentioned that alginate rope was easier to use (p=0.011). No data are given. <p>Viciano 2000: This RCT compared hydrocolloid with gauze dressings. Randomised 38 patients with open excision of pilonidal sinus healing by secondary intention, to one of two hydrocolloid dressings, or gauze soaked in povidone iodine. The results are summarised as follows:</p> <ul style="list-style-type: none"> - There was no difference in median time to healing between groups. - “Measured pain per dressing change using a visual analogue scale and compared the groups with the Mann-Whitney test. Pain was lower in the hydrocolloid groups during the first 4 weeks (p<0.05) than in the gauze group. The difference appeared in the first dressing and it persisted until the fifteenth dressing. IN the combined hydrocolloid dressings group pain was significantly lower in the first week; (median 25) compared with the gauze group (median 50) (p=0.05). However, the median weekly difference in pain was not significant during the second to fourth weeks.” - Exudate: “Dressings leaked exudates on 14 occasions in the hydrocolloid group. This was reported to be as a consequence of poor dressing adherence. Leaks were not reported in the gauze group.” - “Undertook microbiological analysis of samples collected from the wounds during the perioperative period. None of the intra-operative samples grew pathogens, whilst one postoperative sample from the hydrocolloid group and five from the gauze group grew pathogens. The study authors reported a significant difference in the growth of pathogens (p=0.03). However, it is not clear how many cultures were collected, and we are therefore not able to calculate a RR or a 95% CI.” - “The hydrocolloid group patient comfort was rated as good or excellent, although how this was measured was not stated. No significant differences were noticed between the two wound dressings.” No data or statistics were reported.

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Patient issues: primary research

Aim

The aim was to explore what patients understand about AWDs, what their experiences and perceptions of them are, and what they wanted from treatment with them.

Methodology

A focus group and six telephone interviews were conducted.

Ethical approval was obtained from NRES Committee West Midlands – Black Country.

Participants were identified and recruited by a frontline tissue viability nurse (AJ) from an NHS board.

The inclusion and exclusion criteria were as follows:

Inclusion criteria: Participants, aged over 18 years, who have (or had) a chronic wound and who have been treated with an AWD product within the last three months.

Exclusion criteria: Participants who could not give informed consent, who have not had a chronic wound or who have not been treated with an AWD were ineligible to take part in the study.

The research was explained to eligible participants using a participant information leaflet. Two consent forms were obtained from participants. One gave consent for basic demographic data to be passed to the Healthcare Improvement Scotland research team. The other gave consent to take part in the research.

The sampling of patients was purposive – ensuring a range of wound types and AWDs were represented.

The final sample group consisted of eight patients consenting to take part in a focus group and 10 patients consenting to take part in a telephone interview. Four of the 10 people who agreed to the telephone interview were not eventually interviewed. This was because of changing their mind, not being contactable or not feeling well.

Focus group participants were sent instructions by mail prior to the focus group, informing them of the location and time. They were also phoned by an HIS researcher a few days prior to the focus group, to ensure that they still wanted to be involved, and to ensure that travel was not a problem. Travel expenses were reimbursed on arrival at the focus group.

The focus group took place on the 26th January 2015 and lasted one hour. One participant was accompanied by a relative, who stated that she would like to be involved in the discussion. She was asked to complete an informed consent form prior to the focus group starting, and her contributions are included in the analysis.

Six telephone interviews were conducted. Once consent was obtained by AJ, participants were phoned to arrange a suitable date and time to conduct the interviews. The interviews were conducted in February and April 2015, and were generally between 10 and 30 minutes long.

The focus groups and interviews were guided by a schedule that consisted of nine questions, each with several prompts/sub-questions (available from Healthcare Improvement Scotland on request). The prompts/sub-questions were only used if needed, to encourage discussion. However, the researchers were flexible, allowing conversations to flow naturally, changing the order of the questions if it made sense to do so, and keeping their input to a minimum.

Both the focus group and interviews were audio recorded and transcribed prior to analysis.

JK facilitated the focus group, and conducted four telephone interviews. NF co-facilitated the focus group. SHM conducted two telephone interviews.

Participants

The focus group consisted of eight people, seven who had experience of chronic wounds, and one who was a relative of someone with a chronic wound. There were seven females and one male. A wide range of age-groups were represented (mid-thirties up to mid-seventies). The wound types that the focus group participants had were: foot ulcers associated with diabetes, venous leg ulcers, pressure ulcers, dehisced surgical wounds, and unspecified chronic wounds. The AWDs that the participants talked about were honey, iodine, silver and Flaminal dressings.

Six people took part in the telephone interviews. There were three males and three females, aged from mid-fifties to mid-seventies. The wound types that the telephone participants had were: foot ulcers associated with diabetes, pressure ulcers, leg ulcers and unspecified chronic wounds. Collectively, the telephone participants had experience of honey, iodine and silver dressings.

To protect the identity of the participants, they are each represented in the text using a number (P1-P14). The letters 'FG' mean that they were focus group participants, and 'TI' means that they were telephone interview participants.

Data analysis

All analysis was carried out in QSR Nvivo10. The data were analysed using the framework analysis technique described by Ritchie and Spencer (reference). This method involves a number of separate but interconnected stages of rigorous and methodical qualitative analysis. It allows for the use of a priori themes linked to the study objectives, and for emergent themes to arise from the data.

A summary of the stages of framework analysis is given as follows:

- Familiarisation – All data sources are read and sorted with reference to the study objective.
- Identify a thematic framework – Key issues and concepts and themes are identified with reference to the study objective.
- Indexing – The thematic framework is applied to all the data sources.
- Charting – A matrix of findings for each theme is developed, allowing the comparison between the focus group and the interviews. Each cell of the matrix contains a summary of the groups or individuals contributions to the theme, with a reference that can be directly linked to the original text.
- Mapping and interpretation – All charts and notes are compared to search for patterns and connections in the data. The process allows for the exploration of consensus and disagreement both within and across cases.

One researcher (JK) performed the analysis of the data, and wrote up the results. A second researcher (SHM) quality assured the analysis (including all the tables of findings) and write-up.

Results

The thematic framework

The framework analysis yielded six themes, each with a set of sub-themes. These are detailed below.

1. Living with a chronic wound

- 1.1 Extensive and ongoing
- 1.2 Pain, odour, exudate and other physical features
- 1.3 Emotional impact
- 1.4 Impaired mobility and restrictions on lifestyle
- 1.5 Support from family and friends

2 The patient and the healthcare system

- 2.1 Negative aspects of interacting with healthcare professionals
- 2.2 Positive aspects of interacting with healthcare professionals
- 2.3 A false economy

3 Knowledge and understanding of AWDs

- 3.1 Understanding the purpose of AWDs
- 3.2 Awareness and knowledge of AWDs, dressings and wounds
- 3.3 Becoming experts in AWDs and wound care

4 Perception of AWDs

- 4.1 Wounds healing, or healing more quickly
- 4.2 Improvement in wound's physical features or symptoms
- 4.3 Length of time for AWDs to work
- 4.4 Side-effects
- 4.5 Impact of AWDs on people's lives

5 What people who have chronic wounds want

- 5.1 Healing, control of symptoms, and prevention of wound deterioration
- 5.2 Wound to be dressed
- 5.3 To try anything

6 How AWDs are used

- 6.1 Length of use
- 6.2 Frequency of dressing changes
- 6.3 One size does not fit all

Themes

Theme 1: Living with a chronic wound

While all the questions we asked related specifically to people's experiences and perceptions of AWDs, the challenges associated with living with a chronic wound came out in the discussions. The impact on the participants' lives was significant. As well as dealing with the inconvenience and physical aspects (like pain and limited mobility), several people talked about struggling emotionally. The sub-themes below largely mirror those that were identified in the qualitative literature synthesis.

1.1 Extensive and ongoing

'...both feet at one time were really, really bad, away at the very beginning, talking about ten years ago now, eleven maybe...' (FG, P7)

'On Monday they suggested, the doctor at podiatry has said eh 'this ulcer, Mr [name], seems to be at a plateau, it seems to have, it should have been healed by now'. And I said 'My dear, it should have been healed in May of last year'. (TI, P12)

Most of the people we spoke to had underlying health conditions which put them at greater risk of ulceration. Their conditions also meant that their ulcers/wounds were harder to heal, prone to deteriorating, and were more likely to recur. Some people we spoke to had multiple and extensive ulcerations.

The study was limited to people with chronic wounds, so all participants had lived with wounds for a long time. For some people, their ulcers/wounds would heal relatively quickly (a couple of months). However for most participants healing took several months, sometimes years; or healing had not yet been achieved.

Participant's commonly talked about their wounds reaching a 'standstill' or a 'plateau'. They said that their ulcers/wounds would reach a point where they would not get better, or get worse; they would just stay the same. This was a source of frustration, especially if they had previously appeared to be progressing well. The need for 'perseverance' was mentioned.

Some participants said that their wounds would start as relatively minor bumps or scrapes which would rapidly deteriorate and get out of hand. In addition, some expressed their disappointment when there were set-backs in their wound's progress; people described ulcers/wounds that appeared to be getting better and reaching the point of healing, which suddenly got worse again, or got infected. This might happen several times, repeatedly dashing peoples' hopes for healing.

1.2 Pain, odour, exudate and other physical features

'...the pain was the worst part of it, you know, and walking on it, you know. I couldn't, eh, do as much as I used to do.' (TI, P9)

'You think 'everybody can smell me'.... I used to dread my visitors, and any visitors that was coming up, at first your 'can he smell anything?' But all he can smell is perfume at the door, because I was like that [mimics squirting a perfume bottle], you know, everywhere!' (FG, P1)

Some people talked about their wounds quite generally, describing them as 'disgusting' or 'yucky'. However, more commonly people discussed specific symptoms that they had to deal with. The wound symptoms that participants discussed the most were pain, odour and exudate.

The pain that participants had to deal with was often significant, impacting on their general quality of life and wellbeing. The consequences of the pain included limited mobility, feelings of isolation and loss of appetite.

While malodour was not reported by everyone, participants often talked about the odour that came from their ulcers/wounds. They were repulsed by the smell, and described it as overpowering and embarrassing. This embarrassment can be isolating for people, who talked about avoiding or dreading social contact.

Some people described their wounds as being very 'wet', or said that they leaked badly. People talked about changing their bedding daily, getting rubber sheets for their bed, and ruining carpets in their house.

1.3 Emotional impact

'Well, when I went to the podiatrist and I had been told, 'well, it's kinda worse', I used to go out on a right downer. Because it had been doing so well, and then, poof, and you think, you know, 'what else, what else?' Because it doesn't take much to put you over the edge, emotionally.' (FG, P2)

People who had extensive ulcerations, or had lived with ulcers/wounds for a number of years, spoke about the impact on their mental well-being. People talked about feeling down, or 'down in the dumps', when their wounds were particularly bad, or when they had taken a turn for the worse. Some people described feeling emotionally vulnerable, on a 'cliff edge', with any small set back sending them 'over the edge'.

Some people had faced the prospect of having an amputation. Most did not actually go on to have an amputation, but even the prospect was difficult to deal with, was sometimes unexpected, and came as a 'terrible shock'.

Less commonly was a feeling of having 'had enough' of trying different treatments to no avail, and an acceptance of amputation as a last resort.

1.4 Impaired mobility and restrictions on lifestyle

'- It's terrible, you can't even get up and walk.

- I walked in the door today to come down here, that's the most I've walked in about a year.

- That's the most I've walked in a long time, too.' (FG, P2, P5 & P7)

Some people we spoke to described being unable to go out, mostly because of physical limitations, but also because of feeling emotionally unable.

For the people who spoke of having limited mobility, this could be attributed to the pain in their ulcers/wounds, or to their co-morbidities. Limited mobility for some was also caused by having to wear bulky foam podiatry boots, not being able to wear shoes, or having to keep weight off pressure ulcers.

Participants described feeling annoyed by their limited mobility, their diminished ability to care for themselves, and their reliance on others for support with daily living. For some people of pre-retirement age, their restricted mobility prevented them from working. People also said that not being able to exercise had caused them to gain weight, or to lose muscle and body strength.

1.5 Support from family and friends

'But then I've always thought, 'what happens if I'm single?' You know, 'what if I'm...' (FG, P3)

Several of the participants relied on support from family members (children/partners/siblings). This included emotional support, help with dressing changes, assistance with day to day living, and assistance during hospitalisations. Some people implied that without this additional support, they might not have been able to cope.

Theme 2: The patient and the healthcare system

The participants talked about positive and negative elements of their care. While several had some negative experiences, most people referred to health professionals who they had clearly developed a good relationship with, who they trusted and who they felt went the extra mile for them. There was a general feeling at the focus group that clinicians who were not providing AWDs were purely motivated by costs, that this was short-sighted, and that there was a need to 'speak up for yourself'.

2.1 Negative aspects of interacting with healthcare professionals

'And they were saying 'We shouldn't be giving you that'. It should be just initial and you'll get the dressings from your GP but you know the girls are there to help us out so they would just give us what we need to go away ...you know, they shouldn't...they said they shouldn't be giving out dressings on a long term basis like that.' (FG, P3)

'...nobody told me they were plastic surgeons, they were doctors. So I was sitting thinking later on 'I wonder what they're thinking, are they thinking of cutting my foot off, is it that bad?', because I couldn't see it.' (FG, P2)

The main problem that participants reported related to inconsistent care in relation to the provision of AWDs. Some of the people that we spoke to had experienced inconsistent access to AWDs. Examples were given of how people had been treated with AWDs in one care setting/department (for example, in hospital), but were then unable to get the same AWDs in another care setting/department (for example, from GPs). As a consequence, they 'stocked up' on AWDs, given to them by clinicians who used them. This inconsistency was frustrating and inconvenient, and appeared to be an additional burden to people. Participants clearly valued the healthcare professionals who provided them with stocks that would enable them to continue using their preferred AWD.

Other negative aspects of health care related to treatment becoming less personal, with some participants saying they felt like a 'number', or like they saw different healthcare professionals on every visit. Communication with healthcare professionals was not always satisfactory. For example, a participant described having a wound assessed by plastic surgeons, but not being made aware of

who they were. This person had been left theorising unnecessarily about what was happening, and worrying that they were facing an amputation.

In addition, someone described how their access to a tissue viability nurse had been delayed due to a 'breakdown in communication' amongst healthcare professionals.

While not discussed at length, there was agreement from everyone at the focus group that there was a need not to just accept any treatment, but to challenge restricted access to preferred treatments.

2.2 Positive aspects of interacting with healthcare professionals

'But I cannae fault the nurses. The nurses have been brilliant. They have been great.' (TI, P13)

'But when I had him, I did, I used to say it all the time, 'I'd take poison off a spoon from him'. Because, I trusted him so much. I did, I trusted him so much...' (FG, P2)

People we spoke to also discussed positive elements of their care, with several referring to named healthcare professionals. People valued healthcare professionals who they trusted, who used their initiative, who challenged budgets, or who they felt did not 'give up' on them.

Some people had clearly developed good relationships with their treating healthcare professionals, saying they had 'known them for years', and talked about having 'banter' and 'a good bit of fun'. This helped to foster good working relationships, and appeared to make people feel supported and like they were getting 'personal' treatment.

The importance of good chiropody was mentioned by one participant, who said that something as small as cutting a toenail properly could give people a 'new lease of life'. This implies that the value of seemingly quite simple things should not be underestimated.

2.3 A false economy

'If someone said to me 'this is the cheapest product [name] and you'll be healed in six months, or this is a dear product [name] and you'll be healed in six weeks'. I know what one I'll take. And I think that's for a, for a healthier Scotland, I think that's the direction they should be looking at. Spending money looking, you know, upfront to save money in the long term.' (FG, P6)

The focus group participants felt that restricted access to AWDs was purely due to the cost. This was viewed as a 'false economy'. They felt that AWDs helped to heal wounds faster, were better than non-AWDs, and that this was not being considered in decisions around provision. They argued that by not using AWDs the costs would be greater in the long run due to increased staff time and amputations.

Theme 3: Knowledge and understanding of AWDs

Most participants were aware when an AWD was used on their wounds, and knew that the purpose was to treat localised infection. Knowledge of AWDs was surprisingly high, suggesting good communication from healthcare professionals. People were aware of brand names, understood how the dressings should be used, and several had developed expertise in dressing their own, or their relatives', wounds.

3.1 Understanding the purpose of AWDs

'They kill off the bacteria in the wound so that healing can take place, that's what I know about.' (FG, P2)

Understanding about the role of AWDs in treating infection in a wound was high. Some patients appeared to have detailed knowledge about dressings in general, talking about them reducing 'slough' and promoting 'granulation'. Despite this, there was varying levels of knowledge, and some patients may have no understanding of the purpose of AWDs.

3.2 Awareness and knowledge of AWDs, dressings and wounds

'We've used the three [iodine, silver and honey dressings] on [relative's] leg and at present we are still using the honey. Activon tulle we are using.' (FG, P8)

People's knowledge around dressings, and wound care more generally, was good. Some people claimed not to know very much, but would then go on to talk in detail about the treatment they had received.

Most participants were aware that they had been treated with an AWD. They were able to tell us what different types of AWD they had been treated with, for how long, and the ones they preferred. Most people even referred to specific brand names. People also seemed to have a good understanding of how the AWDs were used, and could describe in detail what happened at their dressing changes.

Some participants also seemed to have a good understanding of how factors other than dressings impact on wound healing. For example, people talked about keeping weight off pressure ulcers, compression bandaging for venous ulcers, and how important it was to remain in 'good diabetic control'.

Despite all this, it is apparent from our discussion with the participants that sometimes people are treated with an AWD and are not aware.

3.3 Becoming experts in AWDs and wound care

'the nurse obviously says to me 'you know what you're doing [name]'' (TI, P11)

'and I had to actually go up and dressed it. And then the nurse says, 'could you show how you are doing that dressing?'' (FG, P8)

The participants who had extensive wounds, or had lived for wounds/ulcerations for a long time, had become experts themselves in wound care. Several participants also spoke about how they relied on family members (partners, children or siblings), who had developed expertise in how to look after the wounds, and use the dressings. This expertise was sometimes shared with healthcare professionals, who had not cared for the participants previously.

There was variation in how much information participants sought on dressings. Some talked about going home to 'google' them, to read more about the research behind the dressings. Others were satisfied with the level of detail that they got from their healthcare professionals.

Theme 4: Perception of AWDs

The people we spoke to were generally positive about AWDs. Most felt that they had helped to heal their wounds, or to heal their wounds faster, although this was not universal. Several also talked about AWDs improving wound symptoms, with some saying that the effects were notable very quickly. Some people said that AWDs had allowed them to get their life back, or had meant that they had avoided a far worse prospect (for example, amputation).

4.1 Wounds healing, or healing more quickly

'And I think it helps a good bit. It has healed me.' (FG, P1)

'Well, I've not really had enough experience of them so far so I don't really know whether it's going to make a difference' (FG, P4)

'I hoped it, it hoped the ulcer would get smaller, you know. And heal. But nothing happened. No matter what they did, nothing happened.' (TI, P13)

A dominant finding was that participants felt AWDs had helped (or were helping) to heal their wounds. For some, the effects of the AWD appeared considerable. The improvement in wounds was described as 'unbelievable'. However, this was not universal, and for some there was uncertainty of the helpfulness of AWDs in wound healing, or a perception that they had made no difference.

There was no one AWD that stood out as being a favourite. Some people attributed their wounds healing to honey, others to silver, or to iodine or 'flagogel' (likely to mean 'Flaminal'). Several participants had been treated with more than one AWD. It was apparent that a trial and error approach had been used in these people, with several dressings (including AWDs) failing to make a difference. Eventually, an AWD was tried that they perceived as helping their wound/ulcer. As a result, these participants tended to credit one particular AWD for marking the turning points in their wounds progress.

For some people, their wound/ulcers healed relatively quickly (in a few months), others took longer. For people who had recurring ulcers, there was a perception that AWDs healed their wounds faster than non-AWDs that had been tried previously.

4.2 Improvement in wound's physical features or symptoms

'There was a lot of pain, right enough, but ehm once they started treating it, you know, the pain started to diminish' (TI, P10)

'And it's the first year I haven't been in hospital with an infection which is a big thing for me because sometimes it can be two and three times a year.' (FG, P7)

Other improvements in ulcers/wounds, besides healing, were attributed to AWDs. The improvements most frequently mentioned related to pain, odour and control of infection. These were important outcomes to the participants.

Several participants told us that the AWDs had helped with the pain they felt in their wounds, or with the odour. Even in participants whose wounds/ulcers had not yet healed, and where the

likelihood of healing was uncertain, there was a feeling that AWDs helped to control odour, or more extensive infections (that might have required hospitalisation or antibiotic treatment).

Most people talked generally about their wounds improving with AWDs. They talked about wounds appearing healthier, an improvement in slough, and seeing the edges of the skin trying to come in.

4.3 Length of time for AWDs to work

'...at first I was thinking 'mmm is there going to be much improvement here' but in four weeks eh I started to see improvement. I wouldn't say it worked straight away but I did see an improvement in the last month. I would say I was on it two months, uh huh. I must admit I do see an improvement.' (TI, P11)

'Really and it was horrible. And then started with honey and then it was, maybe a few weeks, that's when we've started seeing it and now it's, like, totally levelled.' (FG, P8)

A number of the participants perceived an improvement in their (or their relative's) ulcers/wounds quite quickly after starting treatment with an AWD. As already stated, they implied that wounds 'turned a corner' with a particular AWD. Some people said they noticed improvement in symptoms (like odour) 'the minute' an AWD was applied. For others, it took a few weeks, or months, before improvements were seen.

In some people, AWDs had been used for a long time, and there were reports of wounds deteriorating when AWDs were stopped.

4.4 Side-effects

- *'I do. It's got a drawing effect I must say. But I find that good cause I know it's doing something.'*
- *Yeah, it's a throbbing so you know it's working.*
- *It's taking something away.*
- *Yeah, mmm, it's like a drawing effect.'* (FG, P1, P3 & P6)

Participants mostly reported that they had not experienced any side-effects with AWDs. With prompting from the researcher, there were reports of honey causing a 'throbbing', 'drawing', 'nipping' or 'stinging'. The pain was enough for some people to take over-the-counter painkillers. Honey dressings also leak for some people. However, the leakage and pain did not put participants off using honey. In fact, some perceived the pain as a sign that the honey was doing something beneficial.

For some, dressing changes can be painful, particularly if a dressing has dried onto a wound. For others, dressing changes do not cause considerable discomfort. Unsurprisingly, people with less extensive wounds reported less pain at changes.

4.5 Impact of AWDs on people's lives

'...and to me I think if I never got the treatment, this kind of treatment, I don't know what kind of wound I would...' (FG, P1)

Most participants were positive about AWDs. Even in people whose wounds had not healed, they felt that AWDs had helped with their wound symptoms.

However, some people implied that the impact of AWDs on their lives had been considerable. They said that AWDs allowed them to get 'back on their feet again' or back to their 'day to day' business. In addition, there were people who felt that AWDs had meant that they had to attend less clinical appointments, or had avoided hospitalisation. Finally, some said that thanks to AWDs, they had avoided a far worse situation, including amputation.

Theme 5: What people who have chronic wounds want

Participants were asked specifically what they wanted from treatment. For people with chronic wounds, the thing they want the most is for the wound to heal. Control of symptoms, and not allowing wounds to deteriorate were also important. This mirrors what was highlighted as important to patients under theme 4, and so subtheme 5.1 has not been discussed at length. Some people said they were prepared to try anything to achieve these outcomes.

5.1 Healing, control of symptoms, and prevention of wound deterioration

Wound healing was important to the participants, regardless of whether they had their wounds for a few months or several years. People also said, more specifically, that they valued anything that would heal their wound faster.

Control of symptoms (like pain and odour), and wounds not being allowed to deteriorate, were also highlighted as important to patients.

5.2 Wound to be dressed

Although not frequently mentioned, leaving wounds undressed might cause distress for people with extensive ulcers/wounds. This can lead to feelings of anxiety, and a perception of being more vulnerable to infection.

5.3 To try anything

'And to be perfectly frank, having endured this thing since May last year, if the guy said, 'you know, we are going to bring in a parrot, it will bite off the scabs', I would endure that as well. If it had to be.' (T1, P12)

Some of the participants reported wanting to 'try anything' or feel that 'anything is worth a shot'. Even if AWDs had not worked, some people were glad they had tried them, and felt that to try different things was people's 'right'. Innovative products, which have just come from 'the factory floor', were viewed favourably by some.

Amputation was viewed as a last resort, with people wanting to be sure that they had tried everything else before taking that path.

Theme 6: How AWDs are used

Most of the participants said that AWDs had been used for a long time on their wounds, but it was not always clear if this use was only limited to times when the wound was infected. Wound

dressings needed to be changed several times a week. There was no one favourite AWD, with what worked for one person not working for another.

6.1 Length of use

Some people we spoke to implied that they had been treated with AWDs for quite a long time (several months in most cases, years in a few cases). However, it was not always clear if this use was consistent, or if the healthcare providers were switching between AWDs and non-AWDs. Some people specifically said that they had been treated with AWDs on and off for several months/years, with AWDs only being used if their wound was showing signs of infection.

In other people, AWDs had only been used for a short time (weeks). These people had less extensive ulcerations.

6.2 Frequency of dressing changes

All participants had required (or still required) fairly frequent dressing changes. This varied from once a week, to every second day. As people's wounds progressed towards healing, the dressing changes became less frequent.

6.3 One size does not fit all

'- But everybody's different.

- Aye. oh aye, we're all different

- It's not like one size fits all. It doesn't.' (FG, P2 & P6)

As mentioned previously, it was apparent from speaking to all the participants that the AWD that worked for one person, did not work for another. Participants themselves were aware that it is not a 'one size fits all' situation.

Discussion

With regards to peoples' experiences of chronic wounds, this research mirrors the results of the qualitative synthesis. Accounts of the physical and emotional impact, and the reliance on family members were corroborated. This research also adds to the existing knowledge, by describing peoples' experiences and perceptions of AWDs specifically.

Limitations

The aim of the primary research was to describe people's experiences and perceptions of AWDs. Given that the sample was small and non-randomised, it is not appropriate to make any quantitative or comparative statements. Such a small study is not expected or able to represent the entire spectrum of the potential patient population. In addition, the people who volunteered to take part in the research might differ from people who did not. Despite this, a variety of people (in terms of gender, age, wound types and AWDs) were successfully included in the research.

A practicing tissue viability nurse recruited participants to a study. It is possible that if she had strong feelings in favour of AWDs, this could have influenced her selection of people to the study. However, while most participants had positive experiences of AWDs, a spectrum of views were represented.

Some people talked about particular AWDs that had not worked for them, but spoke passionately about another AWD that had. Some people had extensive experience of several AWDs, others had limited experience of one. Participants also freely discussed positive and negative elements of their care more generally.

Participants' appeared to be engaged in the focus group discussion. Everyone contributed, and prompts/questions from the researchers were kept to a minimum. Contributions were often responses to other participants' comments, rather than responses to research questions. On the other hand, sometimes the conversations in the telephone interviews did not flow as well. It was difficult to establish a rapport with someone without the face-to-face element. Telephone interviewees tended to give shorter answers, and required more prompting. Despite this, all participants provided meaningful and useful input, and all expressed an interest in the work.

Both the researchers who facilitated the focus group agreed that the participants appeared to have suspicions about AWDs being made unavailable. When asked specifically at the end of the discussion if they had heard rumours to that effect, they said they had not. Given some participants' experiences of inconsistent access to AWDs, and their perception that it was due to costs, it was possible that they have become concerned about their ongoing provision.

Conclusions

- The impact of chronic wounds on the participants' lives was significant. As well as dealing with the inconvenience and physical aspects (like pain and limited mobility), several people talked about struggling emotionally.
- People valued care that they felt was personal, and from healthcare professionals who they trusted and who were persistent.
- Some participants spoke about inconsistent access to AWDs, with them being treated with an AWD in one setting/department, but then being told that they were unavailable in another setting/department. This was reported as being frustrating and causing considerable inconvenience. Participants worked around this problem by getting the AWDs they preferred from the healthcare professionals who used them.
- Knowledge and understanding of AWDs was surprisingly high, suggesting good communication from healthcare professionals.
- The people we spoke to were generally positive about AWDs. People felt that they helped (or were helping) to heal their wound, and/or helped with wound symptoms.
- For people with chronic wounds, the thing they want the most from treatment is for the wound to heal. Control of symptoms and local infection, and not allowing wounds to deteriorate were also important. Some people said they were prepared to try anything to achieve these outcomes.
- Most of the participants said that AWDs had been used for a long time on their wounds, but it was not always clear if this use was only limited to times when the wound was infected. Wound dressings needed to be changed several times a week. There was no one favourite AWD, with what worked for one person not working for another.

1. Consensus guidelines

1.1. Introduction

On the whole, published literature provides insufficient evidence draw conclusions on the use of AWDs in chronic wounds with local infection. These dressings are being used for this indication in NHSScotland. While the HTA has not been able to guide usage of AWDs in chronic wounds with local infection, it has identified the importance of a more consistent approach across NHSScotland. Therefore, until the evidence becomes more compelling, guidance on AWD use based on the consensus of clinical experts was sought.

1.2. Methods

Questions on the use of AWDs were developed, based on the findings of the staff survey (see the organisational issues chapter). In addition, clinical experts emailed Healthcare Improvement Scotland researchers separately detailing the clinical questions that they felt would be most usefully answered using consensus methodology.

A call for volunteers went out across NHSScotland. This involved placing an advert on the SIGN and Healthcare Improvement Scotland website; sending targeted emails to certain clinical topic groups/experts; asking the topic group to forward to colleagues; and sending blanket emails via various in house distribution lists. Clinicians who treat, or are involved in the treatment of, chronic wounds were eligible to be involved. Undergraduate students were not eligible to be involved.

Consensus was reached using a modified Delphi approach. This involved three rounds of questioning, all done via email. Participants were given one week to respond to each questionnaire. They were informed of the dates that they would receive the questionnaires at the start of the process, to ensure that they set aside sufficient time to be involved.

After each round the results were analysed and fed back anonymously to participants. They were asked to consider their answers in light of everyone else's responses. The questionnaires were refined for each round.

The threshold for consensus was 70%.

To ensure transparency, the results of each round were documented. These are available, along with the three questionnaires, from Healthcare Improvement Scotland on request. All participants were required to complete 'declaration of interests' forms.

1.3. Results

59 people volunteered to take part in the process.

30 people took part in round 1 (51% response rate). The 29 people who did not take part were excluded from the remaining rounds. The following specialities were represented: tissue viability nursing; district nursing; staff nursing; podiatry; practice nursing; pharmacy; community staff nursing; and dermatology. The following NHSScotland boards were represented: Greater Glasgow and Clyde, Fife, Lanarkshire, Forth Valley, Highland, Lothian, Tayside and Orkney.

23 people took part in round 2 (77% response rate). The seven people who did not take part were excluded from the remaining rounds.

21 people took part in round 3 (91% response rate).

1.3.1. Consensus statements

1.

- a. *When treating a patient with a chronic wound, symptoms of localised infection must be present before use of an AWD is commenced.***

Consensus was achieved on this statement in round 2 of the process (21/23 people agreed or strongly agreed).

- b. *However, in certain patients with underlying health conditions some of the signs and symptoms of localised infection might be masked.***

Consensus was achieved on this statement in round 3 of the process (18/21 people agreed or strongly agreed).

2.

- a. *Clinical experts agreed that the most commonly observed signs and symptoms of localised infection, which might prompt use of AWDs, include:***

- ***Pain/increased pain***
- ***Erythema/redness***
- ***Heat***
- ***Wound deteriorating/getting bigger***
- ***Exudate: thick, haemopurulent or purulent and/or high volumes***
- ***Inflammation/swelling/oedema***
- ***Positive wound swab***
- ***Delayed or stalled healing***
- ***Malodour***

Consensus was achieved on this statement in round 2 of the process (21/23 people agreed or strongly agreed). The addition of 'positive wound swab' was questioned, and there was disagreement about whether it should be on the list. It was argued that this could increase inappropriate swabbing of wounds.

- b. Some of the above signs and symptoms can be caused by patient factors other than localised wound infection. Therefore, a holistic assessment of the patient is required to rule out causes other than localised infection.***

Consensus was achieved on this statement in round 3 of the process (20/21 people agreed or strongly agreed)

- 3. After two weeks of using an AWD, if the symptoms of localised infection have ceased entirely, stop using the AWD and dress wound as per formulary recommendation***

Consensus was achieved on this statement in round 2 of the process (22/23 people agreed or strongly agreed).

- 4. After two weeks of using an AWD, if the symptoms of localised infection have improved but not ceased entirely, consider continued use of the AWD but review at weekly intervals.***

Consensus was achieved on this statement in round 2 of the process (22/23 people agreed or strongly agreed).

- 5. If, after two weeks of using an AWD, the symptoms of localised infection have not changed or have become worse, follow the guidance given in stage 3 of 'The Ropper Lothian Ladder' in tandem with your local policies and procedures.***

(Ladder will be included as an appendix – but need to arrange permissions first)

Consensus was achieved on this statement in round 3 of the process (19/21 people agreed or strongly agreed). However, there was debate around this as swabbing would not be supported by some boards for localised infection.

- 6. Do not use an AWD for longer than two weeks without reassessing wound progress.***

Consensus was achieved on this statement in round 2 of the process (everyone agreed or strongly agreed).

- 7. AWDs should not normally be used for longer than recommended by the product information, or as documented within local policies or procedures.***

Consensus was achieved on this statement in round 3 of the process (18/21 agreed or strongly agreed). However, there was some disagreement around the value of this statement.

- 8. Having taken into account patient and wound specific factors, the costs of dressings relative to their benefits should guide their use.***

Consensus was achieved on this statement in round 2 of the process (22/23 either agreed or strongly agreed).

1.3.2. Areas where consensus was not achieved

- Consensus could not be reached on which type of AWD to use in different wound types. Therefore, when selecting AWDs, clinicians should be guided by their local formularies and guidelines.
- It was not possible to obtain consensus on how long to use AWDs in chronic wounds in which signs of infection were improving, but not clearing entirely (other than to review at weekly intervals, as statement 4 suggests). In such cases, AWDs could theoretically be used for extended periods of time. This is an area for which more consensus work is needed, as AWDs should not be used for indefinite periods of time.